

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 II

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 8:30 a.m. on Wednesday, May 10, 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



C O N T E N T S

Volume II
May 10, 2006

PANELISTS (in alphabetical order).....	3
REVIEW OF DAY 1 AND GOALS FOR DAY 2	
Dr. Wheeler.....	5
Dr. Kapil.....	10
PUBLIC/OBSERVER COMMENT PERIOD.....	13
PANEL DISCUSSION: CT SCANNING.....	43
RESPONSE TO ATSDR QUESTIONS	
Question No. 1.....	58
Question No. 2.....	66
Question No. 3.....	77
Question No. 4.....	97
Question No. 5.....	100
Question No. 6.....	113
Question No. 7.....	114
Question No. 8.....	115
WRAP-UP	
Dr. Kapil.....	122
Panelists' Closing Remarks.....	124
Dr. Forrester.....	135
REPORTER'S CERTIFICATE.....	140

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

NANCY LEE & ASSOCIATES

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
[microphone]	Speaker is off microphone

P R O C E E D I N G S

8:45 a.m.

1
2
3 DR. HOLGUIN: Good morning. Welcome back. Let me
4 just give you a quick overview of the working agenda for
5 this morning. We will start the day. The folks from
6 ATSDR would like to give a sort of wrap-up overview of the
7 discussion yesterday, and then that will be followed by
8 the public comment period -- public-observer comment
9 period, in which we are planning to open it to all the
10 audience members who may wish to make comments, as long as
11 we don't go beyond 30 minutes, remembering that each
12 person has five minutes to talk. And then I guess we'll
13 proceed to the homework that the panelists spent their
14 night working on. So I'm going to pass on the microphone
15 to the ATSDR table.

16 DR. WHEELER: I thought we would just start this
17 morning with kind of a brief of what we heard yesterday.
18 I'm sure there's several points that will be left out,
19 but, hopefully, we've captured the main things.

20 We started off talking about fiber burdens that could
21 be measured at autopsy. We learned that this is not a
22 simple calorimetric test that you just easily do. There's
23 a lot of expertise required. There's a lot of experience
24 required in how you do these measurements. There's a lot
25 of analytical considerations. There's considerations of

1 how you would collect the samples in the lungs, whether
2 you might pool those samples or whether you would look at
3 samples individually.

4 There was a big problem with temporal considerations,
5 in that the lungs of an 80-year-old, due to clearance and
6 other mechanisms, may not reflect that person's exposure.
7 And we also learned that autopsy material is getting very
8 rare. It's very hard to find these materials and that we
9 might not be able to do these simply from the lack of
10 material.

11 We might be able to use young accident victims to get
12 around some of these problems, but that would be in a very
13 limited situation. Our overall thoughts and conclusions
14 were that this might be useful, but it would be in a very
15 limited situation, a very well-defined situation, and we
16 would probably have to use young tissue samples.

17 Fiber burdens in living humans: Because of the risk
18 associated with these procedures, it shouldn't be
19 performed medically unless there's some other kind of
20 medical testing that's going on there, and there are some
21 ethical considerations there. But when you use material
22 from people that are undergoing other procedures, that may
23 bias the sample. Those people may already have lung
24 cancer. So you're looking at predominantly samples that
25 have -- people that have led to lung cancer. There may

1 also be problems with -- tumors may cause some kind of
2 difference in the lung fiber burdens and may skew the
3 results that way. So we didn't think that that technique
4 would probably be useful at all for evaluating
5 communities.

6 Sputum samples: I think the discussions show that
7 those were very insensitive techniques. There was
8 virtually no correlation with exposure and virtually no
9 correlation -- or nobody even talked about risk really.
10 It was too much of a stretch to even discuss that. All
11 spitters aren't alike. Different people produce sputum in
12 different manners, which is kind of unfortunate. In Oak
13 Ridge, we had a high school and you've got a lot of high
14 school boys. There ought to be a lot of sputum around,
15 but...

16 And measuring uncoated fibers with TEM or some other
17 method may be promising, but it's not validated enough or
18 not ready for prime time yet. So our conclusion was that
19 it was really too insensitive to use in a community
20 exposure, but it could provide some limited information in
21 conjunction with some of these other tools.

22 Bronchoalveolar lavage: That seemed to be one of the
23 more promising things that we talked about yesterday.
24 There seems to be a fairly good correlation with lung
25 tissue burdens. There's considerations on how you recover

1 the lavage fluid, and that's more of an art than it is a
2 science apparently. You could perform this on healthy
3 volunteers. You can recruit people with enough money to
4 do this. It's not something that you're ethically too
5 challenged to do because it's not that invasive.

6 One of the discussions that came up was about
7 background and how you get a good background to compare to
8 the samples that you're getting, and that was a critical
9 component. It seems to be a promising technique for
10 measuring exposures in humans and something that we might
11 want to look at further.

12 There was some discussion about asbestos bodies that
13 accompanied both the BLA [sic] and the sputum sample
14 discussions. One of the questions that I had was that,
15 apparently, most asbestos bodies or ferruginous bodies
16 form on long fibers, and I wasn't quite sure what the
17 mechanism there would be other than perhaps the residence
18 time of the fiber in the lung. I also was kind of
19 wondering last night, if you see asbestos bodies and they
20 only form on long fibers, is there something we can say
21 about the distribution of the fibers that those people
22 breathe to produce those asbestos bodies? One of the big
23 confounders was that apparently not all people produce
24 asbestos bodies.

25 Then we had a discussion on sentinel animals. It was

1 shown that animals certainly do accumulate asbestos in
2 their lungs and they do settle at different sites above
3 what you would expect in background rates. It was nice
4 data to have to show that there was a potential within a
5 community or an area that for some kind of fiber exposures
6 to humans, but it does not necessarily prove that human
7 exposures are occurring.

8 Correlation between animal exposures and human
9 exposures really -- it's beyond the scope of that
10 technique at the moment. We also had a little bit of
11 discussion of variability in animals, and Mickey Gunter
12 brought up the fact that there's a lot of variability in
13 humans also, and so there will be variability problems in
14 making any of those kinds of extrapolations.

15 Our conclusion was that it was useful information to
16 show that there's fibers in the environment that can
17 become airborne and could lead to human exposures, but to
18 make any kind of conclusions about human exposures going
19 on is a bit of a stretch.

20 We then had a discussion on mesothelin and
21 osteopontin. I think the panel mainly agreed that this is
22 in the early stages of development. It's a very promising
23 technique. There is a lot of concern about how the false
24 positives and the false negatives would be -- what kind of
25 situations that would lead to in the community and whether

1 or not you would alarm people or whether or not you would
2 perform procedures that didn't need to be done on false
3 positives or whether you would give people that had false
4 negatives assurances that they perhaps shouldn't have. It
5 doesn't seem like the technique is quite ready for prime
6 time. It's a technique that's in development and shows a
7 lot of promise.

8 I'm going to let Vik talk about the x-rays and
9 spirometry.

10 DR. KAPIL: Do we want to stop and ask the panel to
11 comment on any of John's statements first, or shall we
12 just go through all of them first and then -- your
13 preference.

14 DR. ROGGLI: Go through all of them.

15 DR. KAPIL: Okay. All right.

16 So on plain films, on plain chest radiographs, we did
17 discuss that chest x-rays were noninvasive, relatively
18 risk free, cheap. But they are also sort of associated
19 with significant issues related to sensitivity and
20 specificity in detecting asbestos-related disease.

21 We also talked about the ILO system and what -- and
22 for application of the ILO system and B-readings on things
23 that could be done in terms of structuring the readings,
24 especially in epidemiologic studies, and how to improve
25 the quality of the findings, including things like using

1 readers that had no vested interest, using readers that
2 didn't -- I think the gist of the discussion was to use
3 readers that didn't read exclusively one way or the other;
4 to use some quality controls; perhaps consider blinding;
5 and also to consider using a panel of readers, a minimum
6 of two or three readers; and using some central result,
7 some central reading result, rather than individual
8 results.

9 The second issue we talked a little bit about was
10 spirometry, and again, I think the -- by the way, I think
11 as distinguished from complete pulmonary function studies,
12 we were, I think, primarily focused on spirometry. We
13 talked about, again, issues related to sensitivity and
14 specificity; reproducibility, particularly because of the
15 method, the technique, calibration issues, issues
16 individual to the testing protocols itself.

17 And we talked about detecting functional impairment
18 versus simply detecting some abnormalities with or without
19 impairment. We talked actually quite a bit about that.
20 In other words, is -- can spirometry detect -- or does
21 spirometry detect functional abnormalities in people that
22 have, for example, radiographic abnormalities, or is it
23 too insensitive a method?

24 We also had a homework question on carbon monoxide
25 diffusing capacity, and I presume that that will be

1 discussed somewhere along the way later.

2 We didn't actually have a significant CT discussion,
3 although I presume that that also is on the agenda for
4 some time later today. We did, I think, table that to
5 today. We did briefly, I think, discuss the issue of CT
6 being a very sensitive technique, and probably a couple of
7 words were said about implications in screening -- using
8 CT in screening either for lung cancer or for asbestos-
9 related disease, and the issue that it is very sensitive.
10 So I presume we'll have further discussion along those
11 lines later today.

12 That's it. Oh, and may I take a moment to make one
13 announcement?

14 Dr. Carbone has some outstanding slides of some of
15 his work in Turkey, and he's graciously agreed to allow us
16 to view those slides. What we thought we would do is not
17 do those as a part of the panel discussion. But after the
18 panel is finished, for those that are interested after the
19 panel is done -- and we think we'll be finishing a little
20 earlier than expected today -- he's graciously agreed to
21 stay back and actually allow people to view those slides,
22 and he'll show those slides. So for whoever is interested
23 and would like to stay, please feel free to do so.

24 DR. DYKEN: It looks like we lost our moderator.
25 Well, it's almost nine o'clock, and that's scheduled for

1 the public- and observer-comment period. So I think we
2 had a number of people signed up. I don't actually have
3 the list of what order. I think Vicki Barber and William
4 Wright had signed up to make comments, but they're not
5 here.

6 William, did you have a comment to make for --

7 DR. SPAIN: I do.

8 DR. DYKEN: Okay. So if you could stand up, you have
9 five minutes for your comments. And please identify
10 yourself and your affiliation in addressing your comments
11 to the panel. Thank you.

12 DR. SPAIN: Thanks. Is the microphone up? Thanks.

13 William Spain, S-p-a-i-n, with the State of Georgia
14 Environmental Protection Division. I'm the director of
15 enforcement and compliance for the lead-based paint and
16 asbestos program. I've had the opportunity or obligation
17 to be involved in asbestos detection and control
18 activities through a variety of agencies and organizations
19 for the last 30 years.

20 I want to start out by saying a great thanks to ATSDR
21 for assembling the panel and allowing people to attend.
22 This is, as I described last night and turned down an
23 opportunity to go teach someplace today instead, a once-
24 in-a-lifetime opportunity. So I really am appreciative of
25 being able to be here, as I suspect other people are, and

1 hear the input from these distinguished individuals.

2 In the report of naturally occurring asbestos, USGS
3 identified that we have 52 sites in the state of Georgia
4 that is of concern to federal EPA, that is of concern to
5 the Environmental Protection Division of the State of
6 Georgia and a variety of other organizations, I suspect,
7 concerning -- including ATSDR.

8 We are trying to make plans and investigate these
9 sites. We have already been to many of these sites and
10 have started to perform some investigative activities at
11 these sites. I want to start out with the issue of what
12 we're calling these sites. Someone had made the decision
13 to call it naturally occurring asbestos. Well, in 30
14 years, I always thought -- I'm not a geologist. I'm a
15 chemist. But I thought all asbestos was naturally
16 occurring, and I think it is a bit misleading if we
17 continue to call it naturally occurring asbestos.

18 I realize that each one of us could say that we're
19 not the one who made that decision, but if someone doesn't
20 address and start pushing the issue, that's what it will
21 be called forever. I would recommend that we consider
22 some other more appropriate term, such as free-range
23 asbestos or free-range asbestos fibers or free-range
24 amphiboles, but some term other than naturally occurring
25 asbestos. Isn't that where we find it all? Okay.

1 As we think about what we needs to be investigated
2 and how we might approach it, we believe it is a
3 complicated issue. There are many pertinent questions,
4 such as: Is asbestos present at an individual site? If
5 so, which type of asbestos fiber or fibers? Is it on the
6 surface, or is it subterranean? Is it mining tailings, or
7 is it only naturally occurring that has not yet been
8 disturbed? Those have many potential ramifications.

9 The next question -- the next major question is: Will
10 airborne fibers be generated? And if so, at what
11 concentrations during what activities? Next question:
12 Will exposures occur? Because airborne fibers could be
13 generated, particularly by natural occurring phenomena
14 such as wind, and there will be minimum opportunity for
15 exposure. But will exposures occur?

16 And I think we're going to come back to the issues
17 that there'll be many different kinds of activities that
18 will result in many different kinds of exposure, some of
19 which will be chronic and some of which will be acute and
20 some of which probably will be super acute.

21 If the preceding things occur, will disease result?
22 And if so, what diseases with what latency periods? And
23 then pertinent questions of: Can we do anything about it?
24 And if there is something that we can do about it, what is
25 it that we should do and in what priorities? So it

1 becomes a very complex question. And of course, this two-
2 day hearing fits very much into that protocol, but we need
3 to keep in mind that there are many other questions that
4 need to be addressed simultaneously with multiple
5 organizations being involved.

6 We expect that exposure will vary greatly. Probably
7 high exposures will occur from activities such as
8 landscaping, particularly landscaping associated with
9 construction, initial construction; and then landscaping
10 occurring on an ongoing basis, including mowing the lawn.

11 Then there will be some probably medium exposures
12 from children's activities, depending on the type of
13 facility that's constructed there; and then there may be
14 minimum exposure to other sources such as elderly
15 occupants who are relatively docile in their occupancy.

16 One of the things -- as you and we communicate with
17 other people, I suggest that we keep in mind that not all
18 people understand scientific concepts or units equally
19 well. Many people who even work in these fields regularly
20 have difficulty understanding scientific notation, and the
21 general public and nonscientific even working for agencies
22 have difficulty understanding issues such as fibers per cc
23 when we start talking about decimal points, especially
24 decimal points with lots of zeros. So I encourage us to
25 consider things such as expressing concentrations in

1 fibers per liter or fibers per cubic meter so people can
2 understand whole numbers.

3 And the last thing I want to say, obviously, many
4 people are working on these issues simultaneously. So I
5 ask: What would ATSDR and others like people such as
6 ourselves and the others to do while we are designing and
7 completing our investigative activities in the field? It
8 would be a missed opportunity if we didn't communicate.
9 Thanks.

10 DR. HOLGUIN: Do we have anybody else? Let me remind
11 people that we're opening public comment, not only for
12 people who signed up, but for anybody who wants to take on
13 the microphone.

14 DR. GUNTER: Can we make some comments about -- or
15 should we wait to make comments about what he said?

16 DR. HOLGUIN: ATSDR?

17 DR. DYKEN: You can.

18 DR. GUNTER: That was excellent. I mean, the last
19 part though about if you want to explain to people in ways
20 they'll understand -- I don't think most people -- liters.
21 I know I think cubic feet or a cubic yard or something is
22 more a term that we understand -- most people, I think.

23 But your very beginning part, I can't even utter the
24 word "naturally occurring" in anything. I shudder when I
25 hear that; absolutely shudder. Do you remember my

1 comments on that? I shudder because I think it adds so
2 much confusion to trying to explain this to people.

3 Personally, I would not even like to use the word
4 asbestos. I like the words asbestiform and nonasbestiform
5 better. And while I like the free-range amphibole thing
6 -- I really like that. I think maybe -- I don't even know
7 if you need to distinguish it. It's an amphibole, and by
8 definition, it's a mineral, and by definition, it's
9 naturally occurring. And if you do want to distinguish
10 it, I think "noncommercial" is the term to use, although I
11 like free range a lot better.

12 DR. ROGGLI: I think I can appreciate the --
13 appreciate the position of mineralogists and environmental
14 regulators over the concern of use of the term "naturally
15 occurring asbestos." I think if you think about the past
16 exposures that we've had in this country and the current
17 exposures, the vast majority of asbestos exposures that
18 cause disease in this country are due to asbestos in man-
19 made products.

20 Exposures occur as a result of individuals using man-
21 made products or in buildings that men have -- that human
22 beings have constructed that contain asbestos. And I
23 think that the term "naturally occurring asbestos" has
24 been used to try to make that distinction between asbestos
25 to products that have been manufactured in the workplace,

1 which is the vast majority of the exposure versus what is
2 occurring "in situ," if you wish, in the environment. And
3 that -- if you make that distinction clear to individuals
4 and the people who are concerned about it, I think that
5 the problems with that term would somewhat go away.

6 With regard to asbestos, free-range asbestos, if you
7 like, or asbestos in situ, that has always been believed
8 to be one of the sources and maybe one of the major
9 sources of background levels of asbestos which we find in
10 the environment, either in air samples or in lung tissue
11 samples. It may not be the only one because living in the
12 industrialized society which we have, it's almost
13 impossible for someone to go a lifetime without being
14 exposed to some manufactured product that contain some
15 amount of asbestos. But, certainly, the naturally
16 occurring asbestos, or in situ asbestos, is probably
17 contributing to that.

18 So what is really a concern -- it seems to me -- is
19 areas in the environment where you have particular hot
20 spots. And sometimes those hot spots result, not from the
21 asbestos being there, but from man-made activity with
22 respect to those hot spots such as occurred in Libby,
23 Montana. And I think those are the main sort of areas we
24 need to be concerned with, to identify those areas, and
25 then to try to control any levels of exposure that occur

1 as a result of those hot spots in the environment.

2 DR. HOLGUIN: Thank you. Would you mind saying your
3 name and affiliation, please.

4 MR. DEN: Arnold Den, EPA, San Francisco.

5 There was a really good discussion yesterday, which
6 focused, I think, more on the mesothelioma end point of
7 disease. But as we see up in Libby, there may be actually
8 more noncancer disease or lung cancer rates are much
9 higher. And I was wondering if the panel this morning
10 would touch on that area a little more because, again,
11 mesothelioma is just one aspect, and EPA faces this when
12 it does its risk assessments because there's only a cancer
13 slope factor and not the noncancer. But I think we see up
14 at Libby much higher rates in noncancer than we do in
15 cancer. So just if we can get some recommendations on
16 biomarkers for that as well.

17 DR. CARBONE: What do you see in Libby?

18 DR. KAPIL: As we discussed yesterday, you know,
19 we've seen -- the issue, I think, and part of the answer
20 to the question is probably the latency issue, and I think
21 this is where you're going.

22 But what we've seen so far in Libby is a significant
23 amount of pleural disease or pleural abnormalities. As I
24 mentioned yesterday, you know, 18 percent of the people
25 that were screened, of community members, workers,

1 household contacts, had pleural abnormalities. Relatively
2 speaking, a very small number have any radiographic
3 evidence of interstitial disease, and similarly,
4 spirometric measures also show pretty small numbers of
5 people with restrictive disease.

6 You know, lung cancer mortality is elevated in Libby,
7 in Lincoln County. Mortality due to asbestosis is
8 elevated. Mesothelioma mortality is also elevated,
9 although the numbers of mesotheliomas vary depending on
10 which mortality review you would -- you know, you look at.
11 If you look at our strict 20-year-mortality review, people
12 that died in Libby is a much smaller number than the 25
13 that Aubrey mentioned yesterday, which includes people
14 that migrated out of Libby or died elsewhere. So that's
15 where we're at right now. Obviously, it remains to be
16 seen where the experience of the population in terms of
17 mortality goes in the future.

18 DR. CARBONE: And do you want to worry about the
19 pleural abnormalities or not? In other words, I think
20 that most of those pleural abnormalities probably do not
21 have clinical symptoms; am I correct?

22 DR. KAPIL: Interestingly, based on our screening, as
23 I mentioned yesterday, we haven't done diagnostic
24 evaluations on those individuals, so I can't really
25 comment based on our work on symptoms and presence of

1 symptoms or presence of functional impairment because we
2 simply didn't evaluate people for all of that.

3 Based on our limited data on the spirometry data,
4 you're right. We have, relatively speaking, very few
5 people with pulmonary -- with spirometric impairment.
6 However, if you talk to physicians in the community, they
7 feel that a number of those people with pleural
8 abnormalities actually have significant functional
9 impairment. And this is one of the reasons this question
10 about carbon monoxide diffusing capacity came up because
11 they've, for example, documented a number of cases in the
12 community where people have actually normal pulmonary
13 function tests essentially except the carbon monoxide
14 diffusing capacity is significantly decreased, and they
15 may have no other radiographic findings either other than
16 just some pleural abnormalities.

17 It's a complex issue, and I'm not sure all these
18 questions are totally answered yet. Does anyone else have
19 anything to add about Libby as far as those questions?

20 DR. MILLER: I just want to add a little to -- this
21 is Aubrey Miller with EPA in Region 8.

22 I'm going to just add a little bit to what Vik was
23 saying. As far as the government's focus has been, it's
24 not documented. The clinical -- some of the clinical
25 evidence associated with just the pleural abnormalities,

1 but there are some -- there's a paper that was done
2 recently by Dr. Whitehouse, who's a treating physician up
3 there, who has followed patients and shown a significant
4 decreases -- fairly rapid decrease in pulmonary function
5 in patients with just pleural abnormalities in this
6 population. And he has, certainly, a number of clinical
7 cases that he's shown at lectures and conferences that
8 have shown significant disease and impairment with really
9 -- and fairly progressive abnormalities. So we've seen
10 these cases.

11 I think he's writing this up now and progressively
12 trying to write up some of these cases. But I think the
13 government has not undertaken that particular study at
14 this time though. There is some work that shows this as
15 well is the -- that ATSDR's doing now with the University
16 of Cincinnati, which has looked at people over time and
17 just looking at radiographic impairment and how much
18 progression there is in radiographic impairment from, I
19 think, 5 percent to about 26 percent in this group of
20 Marysville workers, which were relatively lower exposed
21 population of workers, that were started in 1980 and then
22 rereviewed just last year.

23 So there is consistency in what we're seeing. I
24 think there's also a consistency in other amphibole-
25 exposed populations. The amosite workers in Texas that

1 Erlich and Shepard had reviewed also showed similar, you
2 know, progressive rates of disease. So I think what we
3 may be seeing here is certainly an amphibole-exposed
4 population, a lot of pleural abnormalities, and it appears
5 to be progressive pleural abnormalities in evidence at
6 least in the paper that was presented recently, a finding
7 out of Whitehouse, of physiological impairment progressing
8 fairly rapidly in the number of these individuals.

9 DR. KAPIL: So again, just to reiterate, the
10 Marysville data that Aubrey just mentioned is, again,
11 radiographic progression in terms of numbers of people
12 with pleural abnormalities. Again, even in the Marysville
13 screening data at least, so far the preliminary data
14 primarily shows pleural abnormalities as supposed to
15 interstitial after 25 years.

16 DR. ABRAHAM: I understand that the one patient who
17 we reported who died that had extensive pleural
18 abnormalities and pleural restriction. You know, there
19 was entrapment of the lung by the progressive pleural
20 fibrosis that was very significant physiologically. So
21 there's something unusual in the exposures to the Libby
22 amphibole compared to a lot of pleural disease that we
23 otherwise see with asbestos exposures elsewhere.

24 DR. MILLER: Let me go back to your question about is
25 the government interested. You know, we are interested in

1 pleural physiology and pleural abnormalities and the
2 extent to which this is having a detrimental impact or
3 pathophysiological adverse effects on the individuals.

4 There's a number of papers that have looked at
5 populations of those with pleural plaques compared to
6 those without. There's a number by David Schwartz as well
7 as others in the occupational health literature over the
8 past decade which really shows kind of consistency of --
9 if you have pleural plaques, you have decreased pulmonary
10 physiology or impairment compared to a population that
11 doesn't.

12 So, you know, those are the kinds of things that, you
13 know, is this an adverse effect? Does it tend to
14 progress? What's its risk for malignancy, either directly
15 or an associated finding? So those are the elements at
16 least, you know, that we in EPA have been looking at
17 closely and with respect to our work on IRIS and looking
18 at, you know, noncancer healthy effects and slope factors
19 and risks.

20 DR. ROGGLI: Based on the information we've been
21 given today about the Libby cohort, there's a number of
22 discrepancies in what you've told us that need to really
23 be addressed and thought about. What you're mainly
24 finding is patients with -- in your screenings that have
25 been done is no impairment and pleural plaque formation.

1 And yet you tell us that there's increased mortality for
2 asbestosis and increased lung cancer mortality.

3 In terms of pleural plaques, we discussed this
4 somewhat yesterday. Dr. Hillerdal has done the studies
5 that show if you have very strict criteria for diagnosing
6 plaques so you definitely know you've got them --
7 bilateral at least 5 millimeters in thickness or
8 calcification -- that you have a very modest increase in
9 lung cancer risk: only 40 percent.

10 And so a lung cancer mortality that's going to be
11 exceeding that is going to be difficult to detect. Unless
12 you exceed that, it's going to be difficult to detect from
13 epidemiological studies because you're talking about a 40
14 percent increased risk here from well-defined bilateral
15 pleural plaques versus a 2,200 percent increased risk from
16 cigarette smoking. There's a vast difference in what
17 you're talking about as far as risks are concerned for
18 lung cancer mortality.

19 These days, it's very uncommon to see individuals who
20 die from asbestosis. So my question would be: Is the
21 mortality from asbestosis all accounted for, pretty much,
22 by miners and millers in this area? And is that also
23 accounting for your increased lung cancer risk, or is
24 there something else that needs to be looked at in this
25 environment?

1 Rapid decrease in pulmonary function in patients with
2 pleural disease is essentially unheard of in pleural-
3 plaque-only cases, and it's quite different from, as Dr.
4 Abraham pointed out, in patients who have diffuse visceral
5 pleural fibrosis, which can cause a trapped lung, which is
6 much less common in the pleural plaques. In fact, in my
7 experience, it's very uncommon to see individuals who have
8 pleural plaques and diffuse visceral pleural fibrosis. I
9 can't even recall a single case I've seen. Usually, you
10 go one way or the other with that sort of reaction.

11 Radiologists can make that distinction very early
12 between diffuse visceral pleural fibrosis and pleural
13 plaque formation. So there seems to be a disconnect from
14 -- between what you're finding in your screenings versus
15 what's being reported in terms of mortality from
16 asbestosis and lung cancer in this cohort. And so you --
17 there's some discrepancies here that need to be addressed,
18 and I think pathology may be able to help in all of those
19 cases in sorting out, for example, whether the cases that
20 are actually called asbestosis are asbestosis.

21 I've seen many cases in my practice where a patient
22 was diagnosed as having asbestosis. An autopsy is done
23 and the patient has severe emphysema from cigarette
24 smoking and no asbestosis at all. So these are questions
25 that need to be examined and sorted out.

1 I don't think that you want to end up with a
2 population of individuals at Libby who have pleural plaque
3 formation and are worried that they're going to have
4 rapidly decreasing pulmonary function or a markedly
5 increased lung cancer risk or that they're going to die
6 from asbestosis. That just doesn't fit with what we know
7 about these diseases.

8 DR. HILLERDAL: It's not quite true what you said. I
9 have seen a number of patients that have pleural plaques
10 and then develop diffuse pleural thickening. The problem
11 is once you have diffuse pleural thickening, the plaques
12 will get completely hidden. There is no way of finding
13 them with a chest x-ray or with pathology either because
14 it's just overwhelmed by those other things.

15 Secondly, I think this is mainly a question of
16 exposure. If you have a very low exposure or if you have
17 a very high exposure, that does not -- that doesn't seem
18 really very much to affect the incidence of plaque. You
19 have plaques anyway. Even at low exposures, you can have
20 plaques. At high exposures, you can have plaques. But if
21 you have a high exposure, you will probably get plaques
22 first. But then you have, of course, a very increased
23 risk of asbestosis and, I think, also diffuse pleural
24 thickening.

25 And unfortunately, people talk about pleural lesions,

1 pleural changes and they don't really define whether they
2 mean plaques or diffuse pleural thickening. There's a
3 huge discrepancy between these. And diffuse pleural
4 thickening is much more dependent also on exposure, on
5 dose. If you have a high exposure, you will probably get
6 pleural plaques, but you also have a higher risk of
7 getting diffuse pleural thickness.

8 And the same goes for lung cancer. That is also
9 completely correlated with dose -- actually, not
10 completely, but there's a very good correlation. And of
11 course, asbestosis is the most -- the most correlated of
12 these diseases.

13 So I think much of this comes from the fact that you
14 cannot -- you see a person with pleural plaques and
15 nothing else, and from that, you cannot gauge the degree
16 of exposure that he has had. He might have had quite
17 extensive exposure, but it hasn't come up yet. Because
18 what asbestos does is that it starts the low-grade
19 information which will end up with pleural plaques,
20 pleural -- diffuse pleural thickening and maybe asbestosis
21 in just a matter of time. The higher the exposure, the
22 faster some of these changes will come. Others will be
23 independent of that. Plaques are dependent on time of
24 first exposure, not of level of exposure, to simplify
25 matters.

1 DR. ROGGLI: I appreciate your comments, but that --
2 Dr. Hillerdal, but it seems to me that since it takes 20
3 to 30 years for plaques to develop, how often do you see a
4 patient who 20 to 30 years after exposure has plaques but
5 no asbestosis but then goes on to die of fatal asbestosis?
6 I think that would be very uncommon.

7 DR. HILLERDAL: No. He won't die from fatal
8 asbestosis, but if you wait another -- if you take this
9 man who has beautiful small plaques and you wait 20 years,
10 then he will have much bigger plaques and probably also a
11 slight asbestosis, depending on the dosage. So that's not
12 what happens.

13 The really interesting thing is with the diffuse
14 pleural thickening because they can come very sudden. I'm
15 sure that the immune system somehow is involved in this
16 because you can see it from -- one, if you follow them,
17 which I did every second year for a very long time, you
18 could have very nice plaques and the next time the patient
19 came he had bilateral diffuse pleural thickening, a very
20 sudden occurrence. So that's very difficult to measure
21 that.

22 But you are right. If you have -- if you have high
23 exposure, you will get an early asbestosis, and these are
24 the ones who will die from asbestosis. If you have -- the
25 more exposure, you will have beautiful pleural plaques and

1 you would probably find this man in his eighties. He has
2 a slight asbestosis visible on the chest x-ray and the
3 lung function, but not really giving him any trouble.

4 DR. HOLGUIN: Dr. Dodson.

5 DR. DODSON: Yeah. I was just going to ask a
6 question as a clarification. We've talked about Libby.
7 We've talked about California. In both of those areas, we
8 are talking about asbestiform exposures in populations.
9 We saw a map of population growth versus a correlation
10 with geological presence of asbestiform structures.

11 Okay, Mickey.

12 DR. GUNTER: I'm good.

13 DR. DODSON: But one of those sites -- one of those
14 sites -- all those orange dots -- what do you call those
15 agencywise where all of this was taken for processing,
16 et cetera? There are clinical alerts at each of these
17 areas, and some of them do not have asbestiform structures
18 in the geological surrounding areas, but a tonnage of
19 material had been brought there from Libby, which made
20 them micro-Libbys. How do you -- how are you dealing with
21 the populace in that area and/or x-number of people that
22 may have been exposed over time frames to the same
23 material of the people that worked in Libby with the
24 material were exposed to?

25 DR. WHEELER: Well, we call those the Sons of Libby,

1 and there were about 260 different areas that we were able
2 to identify that actually received vermiculite from Libby.
3 There was predominantly about 28 of those sites that
4 received the majority of material, and we looked at the
5 shipping records and the records that Grace provided us
6 and whatnot to identify those sites and try to prioritize
7 what we're doing at those sites.

8 And that's how Marysville came up. It was one of
9 those sites that received a lot of vermiculite, and most
10 of those -- most of those areas were exfoliation sites.
11 They did the same kind of processing that they did in
12 Libby, but they sent the ore to those sites, and they
13 heated the ore there and popped it, and then it was sold
14 for concrete mix or for wallboard or for whatever.

15 We've now gone to those sites and investigated those
16 sites and looked at the populations that lived around
17 those sites and tried to get air data from those sites.
18 And it's been a very difficult process because this is all
19 a historical look at things when there wasn't so much
20 environmental sampling going on, and the sampling
21 techniques were different and whatnot. What we're now in
22 the process of producing a summary of what we've found at
23 all those sites. And essentially, what we've found is
24 that the communities that were around them in most areas
25 were fairly removed from the facility itself, so there

1 probably was not a lot of air deposition into the
2 community.

3 But there were workers that worked at that site that
4 lived in the communities, so there may have been the same
5 kind of take-home problems that we saw in Libby. And
6 there were also the same kinds of problems that we saw in
7 Libby with the workers themselves. This was a time period
8 in which the OSHA guidelines were continuously being
9 revised and moved downwards and new types of personal
10 protection were being put in place. And so over time, we
11 saw workers being exposed to less and less material. But
12 prior to 1970, 1980, there were some significant exposures
13 going on.

14 DR. DODSON: Has there been communication for
15 clinical sensitization to this area -- in those areas?
16 The docs that may see the patients --

17 DR. WHEELER: We're in the process right now of
18 trying to figure out how we're going to go back and
19 identify those individuals and notify those individuals.
20 There's been some discussion about we might be able to add
21 those people to the Tremolite Asbestos Registry that Dr.
22 Kapil talked about that's going on in Libby. There's been
23 some other discussions on how we'll go about doing that.
24 We're in the middle of that process now.

25 DR. ABRAHAM: How far back chronologically did you go

1 back? Was it only with Grace, or did you go back before
2 Grace?

3 DR. WHEELER: We went before Grace. All of the
4 facilities we're looking at right now are exfoliation
5 facilities except, I think, there was one wallboard
6 facility. Does that answer your questions? I'm not quite
7 sure if I did.

8 DR. DODSON: Thank you. It did.

9 DR. MILLER: I could add a little bit to that. So
10 what we had -- this is Aubrey Miller with EPA in Region 8.

11 What we had was information of where the vermiculite
12 was shipped from the Libby facility. It became available
13 to EPA, and we've been looking at those types of elements,
14 and I think ATSDR may have pursued some other avenues as
15 well, and that helped us identify which processing plants.
16 EPA regional offices went out and tried to evaluate a
17 number of those.

18 The efforts varied somewhat by region. And in a
19 number of facilities, the efforts were undertaken to clean
20 them up or evaluate the neighborhoods. There are large
21 efforts ongoing in Minneapolis, Minnesota. It's probably
22 the most well -- largest and most-well defined effort in
23 the nation as a sister-Libby site, or Sons of Libby site,
24 as John referred to it as.

25 So there are -- there is evidence of disease,

1 certainly, in the occupational population around these
2 sites. One case report that Dr. Roggli wrote up a number
3 of years ago was of a child who played in piles of waste
4 material at one of these sites in Minneapolis, as a matter
5 of fact, for a few years of his life and apparently died
6 of asbestosis and lung CA at an early age. I think it was
7 42.

8 So there is, certainly, evidence of environmental
9 exposure, environmental contamination, occupational
10 disease at these sites as your case report also evidences.
11 And there's an ongoing process between the agencies.

12 DR. WHEELER: One thing I perhaps should add to that
13 is, during this process, when you exfoliate vermiculite,
14 you get a lot of waste rock that falls out, stoner rock,
15 and that rock was dispersed into the community at a lot of
16 these locations. It was given away for free gravel for
17 your driveway or use it as cat litter in your house or do
18 whatever.

19 We've been trying to trace that down, and that is an
20 extremely difficult process, you know. When it goes
21 through that process, the stoner rock seems to -- seems to
22 get somewhat enriched in asbestos because of the way the
23 process works: the lighter material coming. But it's
24 very, very difficult to find where all this has gone in
25 the community.

1 DR. HOLGUIN: David, you want to comment?

2 DR. WEISSMAN: I guess one comment I want to make is,
3 in terms of understanding the relationships between
4 pleural abnormalities caused by Libby vermiculite and
5 exposure, the Marysville cohort is really, really
6 important because it was mentioned the other day one
7 unique feature of that cohort is there is very good
8 exposure information on that cohort.

9 Because of the outbreak of bloody pleural effusions
10 in 1980, there was a study done, and because of the
11 problems that existed, the facility, after that study,
12 stopped using Libby vermiculite. So the workers that are
13 being followed in the cohort have a defined exposure that
14 we know about, which is pretty unique among these
15 facilities. So it's going to be very important to follow
16 these workers to really understand what the clinical
17 outcomes are going to be amongst the many workers who have
18 pleural plaques.

19 DR. JOHNSON: Mark Johnson with ATSDR, Region 5, in
20 Chicago.

21 Just to add to what John and Aubrey had said, we're
22 involved directly with the Minnesota Grace facility where
23 extensive amounts of waste rock were distributed in the
24 community, and EPA has funded the cleanup of about 260
25 homes where this waste material was used as fill

1 throughout the Minneapolis area.

2 And as part of our investigation, we funded the state
3 health department to do an evaluation of exposure
4 pathways, and in that survey, about 7,000 residents
5 indicated that about 600 children, now adults, were
6 exposed by playing in these piles. This is also a
7 valuable cohort then to evaluate in terms of their direct
8 contact with the material, which, as John mentioned, is
9 highly enriched for asbestos, but also represents an
10 opportunity to look at the health impacts of early life
11 exposure because you have a much longer observation time
12 for the onset of disease. So I think there's an
13 opportunity here to really characterize this type of
14 impact.

15 Thank you.

16 DR. ROGGLI: I think -- so far, in the last day and a
17 half, I don't think anybody's commented about the similar
18 circumstance in Louisiana with the Manville driveways, the
19 Manville playgrounds. I don't know if the EPA or the
20 ATSDR is involved with the investigation or dealing with
21 that problem or not.

22 But that was a situation where the Johns Manville
23 plant there, which used crocidolite and chrysotile to make
24 cement pipe would have left-over tailings which they
25 offered to the community to make -- for use as driveways,

1 playgrounds, or whatever. And I've seen cases sent in
2 consultation of individuals who worked in an occupation
3 where there was exposure to asbestos and was asked to
4 analyze the lung tissue.

5 And one particular case I had was a bit confusing
6 because the patient had increased levels of amosite which
7 correlated with his work in an oil refinery, which many of
8 these people do in that area of the country. But, in
9 addition, there were lots of very fine crocidolite fibers,
10 more so than the amosite fibers. And in talking to the
11 attorney dealing with that case told me that that
12 individual, yes, did indeed have a Manville driveway.

13 So a potential for exposure to levels that are well
14 above background levels that one finds in lung tissue are
15 certainly there when you have that sort of material in
16 driveways or in playgrounds, and I think it is an area
17 that definitely has to be investigated and dealt with, not
18 only the piles and mounds that kids can play on of
19 tailings, but also the material that's been dispersed more
20 into the community. That's a problem.

21 DR. HOLGUIN: Thank you.

22 DR. KAPIL: Yeah. I wanted to just address Ron's
23 earlier question or comment about evaluation that these
24 other sites, particularly from the health perspective, and
25 it may also relate to Victor's earlier comments on Libby.

1 The -- Libby's really the only place that we've seen
2 -- at least been able to document -- elevated mortality
3 due to lung cancer and asbestosis and mesothelioma. One
4 of the other things that's being done at these sites --
5 these 260 or 240-odd sites that John was mentioning
6 earlier -- that about 100 of these sites we're also doing
7 health statistics reviews in the community where we're
8 looking at cancer registry data, looking at mortality data
9 with all of those limitations that those type -- that that
10 type of data has associated with it.

11 We have looked at nearly 100 sites in association
12 with state health departments, and that work isn't
13 complete yet. It's actually under way. But the sites
14 that we have released reports for so far, we have not seen
15 elevations of lung -- asbestos-related cancer mortality or
16 mortality -- I'm sorry -- asbestos-related cancers from
17 cancer registry data or asbestos-related disease mortality
18 in any of those communities in the sites that we've
19 released the data so far. That's not the case in Libby.
20 So from that perspective, there is a difference between
21 these sites and the health outcomes data at these sites
22 versus Libby.

23 The second thing is follow-up to Aubrey and Mark's
24 comments and John's comments. We are actually doing some
25 specific health screenings at some of these sites or

1 contemplating additional screenings at some of these
2 sites. We have committed to do at least two, probably
3 three screen -- begin at least two and probably three
4 screenings, hopefully, later this year. One of those will
5 be focused on community members in Minneapolis, okay, not
6 workers and household contacts, but actually looking
7 specifically at community members; people that might have,
8 for example, played on piles, people that might have been
9 exposed by other routes, but who lived in the community.

10 The second screening is actually focused specifically
11 at workers and household contacts. That's at the New
12 Jersey site. And the third, of course, I mentioned
13 yesterday. We're hoping, depending on availability of
14 resources and all that, to also look at household contacts
15 at some of these other locations and possibly also at
16 workers and household contacts at the other locations. So
17 that's the direction we're heading.

18 As far as, Victor, you raised the question of
19 somewhat of a disconnect with the Libby cancer experience
20 and mesothelioma and asbestosis mortality. Again, I think
21 there may be a bit of confusion, and sometimes it's a
22 little difficult to explain. But as Aubrey mentioned
23 earlier, we have done only screening evaluations in these
24 communities, so we don't have the luxury of complete
25 diagnostic data on these cases, and we're doing

1 radiographic screening or spirometric screening.

2 So basically -- and of course, there are lots of
3 limitations to cancer registry data and death certificate
4 data, so we have documented very, very significantly
5 asbestiform mortality in and around Libby. However, a big
6 chunk of that is accounted for by worker asbestosis
7 mortality. We haven't seen asbestosis, advanced
8 asbestosis, cases to any huge extent in our screening, but
9 that's different from what we hear reported from the
10 community.

11 The community experience -- the physicians in the
12 communities, their experience is very different as they
13 follow these cases over time. They do -- they have
14 reported and do see a very significant progression in
15 disease. So that's -- maybe that's where -- as far as the
16 cancer mortality, the lung cancer mortality is in the
17 ballpark. I don't have the numbers exactly in front of
18 me, but it is in the ballpark that you and Dr. Hillerdal
19 were talking about earlier, you know, 40, 50, 60 percent
20 kind of ballpark.

21 DR. MILLER: This is Aubrey Miller with Region 8
22 again. Just to add to what Vik was saying, it's not
23 unexpected of what we're seeing in our screening because,
24 frankly, the more advanced cases are not going back
25 through a basic screening. They've been seen and have

1 been followed by clinicians and pulmonologists in the
2 community. So for them to take us up on our offer to come
3 back in for a basic, you know, x-ray and peak flow and
4 spirometry-type screening -- a lot of folks were already
5 being seen by doctors, so those cases that are more
6 significant and have more advanced disease are not coming
7 back through, as we probably anticipate.

8 DR. GUNTER: One comment in regard to the chrysotile.
9 If you go to Canada and look at the Quebec mining
10 districts -- and I showed some of these photos yesterday.
11 Any place there's rock on the roads close to those mines,
12 that rock came from the mine. And you can see it's just
13 chock full of chrysotile.

14 So I would wonder if looking at some of the exposures
15 -- and I've seen some papers on the chrysotile and the
16 background levels and the people -- the folks there.
17 Their exposure levels of chrysotile would be much higher
18 than probably anything in America if you could use those
19 as comparative data because several of the sites were
20 chrysotile sites: the Alaska site, that Washington site.
21 There should be good background data, I would think, from
22 the chrysotile folks.

23 DR. ROGGLI: Well, that's been done. For example, I
24 think Dr. Churg has done some studies where he showed that
25 the background levels of exposure around Thedford are ten

1 times higher than elsewhere and that he's not demonstrated
2 any increased risk of mesothelioma or any lung cancer in
3 any of that population. I think there is an increase in
4 pleural plaques, and those individuals have increased
5 levels of tremolite when you analyze their lung tissue.

6 DR. ABRAHAM: There's another area where disease in
7 the community has been demonstrated, which is around the
8 talc mines in upstate New York, and the people that have
9 lived near tailings there have had pleural plaques and --
10 I'm not sure if there have been asbestosis cases, but
11 there are a few suspect mesothelioma cases.

12 But the recording in the hospitals is very variable,
13 and the radiologic findings -- many patients up there were
14 reported as emphysema when, in fact, further review of the
15 x-rays later by, I think, Dr. Vienna years ago at the New
16 York State Department of Health showed that there was an
17 increased prevalence of asbestosis, and the death-
18 certificate analysis of that area shows increased risk of
19 mesothelioma too -- or increased prevalence of
20 mesothelioma.

21 DR. DYKEN: Okay. Thanks, everyone, for your
22 comments. I think now we're going to get back into our
23 panel discussion, and I think there was one technique that
24 we did not get to discuss fully yesterday, and that is the
25 issue of CT scanning. So if any of the panelists could

1 focus their discussion on -- I think our questions were
2 the advantages and disadvantages of the technique and how
3 useful it might be as a means of assessing community
4 exposures.

5 DR. WEISSMAN: Well, CT, obviously, has a lot of
6 advantages in terms of being a more sensitive, more
7 specific technique. That is the plus side. The minus
8 side is that it's more expensive. The technology of CT
9 has improved a lot, even just in recent years, with the
10 multiple detector spiral CTs.

11 People can have a CT scan performed far more quickly
12 than they used to be able to. Another disadvantage is a
13 little bit of a higher radiation exposure than a regular
14 x-ray. There have been several studies that have been
15 done recently of using, you know, recent, you know, CT
16 technology, which has changed so much compared to even ten
17 years ago. And if you compare regular x-rays and ILO
18 classification of those x-rays and CT scanning -- and if
19 you call CT scanning the gold standard, the sensitivity of
20 x-rays is probably on the order of about 50 percent
21 relative to CT in several studies.

22 It's important to pay close attention to technique in
23 doing CT. It's really important to get both prone and
24 supine scans so that you don't misclassify dependent
25 pressure changes as being interstitial changes.

1 But overall, you know, CT is a really excellent
2 procedure, and if money were no object, it would be
3 preferable. I guess one last thing to throw out for CT is
4 CT is better for pleural changes than regular x-ray, with
5 the notorious exception of diaphragmatic plaques, using
6 the normal axial cuts. Potentially, that might be
7 improved by reconstructing the images in a different way
8 by, you know, reconstructing the images as a coronal or a
9 sagittal rather than just a regular, you know, cross-
10 sectional cut that's normally done. But overall, if money
11 weren't an object, CT would be the way to go.

12 DR. HILLERDAL: Do you realize that with these new CT
13 scans you find a lot of other things as well? And
14 actually, up to 50 percent -- 50 percent -- one half of
15 the persons you investigate you will find small nodules in
16 the lung, which will require investigation or follow-up.
17 And so this will add very much to it, and I don't think
18 the local pulmonologist in that area will be happy when he
19 gets hundreds of referrals for these little lesions.

20 Most of them -- I mean, if they are less than 5
21 millimeters, you should follow them up after six months or
22 one year. There are various investigations that if they
23 are between 5 millimeters and 1 centimeter, then you
24 should follow them every third month to see if they grew.
25 And if they are larger than 1 centimeter, you have to

1 start a complete investigation. And that will add a lot
2 of cost to somebody because it's not ethical to just tell
3 what.

4 Like, I've been told that in these countries you have
5 the city buses going around, and you go to one of these
6 supermarkets, and it says, "Come in and have your CT scan
7 taken." And you pay \$100, and you go in and you come out,
8 and they say, "Yes. We found a little nodule. Go to your
9 local doctor and get that fixed."

10 So you have to put up the whole -- that whole
11 arrangement, so you have everything clear to do -- so you
12 know what to do with what you found.

13 DR. WEISSMAN: Well, I'm a pulmonary physician, and I
14 would love to get all those referrals. But letting that
15 aside for just a minute, I mean, obviously, you have to
16 have strict criteria in the way that your films are
17 interpreted and a plan in place for what to do with
18 abnormalities.

19 DR. HILLERDAL: But that amounts to much more money
20 than the screening itself. You have to realize that. To
21 take a CT scan and look at it, that's not very cost
22 effective. You have to include the cost of following all
23 these findings, following them up later on. Of course,
24 you will find an occasional early lung cancer and possibly
25 save that person by surgery, but it will cost you.

1 Otherwise, I agree. It's a much better way of
2 finding: CT scans. But, again, there is no comparison
3 with autopsy data, which will be very much more
4 interesting. So we don't know -- I think even CT scan
5 will miss a number of small pleural plaque.

6 DR. KAPIL: May I ask a follow-up question for the
7 panel?

8 DR. HILLERDAL: Sure.

9 DR. KAPIL: If one were contemplating the use of CT
10 scanning as a screening tool in a community, number one,
11 would the panel be able to comment on whether this might
12 be advisable in certain circumstances. And number two, if
13 the answer to that is, yes, it may be feasible in some
14 circumstances, what would the significance -- or what
15 significance could be attached to very, very minor, early
16 pleural changes in the absence of any other change on CT
17 in that type of setting in an asbestos-exposed population?

18 DR. HILLERDAL: That's very difficult to say because,
19 again, these very early, small lesions -- they are very
20 unspecific, I think. You would need a control group,
21 really, to say that you have more than that. And what you
22 would end up with is, well, this might be an early pleural
23 plaque. If you want to know, you wait five years and you
24 take a new CT scan and see if there's pleural and then do
25 some pleural plaque. So I don't know really what much

1 good that would do except to the lawyers, of course.

2 DR. WEISSMAN: I guess another issue is the issue of
3 what the prevalence is of the condition that you're
4 screening for in the population because the whole thing
5 becomes more feasible. You know, the higher the pretest
6 probability that the condition is present -- so that's
7 another key thing to think about in deploying this or any
8 other technique is, you know, what's the prevalence of the
9 condition you're looking for.

10 DR. HILLERDAL: And that depends on exposure and on
11 time from first exposures. If you have a middle-aged
12 population who was exposed 30 years ago, then you will
13 expect to find a lot.

14 DR. ROGGLI: Yeah. I agree with that last comment.
15 I think that you have to recognize that using CT scanning
16 in a community is looking for reaction to an exposure.
17 It's not a measure of the exposure itself. So you can
18 have an exposure in the absence of the changes on the CT
19 scan or radiographic findings, and that can either be due
20 to very low exposure or because a very short time from
21 initial exposure. You haven't had time yet for the -- to
22 evaluate the exposure.

23 So it seems to me that CT scanning would be most
24 useful in communities where you've already demonstrated by
25 one of the other techniques or multiple other techniques

1 -- such as BALF, autopsy of ME cases, and measurements in
2 the environment -- that there is a significant exposure.
3 And then you want to follow that community to determine
4 what are the consequences of that exposure.

5 And then recognizing that the small, very early
6 plaques that you might pick up in following such a
7 community is going to have very little significance in
8 terms of -- in terms of subsequent disease for that
9 population, although there may be some finite risk of
10 asbestos-related diseases that could be fatal such as
11 mesothelioma.

12 DR. CARBONE: I would like to add something. I agree
13 with Victor that the CT scan, in fact, should be seen in
14 an integrated effort to establish exposure and risk, and
15 that should not be the first screening procedure because
16 it doesn't seem to me that CT scanning is a screening
17 procedure. It's a confirmatory procedure on whatever
18 screening procedure you use.

19 Of course, the resources is always what limits what
20 you can do, and I have no idea what resources you have nor
21 do I have an idea of exactly what it is that you can and
22 you cannot do. But if one lives on the side of the issue
23 of resources -- assuming you have the resources, I think
24 that it's important not to get paralyzed over the
25 problems, in that we have heard that all the techniques

1 that we have discussed today and yesterday -- they all are
2 problems. And so human nature would be to say, "Okay.
3 This doesn't work. That doesn't work. That doesn't
4 work." And then we do nothing. And then, ten years from
5 now, we are exactly as we are now.

6 So you need to put -- to see what you can do with
7 what you have because you build on what you have. These
8 techniques, all of them, have some advantages so, as
9 they're integrated together, they can give more than each
10 one singularly. So that's the first thing.

11 And into that context, if you can, I would include
12 the mesothelin and osteopontin marker that we discussed
13 yesterday because, in fact, they are the only way that you
14 can do screening. Any other technique is limited. You
15 can't screen in any other way as effectively and quickly
16 than with a serological test.

17 I do agree that right now, as I stated yesterday,
18 these are not ready for prime time. In order for them to
19 become ready for prime time, they need to be tested. I am
20 testing them in Cappadocia and other smaller studies going
21 to be -- larger studies than mine is going to be
22 conducted. But the only way to validate this thing
23 quickly is that more people do that and to join resources
24 at a time in which resources are not excessive out there.

25 So if you have a way to introduce that, you don't

1 need to scare people because you don't need to attach any
2 clinical significance to it. But you start accumulating
3 data so that the moment in which you verify whether the
4 mesothelin or the osteopontin data are ready for prime
5 time you don't have a delay of two or three years because
6 you have to start and then you have to start to accumulate
7 the baseline data. You already have that, and the worst
8 that can come out of that is that, in fact, osteopontin
9 and mesothelin do not prove to be as useful as it appears
10 that they are right now.

11 Well, that will not be a waste of time because, in
12 fact, you will have used the resources to prove exactly
13 that. Therefore, I think that if you integrate the
14 osteopontin and the mesothelin data without attaching any
15 immediate clinical outcome to that -- certainly not do
16 thoracoscopy, not doing anything, but simply seeing what's
17 happening -- integrating them with the rest of the data.

18 Now you could have a prospective study that
19 scientifically will be very important and very valid. And
20 if, in fact, that these studies get validated and they are
21 useful, now you have already the baseline, so you have not
22 wasted two or three years waiting to see what I get in
23 Cappadocia, for example.

24 DR. ROGLI: One additional comment, I think, about
25 the osteopontin is -- and the mesothelin. I think that if

1 you're going to, in communities, proceed with doing
2 screenings that involve BAL fiber analysis in which you're
3 trying to identify if there's been an exposure in a
4 population, it will be very wise in that circumstance to
5 draw blood levels for osteopontin and mesothelin just for
6 comparison purposes because then that would be an
7 excellent way to collect data about what these represent
8 at the same time that you're doing the BALF fiber analysis
9 studies.

10 The one caveat to that is if you run across a case in
11 which you have identified greater than 48 nanograms per
12 milliliter of osteopontin, then you probably committed
13 that person to a thoracoscopy because, if the person has
14 greater than 48, according to the paper, that correlated
15 well with dividing mesothelioma versus not mesothelioma.
16 And if you do a chest x-ray on that person and it's
17 negative, then you're going to have to do a CT scan. If
18 it's negative, you're still going to have to do a
19 thoracoscopy to be sure that there's no tumor present. So
20 you have to be aware of that problem if you do that.

21 DR. HILLERDAL: Which side would you start with? The
22 left first and then the right?

23 DR. ROGGLI: Our surgeons are happy to do them
24 sequentially; you know, one side, one day; and the other,
25 the next.

1 DR. HILLERDAL: I think that's a very dangerous
2 approach really. It is a fairly invasive procedure.
3 Let's say that. And I agree with you, but I still think
4 we have to take time -- the time factor. I don't think
5 there is any use in taking osteopontin and mesothelin
6 levels in people who have not -- if they have not been
7 exposed at least 20 years ago, I would believe. So I
8 think -- I think a CT scan would be used if you have high
9 osteopontin levels or if you find something abnormal in
10 your chest x-ray. Then you should make a CT scan, but not
11 otherwise; not as a screening.

12 DR. HOLGUIN: Just out of curiosity, at that cutoff
13 of ROC level, how many false-positive cases will you
14 expect over 49?

15 DR. ROGGLI: We don't know because, I mean, it's
16 based on the limitations of the size of the study which
17 was done. And when they found that 48 was a cutoff
18 between those who did and did not have mesothelioma based
19 on the size of that study -- if you start screening a much
20 larger population, then you may find an occasional case
21 that falls above the 48, and I think that's going to cause
22 an ethical conundrum: what you're going to do with such
23 individuals when you find it.

24 DR. HILLERDAL: I think if you find this person and
25 you make a CT scan that's absolutely normal, if you then

1 proceed with a thoracoscopy, I think -- I think your
2 chances of finding this very early tumor are very small,
3 and what you end up with, doing bilateral thoracoscopy, is
4 that you have all the remnants and all the scar tissue and
5 everything after that. And then it will be very difficult
6 for you to decide -- to see where the mesothelioma is, if
7 it is there, when it starts growing. I would advocate
8 against that. I think what you will have to do is to
9 follow this poor person with a CT scan every six months or
10 so.

11 DR. CARBONE: That's exactly what we plan to do in
12 Turkey. We are not doing a thoracoscopy to anybody.

13 DR. HILLERDAL: Yeah. Okay. No. Right.

14 DR. WEISSMAN: This specificity in the *New England*
15 *Journal* paper was 95 percent. That means that 5 percent
16 of the population is going to have that high level that
17 you're talking about. That means that you're going to
18 struggle with this problem in 5 percent of the population
19 that you study.

20 You know, I think it points up the real advantage of
21 initially studying this in folks in Cappadocia where
22 there's a very high pretest probability for the condition.
23 It's a really excellent place to really characterize the
24 test and have it -- and have as little of these, you know,
25 sort of struggles as possible. And one advantage to blood

1 testing is that you don't have to run the ELISA at the
2 time that you get the blood. So it could be possible to
3 obtain blood and bank it frozen, and at a time when we
4 have a better understanding of how to deal with the data,
5 you know, run the studies then. So that could be one
6 approach.

7 DR. HOLGUIN: Then if you apply the test on a
8 population where the prevalence is a lot lower, the
9 possible value be -- who knows?

10 DR. WEISSMAN: Yeah. I mean, the lower the pretest
11 probability, the lower the positive are sure to give.

12 DR. HILLERDAL: But you still end up with a number of
13 patients which you have to follow. You find -- if you
14 make a CT scanning, you will find a number of small
15 nodules which you have to follow by CT scan. And if you
16 take osteopontin or the mesothelin, you will find those
17 who have high levels, and you will have to follow them
18 also. So what you will have is a large proportion, maybe
19 20 or 30 percent of all the patients that you have in your
20 study, which have to be followed every six months with CT
21 scan and all that. And it's not a very good idea, I
22 think.

23 DR. CARBONE: But that's the only way that we are
24 going to learn --

25 DR. HILLERDAL: Yes; yes.

1 DR. CARBONE: -- what is the value of these things.
2 If we don't do that, we will never learn it.

3 DR. HILLERDAL: You're right; you're right. But you
4 have to be aware of the consequences when you do a
5 screening. It isn't just doing the screening and then
6 look at the results and say, "Oh, yeah; very interesting."
7 You have to do something about those potentially --
8 potentially important findings that you do find.

9 DR. CARBONE: Well, that would bring another issue
10 that is slowly -- I don't know how related it is here --
11 is can we do something for that, and that would require
12 maybe a different more clinical-oriented panel. It seems
13 that there is a general agreement in the community that
14 the chronic inflammation is a factor in the pathogenesis
15 of asbestos-related disease, but that would make sense.

16 Now, they design something for people at high risk to
17 see if we can interfere with pathway, and it would make
18 sense how should such a clinical trial should be designed.
19 I do not know that the ATSDR deals with that, but,
20 certainly, that would show that we are doing something for
21 the exposed community and not just sitting and watching
22 whether they get the tumor so that we can write a paper.

23 DR. HOLGUIN: Are there any more comments on the
24 usefulness of CT scan?

25 (No audible response)

1 DR. HOLGUIN: Then we are going to take a break.

2 Jill, how long is that break going to be for?

3 DR. WHEELER: Fifteen.

4 DR. HOLGUIN: ATSDR is feeling generous, so they say
5 15 minutes.

6 (Whereupon, a recess of approximately 26 minutes was
7 taken.)

8 DR. HOLGUIN: We have the next item on the agenda
9 will be to go over the questions that ATSDR charged the
10 panel members with. Yes.

11 DR. WEISSMAN: Can I jump in and just make a
12 correction to a statement I made before?

13 DR. HOLGUIN: Sure.

14 DR. WEISSMAN: Dr. Roggli pointed out to me that when
15 I cited the *New England Journal* paper as saying that the
16 specificity was 95 percent on osteopontin -- actually,
17 it's 85.5 percent.

18 DR. HOLGUIN: So even more false positives; right?

19 DR. WEISSMAN: Yeah. So there would be 14.5 percent
20 of the population would be false positive.

21 DR. ROGGLI: And just for context, that's for a value
22 of 48 nanograms per milliliter.

23 DR. HOLGUIN: That was the -- so the cutoff of that
24 ROC. Thank you.

25 So I'll read to you the first question and then open

1 it for discussion. We have a lunch at noon and the rest
2 of the -- I think the other items that are remaining on
3 the agenda is the final conclusions and key
4 recommendations from the panel as well. So those two
5 things are the main things on the agenda.

6 So I'm going to read to you the first question.
7 "ATSDR evaluates asbestos exposure in communities using
8 the health/risk assessment paradigm of obtaining a best
9 estimate of exposure combined with corresponding risk
10 levels to make health determinations. Given the state of
11 biomarkers of exposure and disease, are there any methods
12 ATSDR should be utilizing instead of or in conjunction
13 with health assessment techniques?"

14 DR. CARBONE: What I suggested to incorporate
15 osteopontin and mesothelin in your stats.

16 DR. SPAIN: Bravo.

17 DR. WEISSMAN: Well, I guess I would ask a question.
18 What are the current health assessment techniques that
19 we're comparing to or we're talking about augmenting?

20 DR. WHEELER: We're looking at typical kind of risk-
21 assessment techniques where we'll go into a community
22 and we'll do exposure assessments like EPA has done in
23 El Dorado of activity-based sampling and try to get a
24 exposure level from that kind of activity and the amount
25 of time that is spent in that activity. Then we'll use --

1 what has traditionally been done at EPA is an IRIS file
2 and calculate a km or a kl from the epidemiological data.
3 Presently, there's 14 studies that they use the
4 epidemiological data to compute a risk. They compute a
5 unit risk. We can also use some variants in the Berman-
6 Crump method or whatnot. We can calculate a kl or a km
7 and then use those exposures to calculate what the total
8 risk of that population is.

9 DR. WEISSMAN: Well, I guess I will jump in and, you
10 know, based on our discussions that we've had -- and
11 especially since the underlying, you know, question is a
12 community exposure where we have activity-based, you know,
13 assessments but we don't really kind of know the
14 integrated exposure, you know, that many people actually
15 have over time, there may be a role for well-designed
16 studies using some of these more invasive approaches that
17 we've talked about to get a sense of exposure in selected
18 groups.

19 So I wouldn't rule out -- you know, if it were deemed
20 to -- you know, if the risk and the benefit were deemed to
21 be appropriate, I wouldn't rule out the potential of
22 taking exposed groups and doing something like a lavage
23 study to look at level of exposure. That might be
24 informative and useful to augment in that way.

25 Depending on the site and depending on what we know

1 about background disease, some of the clinical tests to
2 look for the presence of actual disease might be
3 appropriate, but that would depend upon the situation.

4 DR. HOLGUIN: Thank you.

5 DR. ROGGLI: Yeah. I would echo those comments. I
6 would think that in circumstances where your usual
7 paradigm approach has identified what you consider to be
8 an elevated -- but nonetheless, compared to occupational
9 levels, a low-level exposure to asbestos, it may be
10 worthwhile to obtain additional information. That might
11 be helpful if you're dealing with a skeptical community.

12 And examples of that would be autopsy analysis of ME
13 cases from individuals who have been in the region to
14 demonstrate that your finding of increased levels from
15 environmental exposures correlate with increased levels of
16 fibers in lung tissues. And something that would be more
17 immediate in correlation with a time factor would be the
18 BAL, which David suggested.

19 And those would be additional information to indicate
20 that the exposure levels that you've measured in the
21 environment are, indeed, associated with increased levels
22 of exposure to individual patients, and that would be
23 further evidence that you're dealing with increased risk.

24 DR. CASTRANOVA: I would suggest that if we're going
25 to do BAL -- and I agree with that philosophy -- that

1 beyond measuring fiber counts, you should try to measure
2 some things that might, in the future, prove to estimate
3 risk or a health effect. I don't have the silver bullet
4 to tell you what parameter, but what I'm suggesting is, if
5 you have the BAL, analyze the cells for a cytokine
6 expression, growth-factor expression.

7 Perhaps you'll find a cytokine or a growth factor
8 that might be correlative, and then, in the future,
9 perhaps a serum level of that might be correlative. It's
10 too early in the game to say which one it is. In animal
11 models, some people would suggest TNF. Others would
12 suggest TGF-beta as possibilities. But you can build up a
13 database and see if there is a correlation.

14 It seems if you're doing BAL and you're not doing the
15 biology as well, you're just wasting an opportunity
16 because the cost is going to be in the counting of the
17 fibers. There's minimal cost additional for doing the
18 biology.

19 DR. WEISSMAN: I think that in terms of autopsy the
20 discussion we had yesterday in terms of focusing on
21 looking at samples from younger people is particularly
22 relevant to communities where one of the biggest concerns
23 is exposures to children and to young people who are
24 engaged in things like playing soccer and four-wheeling
25 and riding dirt bikes.

1 And if young people from such communities should
2 unfortunately pass away, looking at lung fiber burdens in
3 those people might well be a way for us to get a handle on
4 what the real exposure to that target susceptible
5 population is.

6 DR. CASTRANOVA: Once again, if I had the lung tissue
7 and I had to do to the fiber counts, at the same time, I
8 would take samples of that tissue, do RT-PCR to see if, in
9 fact, I'm seeing a biological response to those fiber
10 counts.

11 DR. ABRAHAM: Let me mention about something we
12 haven't discussed that occurred to me as sort of out of
13 the mainstream thinking a couple of years ago is a way to
14 measure fibers in the air. Has anybody ever looked at
15 automotive and air filters where you have dates when
16 they're changed and miles driven in between and things
17 like that as some sort of measure of air through them?

18 DR. GUNTER: Yeah. I've x-rayed -- using powder
19 x-ray diffraction, x-rayed the air filter of my car. So I
20 mean, this out-of-the-box thing is stuff that I do. But,
21 no. You're exactly right. The particle size will be big.

22 DR. ABRAHAM: It's not the ideal kind of filter to
23 use.

24 DR. GUNTER: But you've got lots of them. And you've
25 almost got them -- and again, this is the sort of thing I

1 think of, for better or worse. On gravel roads where we
2 live, you drive one car behind the other car for a while,
3 and you get a good -- it's like the road then is
4 separating the dust for you.

5 So there are all sorts of ways -- and this was my
6 comment on animals. Like where we live in Idaho, elk -- I
7 mean, because these things are killed and brought to
8 gaming stations. So there's all sorts of innovative ways,
9 good or bad, to look for air data that's not typical.

10 DR. ROGGLI: What did you find in x-ray diffraction
11 of your car filter?

12 DR. GUNTER: Exactly what you'd think. It's about --
13 now, where we live, it's about 15 percent quartz, 35
14 percent feldspars, and the rest is volcanic ash.

15 DR. ROGGLI: No detectable asbestos?

16 DR. GUNTER: I've got to go back and look carefully
17 for amphiboles because I think there should be probably --
18 my guess is there's a 1 to 2 percent level of amphiboles
19 in our air. That's a guess. I've got to go back and look
20 at that. I've got the air samples. I just haven't done
21 any.

22 DR. DODSON: Fibrous amphiboles?

23 DR. GUNTER: You really can't tell with powder x-ray
24 diffraction.

25 DR. DODSON: Yeah. That's why I asked the question.

1 Okay.

2 DR. ABRAHAM: I tried extracting fibers from some of
3 those amphiboles. It's a challenge that hasn't been
4 perfected yet.

5 DR. GUNTER: Because a lot of those filters contain
6 -- they contain -- well, a lot of those filters are made
7 out of like -- I mentioned the EPA, the PM-10, PM-2.5
8 high-vol samples. Those are deposited on -- people will
9 say quartz filters. They're not made of quartz. They're
10 made of fused silica, so you take quartz. You basically
11 heat it. You turn it into glass and make those things.

12 So those things are made of SIM-2. They're pretty
13 indestructible, but you can do powder x-ray diffraction on
14 those filters --we've done it -- and determine the quartz
15 contents of the filter. But it's difficult to name
16 particles from them because all the particles -- you'd be
17 pulling off fibrous silica particles.

18 DR. ABRAHAM: Well, you can look at particles that
19 are absorbed to the surface of those, but it's certainly
20 not an ideal medium for electron microscopy.

21 DR. GUNTER: But for x-ray powder diffraction, given
22 these large amount of samples, it's a great way to figure
23 out what's in the air, the total thing, and also to figure
24 out total amphiboles. And then if you could separate
25 some, you could then determine the percent -- asbestiform

1 versus nonasbestiform -- with the microscopy technique.

2 DR. ABRAHAM: It's not too invasive.

3 DR. DODSON: I think the BAL is a useful -- useful
4 tool. I think in order to apply it you have to answer --
5 to answer the question of ethically okay. That can be
6 reasonably handled. Economically, what do you want to
7 achieve? Do you want to look for 18-wheel trucks in it or
8 tricycles once you've got it? And that's both time
9 dependent and instrument and technique dependent. If you
10 want to get down to the finest level to look -- looking
11 for the fibers that may be there.

12 The bit about estimating increased exposure -- and
13 you have air samples. You know what's respirable
14 component of air samples. I mean, that's - that's where
15 you got your exposure. The lung reflects what has been
16 there and what is there at the time you do it.

17 The other thing that is a concern for me is with the
18 discussions we've had concerning the issue of meso is the
19 sampling of the lung. As Sebastien said in '80, it may
20 not reflect what's in the extrapulmonary sites. And that
21 poses a whole different issue of concern about how you
22 sample and what you're looking for in those sites outside
23 of the lung, which is the target sites for the meso.

24 DR. GUNTER: And while we're outside the box a little
25 bit, you could put those air filters on your lawn mower

1 and look for -- you could design special kind of filters
2 to put on devices like that, that you would then be able
3 to work on.

4 DR. ABRAHAM: Or house vacuums.

5 DR. GUNTER: Or house vacuums. We looked at that
6 too. So any kind of dust that we've looked at from --
7 mainly, again, powder x-ray diffraction is a way to get --
8 because we were looking for quartz.

9 DR. HOLGUIN: Any more comments?

10 DR. ABRAHAM: Maybe ATSDR could design a new filter
11 medium that they would distribute to homes and cars that
12 would be a more standard medium for a subsequent analysis.

13 DR. HOLGUIN: Would ATSDR comment on that?

14 DR. WHEELER: Funding.

15 DR. KAPIL: I think that's a little bit outside the
16 scope of our work, but maybe not.

17 DR. HOLGUIN: From the panel, anyone else want to
18 comment on Question 1?

19 (No Audible Response)

20 DR. HOLGUIN: Okay.

21 (Reading) "BAL appears to present the best
22 correlations to lung fiber burdens and also presents a
23 test that can be performed ethically and economically.
24 What would need to be done to make this technique useful
25 for estimating increased exposure or increased risk?"

1 And I know, more or less, it has been commented upon,
2 but if somebody would like to expand.

3 DR. ROGGLI: Well, you need to know what baseline
4 levels, however you're going to define that, which has
5 been discussed here previously. Background can be
6 notoriously difficult to identify and to define.

7 So if you're looking at any one community, then it's
8 probably important to do a case-control analysis for that
9 community, looking at individuals who are in -- either
10 another community or part of the community where they're
11 not exposed to the site that you're worried about compared
12 with those who are exposed and then look for differences
13 in BAL levels.

14 And I think, as also we've discussed here previously,
15 if you indicate -- if you identify evidence of increased
16 exposure, then, from what we understand about mesothelioma
17 and pleural disease, you have identified an increased
18 risk, and that's going to be proportionate to the
19 exposure. It's in the best model we have.

20 DR. HOLGUIN: Sure.

21 DR. HILLERDAL: How many persons do you have to do it
22 to -- to do these, how many controls do you need? How
23 many exposed do you need to get some significant changes,
24 do you think?

25 DR. CASTRANOVA: Well, when we were doing coworkers'

1 pneumoconiosis, we were doing about 15 controls, 15
2 exposed, and with some cytokine expression, you could see
3 significant differences easily. So you don't need large
4 numbers.

5 But it's interesting -- your baseline population. As
6 you said that, I thought that that should be simple, but
7 it might not be simple, because you really need a good
8 history on the people you're taking baselines on to make
9 sure -- did they go to a school that has an asbestos
10 problem even if they were in a different community?

11 DR. ABRAHAM: How would they know?

12 DR. CASTRANOVA: It would take -- it would take a lot
13 of investigation, but you're right. That's critical to
14 get the baseline.

15 DR. DODSON: Maybe not as critical if you have a
16 specific exposure to a specific type of fiber. I think --
17 I think that maybe that's -- Dr. Roggli agrees with that.
18 Maybe make it a little simpler. Does that makes sense?

19 DR. ROGGLI: Yeah. It has to do with the question in
20 mind. If your question has to do with what you believe to
21 be a hot spot in the environment of a certain fiber type,
22 then the question is: In the people who are exposed to
23 that versus those that are not exposed to that, is there a
24 difference? And it doesn't matter if you find fibers for
25 that question if you fibers in your controls --

1 DR. DODSON: Exactly.

2 DR. ROGGLI: -- because you're only trying to answer
3 is there a significant exposure from this particular hot
4 spot in the environment.

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

6 DR. CASTRANOVA: And you would anticipate that you
7 would find fibers in your controls but that it would be
8 lower.

9 DR. HOLGUIN: And you would expect sort of a large
10 magnitude of difference in terms of the fiber
11 concentration.

12 DR. ROGGLI: Not necessarily. If you found no
13 difference between the two groups, then you would assume
14 that whatever is contributing to the fiber levels in the
15 BAL level in the two groups -- that this particular
16 exposure you're looking at is not a significant factor.

17 DR. HOLGUIN: Because if the magnitude is not that
18 great and there's considerable overlap, then you're going
19 to have a huge population sample to detect differences on
20 now.

21 DR. CASTRANOVA: And you could screen out for
22 confounders like smoking and things like that and not do
23 those.

24 DR. ABRAHAM: Or you could do them as they would
25 retain things and be a more sensitive indicator.

1 DR. CASTRANOVA: But you would have to document
2 whether it was smokers or not because you're likely to get
3 BAL. If you're going to do any biological assays, you're
4 going to likely get BAL changes from smoking.

5 DR. HOLGUIN: If you were going to design a study for
6 BAL in a community where there's high level of exposure,
7 what would be the best place to start? Like, who would
8 you start enrolling first? People that have been there
9 for how many years? Representative of each strata of age
10 population? I mean, how would you design the
11 subpopulation that you're going to sample, just as a
12 thought?

13 DR. ROGGLI: I think it's going to depend on the
14 community and where the source is and how widespread that
15 source is and how long that source has been a potential
16 problem to the community. That's going to depend on what
17 age groups that you're going to target and could depend on
18 where you find your control groups.

19 If it's a fairly ubiquitous source, then you may have
20 to go to a community that's some distance away to get your
21 controls to be sure that they weren't exposed to a fairly
22 ubiquitous source. So it has to be tailored, I think, to
23 the question at hand.

24 DR. HOLGUIN: To each place; mm-hmm.

25 DR. CASTRANOVA: And you could age-match, smoking-

1 match so that you control for that.

2 DR. WEISSMAN: I mean, the other elements of the
3 design, of course, are to be sure that there's a
4 standardized approach to performing the lavage, how much
5 fluid you put in, how many aliquots you do, that kind of
6 thing, and a standardized approach to analysis. I guess
7 Dr. Dodson had touched on that.

8 Yesterday we talked about asbestos bodies, and I
9 think it would be useful to look at both asbestos bodies
10 as well as fibers by EM because of, as Dr. Roggli
11 mentioned the other day, the large amount of data, you
12 know, relating lavage asbestos bodies to asbestos body
13 burdens and, you know, the ability to, you know, make risk
14 assessments from that, even knowing, you know, the
15 problems with asbestos bodies that we talked about.

16 But I think it's important to look at both that and,
17 you know, fibers by EM. And then, finally, you know,
18 denominator, you know, agreeing upon, you know, the
19 appropriate way to display the data. So those are also
20 the, you know, kind of things to think about.

21 DR. HOLGUIN: There is a need to get some reference
22 values, I guess, to understand what it's about. No?

23 DR. WEISSMAN: But that isn't to say that we're in a
24 vacuum. We're not in a vacuum. There are values out
25 there that have been published, and there have been --

1 DR. HOLGUIN: For BAL?

2 DR. WEISSMAN: For BAL, there are values that have
3 been published, and there's data that relates BAL values
4 to lung burden values, especially for asbestos bodies.
5 And there are, you know, bodies that have made, you know,
6 judgments about what level of risk are associated with
7 those different levels. So we're not in a complete vacuum
8 here. So it's important to have controls.

9 DR. CASTRANOVA: In the same school of biology,
10 there's a database for background levels of or control
11 levels of cells, cytokines, et cetera.

12 DR. HOLGUIN: So what would newer studies offer?

13 DR. WEISSMAN: Well, I guess we're talking about this
14 because of the potential, you know, benefit to be able to
15 give better information to communities.

16 DR. HOLGUIN: So most of the studies have been done
17 in occupational settings. Yes.

18 DR. KAPIL: I'd just like to pose a BAL question to
19 the panel. Would the panel be able to comment on the
20 risks associated specifically with BAL particularly in
21 older individuals? Is that at all a concern, or is it
22 basically a nonissue?

23 DR. WEISSMAN: Well, it's not a nonissue. I mean,
24 it's never trivial to perform, you know, even a relatively
25 noninvasive medical procedure on someone. And those of us

1 that do bronchoscopy and bronchoalveolar lavage know that
2 most of the time there's no problem, but occasionally
3 there is.

4 If you have an elderly individual who has pulmonary
5 impairment or who has cardiac impairments, of course,
6 they'll be at increased risk. There are problems with
7 anesthesia. People have reactions to anesthesia. It's
8 rare, but it happens. Even if you're just doing a lavage,
9 there's certainly a proportion of people that get post-
10 lavage fevers and post-lavage pneumonias. Some of these
11 things can happen.

12 The risk is low. The risk is far less than, you
13 know, 1 in 1,000 probably for anything really serious
14 happening. But there is a risk, and so you have to
15 consider the risk and the benefit. You can't just jump
16 into doing a study lightly. There has to be a benefit to
17 it.

18 DR. CARBONE: If the risk is 1 in 1,000, the risk
19 that those people get mesotheliomas is only 1 in 1,000.
20 You can't do that.

21 DR. ROGGLI: You mean the risk of fatality.

22 DR. WEISSMAN: Yeah; not the risk of getting
23 mesothelioma.

24 DR. CARBONE: When you say serious risks, what do you
25 mean for serious risk? Define that.

1 DR. WEISSMAN: You know, having to have a pneumonia
2 to where you have to take antibiotics or something like
3 that. I mean, there have been deaths that been reported
4 with research lavages. I mean, there was a death that was
5 reported several years ago, so I don't want to minimize,
6 you know, that things can happen. But, overall, it's a
7 safe procedure.

8 DR. HILLERDAL: Of course, you shouldn't choose these
9 elderly persons with the impaired lung function. For the
10 first place, you wouldn't get much information out of it.
11 It would be difficult. As we said yesterday, you should
12 select the young adults who preferably have been living
13 all the time in these villages.

14 DR. HOLGUIN: I mean, I guess, I'm not an expert.
15 I'm not an expert in asbestos, but I think if you do a BAL
16 on somebody without significant lung impairment, the major
17 risks are just related to conscious sedation mainly, which
18 they are. But the procedure is mainly safe if you don't
19 do a biopsy.

20 DR. HILLERDAL: And you will find a number that will
21 get a post-BAL pneumonia.

22 DR. HOLGUIN: Sure.

23 DR. HILLERDAL: But that's no big problem.

24 DR. CASTRANOVA: There are certainly medical centers
25 who do this on a fairly regular basis, and those would be

1 the sources I would go to, to do it.

2 DR. HOLGUIN: Sure. I mean, you only want to do it
3 in a place where there is, you know, patient care and all
4 those issues that are in place.

5 DR. WEISSMAN: And the point's well taken that the
6 biggest risk is in people who have underlying medical
7 problems and have the procedure done for medical purposes
8 but they're sick.

9 DR. HOLGUIN: I understand there is a recent case of
10 a woman who died. Was it at Hopkins? Somebody with
11 airway disease that was being -- having BAL for research
12 purposes but someone had underlying airway disease?

13 DR. WEISSMAN: Yes. I believe it was someone who had
14 status asthmaticus, severe asthma.

15 DR. HOLGUIN: But you would avoid those patients
16 obviously.

17 DR. ABRAHAM: One question comes out is there's
18 fairly strict NIH guidelines and human-subject guidelines.
19 But what is research and what is not research? You know,
20 is this a community service, epidemiology, or -- because
21 some aspects of it -- well, some aspects of it, like
22 banking things for cytokines later, is clearly research.
23 But if it's something where it's a clinical indication of
24 exposure, some people could argue that that was another
25 kind of test.

1 DR. DODSON: So how does the agency handle that?

2 DR. KAPIL: Ultimately, you know, we have human-
3 subjects folks who would take a look at this. We have to
4 submit this for this type of work for IRB approval. You
5 know, I think -- obviously, I can't comment on -- you
6 know, I can't sort of make a general comment on what the
7 IRB or our human-subjects folks would or wouldn't say
8 about any specific thing, but I think what we're talking
9 about here is doing an invasive test for no other clinical
10 reason other than to document exposure; is that correct?
11 Isn't that what we're talking about?

12 DR. WEISSMAN: Yes.

13 DR. KAPIL: We're talking about a clinical test, an
14 invasive test, to document exposure. And I think we're
15 also talking about doing that in a setting not necessarily
16 for an individual reason, for that patient, but to
17 understand better how exposure occurs in the community, so
18 it's sort of a generalizable result. So, you know, to me,
19 off the top of my head, it sounds like research, but...

20 DR. WEISSMAN: Yeah, it does.

21 DR. DODSON: One of the things our clinical
22 colleagues said, which I think is very important at the
23 end, if you're considering cohorts for assessment is you
24 may have to take the cohort to a site, depending on where
25 it occurred, just as a practicality issue with your

1 plannings.

2 DR. HOLGUIN: Any more comments on BAL?

3 (No audible response)

4 DR. HOLGUIN: Question 3 really has two parts. It
5 states, "Please consider two exposures: a long-term,
6 relatively continuous versus a high-level burst or bursts
7 of exposure at the beginning of the time period. Even if
8 the overall number of fibers was the same, would you be
9 able to tell the difference in any fiber burden test,
10 whether it's autopsy, BAL, or sputum?"

11 And the second question would be, "Would the expected
12 risk of disease be similar or different in both
13 scenarios?"

14 DR. CASTRANOVA: Well, I've done some studies on
15 mineral dust but not asbestos in bursts, spikes versus
16 continuous exposure. And if we're talking about bursts
17 that are reasonably close to the mean -- okay; not 100
18 times the mean, but two times the mean. The things that
19 I've heard from the EPA folks when they're doing the all-
20 terrain vehicles, the exposures may be two, three times
21 higher than normal.

22 In those cases, we see no evidence that spike versus
23 continuous makes much of a difference over the long term.
24 It seems to be concentration times time does the trick.
25 And we've done that with silica, and you could do that

1 with other mineral dusts as well.

2 So that, I think, in the parameters that I'm
3 understanding, the community exposure might be -- those
4 spikes wouldn't be outliers enough to have a clearance
5 problem. Certainly, if you get -- let me again say
6 silica. If we do sandblasters, whose exposure may be 50
7 times the permissible exposure limit -- that spike
8 certainly does something differently than a continuous
9 low-level exposure.

10 But that's an extraordinarily high deviation from the
11 mean. So, otherwise, I wouldn't suspect too much
12 difference.

13 MR. DEN: Can I make a clarification on the exposure
14 bursts, just our study?

15 THE COURT REPORTER: Can you tell me who you are?

16 MR. DEN: Arnold Den, EPA, San Francisco.

17 For El Dorado work, the differences between a
18 stationary monitor that was placed away from the
19 activities versus the activities, for most of the exposure
20 activities, ranged from ten times to as high as 62 times
21 difference than, let's say, the background.

22 For Clear Creek management area, where we used off-
23 road vehicles, those exposure differences were probably
24 1,000 and higher because we recorded one to two fibers per
25 cc PCME versus a stationary monitor would be several zeros

1 before it. So the vehicle stuff is much higher from that.
2 We've also done road studies, both us and the state, over
3 the past 20 years there, and those exposures can be 100 to
4 200 times or even higher; very large concentrations if you
5 run a vehicle over, let's say, unpaved road containing
6 quarry rock. This was chrysotile. Those exposures would
7 be much higher. You get short-term bursts, but they are
8 10, 60, 100,000 times higher for that time period you're
9 doing the activity.

10 DR. ROGGLI: I would agree with Vincent's statements
11 that the dose is the best marker of a risk of disease,
12 irrespective of whether you're talking about a low,
13 continuous exposure or spikes that are discontinuous. And
14 the exception is, as Vincent was indicating, is when you
15 reach levels that are equivalent to -- that go above the
16 overload state of -- overload for clearance. I don't know
17 exactly what those levels are for the human lung. I think
18 they probably are available.

19 But there -- when you're talking about levels of
20 crystalline silica from sandblasting, you've certainly
21 passed the overload state. When you're above the PEL in
22 the workplace, current level of 0.1 fiber per cc, I think
23 that's well below what the overload rate is for the human
24 lung. But even if you're talking about a thousandfold
25 difference -- if you're talking about a difference between

1 .00001 and .01, which is, I think, about a thousandfold
2 difference if I did my zeros right, then that's still well
3 below what the overload rate is. And in that case, it's
4 the total dose that's going to be the determining factor.

5 DR. CASTRANOVA: I would agree with that as well.

6 DR. ABRAHAM: If you think back to the studies that
7 Chris Wagner did with the chrysotile contaminated with
8 tremolite, there you could see that a pulse dose with time
9 for clearance might give you a different equilibrium value
10 for something that's cleared rapidly, like chrysotile.

11 So you might experimentally be able to see
12 differences between pulse doses and continuous doses in a
13 situation like that. And we've seen a case where somebody
14 worked one month a year during vacation, doing mining,
15 where he had silica exposure, and the reaction of the lung
16 appeared somewhat different from somebody that had
17 continuous exposure in terms of the rate of development,
18 and that was different from dose because there was more
19 time for clearance and there was less intervening dust in
20 the interstitium that was almost all consolidated into the
21 silicotic nodules compared to people with continuous
22 exposure that had different distribution of dust in the
23 lung.

24 But I think your point about -- for people in a
25 community with more short-term exposure, not that strange

1 situation, we probably wouldn't be able to tell the
2 difference looking at the BAL or lung burden.

3 DR. ROGGLI: Just for -- to put things in
4 perspective, my recollection is that the levels of
5 exposure that Dr. Wagner were using -- was using was the
6 same order of magnitude as those that Dr. Brode at NIHS
7 used when I was working with him. And those are somewhere
8 between 4,000 and 10,000 fibers per milliliter of dust on
9 -- as measured by phase-contrast microscopy. That's not
10 including all the fibers you couldn't see by EM on those
11 dust levels, and you have to compare that with the current
12 PEL of 0.1 fiber per cc.

13 DR. HILLERDAL: I think in real life there is no such
14 thing as a long-term, low-continuous exposure. In real
15 life, you have those bursts, whether it's occupational or
16 environmental or whatever. So I think it's actually a
17 nonquestion, and nobody can answer it at this moment.

18 DR. ROGGLI: Most people experience both. You have a
19 continuous background low level with bursts superimposed
20 upon them.

21 DR. HILLDERAL: Yes; of course.

22 DR. WEISSMAN: And this something that plays out over
23 many years. I mean, we spoke about the Marysville cohort
24 earlier who had their exposures, you know, before 1980.
25 And at that time, they had on the order of 1 percent

1 pleural abnormalities and then studies again a couple of
2 years ago, you know, they were up to like 25, 26 percent
3 pleural abnormalities.

4 So, you know, this is something that plays out over
5 many, many years. And assuming that you don't get into
6 the dust overload situation, you know, that was discussed,
7 you know, the accumulation of exposures, you know, is more
8 important, you know, than intermittency or continuousness.

9 DR. DYKEN: I wanted to add an extra thing to that.
10 That was my question I made up. So even if -- if someone
11 had the same number of fibers in their lungs -- say it was
12 enough to correlate to a certain amount of risk over time.
13 So is what you're saying that virtually there's no
14 difference, say, if a ten-year-old was exposed to
15 something and then you looked at them when they were 30
16 versus if somebody worked from age 20 to 30 and got the
17 same amount of fibers and then you looked at them at age
18 30? Are you saying there's no difference in the risk of
19 disease?

20 DR. CARBONE: There was a paper by Peter that
21 addresses that, and he published that there was absolutely
22 no difference.

23 DR. ROGGLI: What was your --

24 DR. DYKEN: What was the name?

25 DR. ROGGLI: Would you repeat your scenario because

1 if I --

2 DR. DYKEN: Oh, I don't know if I can repeat it again
3 exactly. Okay. So a ten-year-old gets a burst of
4 asbestos exposure, and then gets no exposure for the next
5 20 years. But then another person is exposed continuously
6 from age, say, 20 to 30 -- well -- okay. So from age 20
7 to 30. Well, then later in life, I guess, you look at
8 them, after it would be time for the disease to show up.
9 So age 50, there would be -- what you're saying -- I'm
10 paraphrasing -- is that there would be no difference in
11 the risk of those two exposures.

12 DR. ROGGLI: If the total dose is the same, that
13 would be correct. What we see, for example, in asbestos-
14 related mesotheliomas for a similar exposure -- if you're
15 first exposed occupationally beginning in your twenties,
16 then we typically see mesotheliomas in individuals who are
17 in their sixties. If you are first exposed as a child in
18 a household where an asbestos worker is bringing asbestos
19 into the household, then we start seeing the
20 mesotheliomas, typically, in the thirties or forties.

21 So for a given dose, similar dose, the latency is the
22 same, and it depends upon when the dose started. If it
23 starts earlier in life, then the disease is going to
24 manifest earlier. But there is some evidence of an
25 inverse relationship between dose and latency; that is, as

1 you lower the dose, it may take longer for the disease to
2 manifest from any particular given time of initial
3 exposure.

4 DR. ABRAHAM: But I think one of the things you
5 mentioned was to correlate the number of fibers in the
6 lung with the risk of disease over time. And, again, I
7 don't think the numbers of fibers in the lung taken at any
8 given point in time have a formula to look for future risk
9 of disease. I think that that's a misconception that
10 there's data available to do that. Victor, do you think
11 that's...

12 DR. CARBONE: No. You are right. There is
13 absolutely no data to support that.

14 DR. ABRAHAM: So I mean, the whole issue of fiber
15 burden and risk is not the same as exposure and risk, so
16 we have to be careful.

17 DR. DODSON: It actually shows the levels that are
18 there at that time and if it's elevated over what we have
19 for that type of fiber. In our laboratory and our
20 experience, in other populations that it stands on its own
21 as an observation.

22 The only thing, when you use the term "burst," I'm
23 not sure exactly we're talking heavy-exposure, short-term
24 type events, and some of that has to be -- I mean, to
25 answer it in a little different way, as I understood your

1 question, how often are those bursts? What's the time
2 frame between the bursts? How likely is there for a
3 cumulative effect between bursts? What impact does
4 clearance have, potentially have? And then, of course --
5 well, it wasn't mentioned a moment ago, but all of us
6 realizes -- was it a smoker or a nonsmoker?

7 DR. ROGGLI: I would agree all those factors come
8 into play, but as long as you don't exceed clearance
9 overload for the bursts, still the total dose, cumulative
10 dose, is going to be the determinant factor.

11 DR. CARBONE: It's going to be the determining factor
12 only in that it is going to cause you at risk of
13 developing the disease. But it does not determine at all
14 who among the people who are exposed is going to develop
15 the disease. It just places you in the risk group.

16 DR. ROGGLI: Of course. I mean, it's the determining
17 factor for what your risk is going to be.

18 DR. WEISSMAN: And in terms of burdens, you know,
19 measured burdens and risk of disease, the one thing that
20 I'm -- obviously, most of it is cross-sectional and it's
21 not longitudinal. There aren't studies where people have
22 had levels measured and then been followed longitudinally,
23 you know, to see what their risk of disease is.

24 The one thing that I'm aware of that's published and
25 widely quoted that attempts to make that relation -- but,

1 of course, you know, it is conjectural -- would be the
2 Helsinki Criteria, where they've published levels that are
3 associated with twofold increase in risk of lung cancer.
4 But, again, it is conjectural, but it's expert opinion,
5 but it hasn't been verified by empirical research.

6 DR. CARBONE: What is it? Can you say it again? I
7 got confused, sir.

8 DR. ROGGLI: Yeah. The work of Karjalainen we talked
9 about yesterday shows that roughly at the cutoff level of
10 somewhere around -- I think it's 5 million fibers per gram
11 of -- amphibole fibers per gram of dry lung tissue, you
12 double your risk of lung cancer, and that correlates with
13 25 fiber cc years of exposure. So that's about the best
14 mark we have of the correlation between fiber burden and
15 risk in terms of environmental exposure.

16 DR. WEISSMAN: And there was an expert panel that was
17 assembled and the so-called Helsinki Criteria -- I guess
18 they were published in the *Scandinavian Journal of Work*
19 *and Environmental Health* like in 1998 or something like
20 that.

21 DR. ROGGLI: '97.

22 DR. WEISSMAN: '97? Okay.

23 DR. ABRAHAM: But that wasn't looking prospectively
24 at risk. It was looking at a group of people that either
25 had lung cancer or didn't.

1 DR. WEISSMAN: As I say, it's a conjectural --

2 DR. ABRAHAM: It wasn't something that could be used.

3 DR. CARBONE: What do you mean it's conjectural?

4 They didn't demonstrate it, or they did?

5 DR. WEISSMAN: Well, there's not empirical data where
6 people obviously have had, you know, autopsies done or
7 surgical, you know, studies done to look at fiber burdens
8 and then those people followed over time to see if they
9 get disease. Obviously, that hasn't been done. But there
10 are relationships between known levels of exposure
11 obtained by history and lung burdens. And what is known
12 is the relationship from any disease is between level of
13 exposure and disease, so based on that, the expert panel
14 made some judgments about what the relationship would be
15 between level of lung burden and level of risk.

16 DR. CARBONE: But you don't think this is an
17 hypothesis?

18 DR. WEISSMAN: Excuse me?

19 DR. CARBONE: It's an hypothesis.

20 DR. WEISSMAN: Yes.

21 DR. HOLGUIN: But you have just really the odds of
22 exposure in both groups; right? I mean, people with
23 cancer are more likely to be exposed in terms of odds?
24 It's not really a risk measure.

25 DR. ROGGLI: It's a little more than a hypothesis.

1 Karjalainen did the study of individuals who had lung
2 cancer who had either autopsy or surgical-resected
3 specimen, analyzed their fiber analysis -- of their fibers
4 in the lung tissue, compared it with a controlled,
5 medical-examiner-obtained autopsy population that did not
6 have lung cancer, correlated or stratified for age and
7 other controlling factors, and found that the fiber burden
8 correlated with the lung cancers in the two groups. And
9 there was a significant odds ratio of lung cancer related
10 to certain fiber levels that he measured in the lung.

11 DR. CARBONE: So it's not an hypothesis?

12 DR. ROGGLI: The data has been published, but there's
13 limited data. Nobody has done a nice case-controlled
14 study of lung cancer risk based on fiber burden analysis
15 other than Karjalainen that I'm aware of.

16 DR. CARBONE: Did he have a D value there or not?

17 DR. ROGGLI: Yeah. It depends upon how you broke
18 down the groups and what you were comparing, but there
19 were some significant associations and some significant
20 trends as well.

21 DR. HOLGUIN: Yeah. Any more comments?

22 DR. ROGGLI: And I should add that the levels that
23 they were talking about that resulted in a significant
24 increased lung cancer risk were far more than you would
25 typically expect to see from environmental type of

1 exposures.

2 DR. DYKEN: Can I add a question to that question? I
3 know you said that as long as the clearance mechanisms are
4 not overloaded. What happens when the clearance
5 mechanisms are overloaded physiologically?

6 DR. CASTRANOVA: When the clearance mechanisms are
7 overloaded, you get an increased rate of disease, at least
8 in animal models, where it's most effectively studied.
9 And so what you get is an increase in pathogenicity of
10 dust that in a non-overload level would have a very low
11 rate of pathogenicity.

12 DR. DYKEN: So would risks of asbestosis or other
13 diseases be higher then?

14 DR. CASTRANOVA: Yes.

15 DR. DYKEN: Okay.

16 DR. DODSON: But it is also true that you can get,
17 under those conditions as defined, relocation of
18 particulates out of the lung that normally would be
19 cleared and handled by the clearance mechanism to
20 extrapulmonary sites.

21 DR. HILLERDAL: What level does this occur in human
22 beings?

23 DR. CASTRANOVA: Well, the model says when the volume
24 of particulate in the lung exceeds 10 percent of the total
25 volume of alveolar macrophages in the lung.

1 DR. HILLERDAL: And what is that in the real world?

2 DR. CASTRANOVA: We do know the number of macrophages
3 in the human lung and we do know the size, so we could
4 calculate the volume and we could calculate, given a
5 particular particle, its size and density. You can make
6 that calculation on the particle.

7 DR. HILLERDAL: So what is it for asbestos? Is that
8 a real possible exposure in real life, do you think?

9 DR. CASTRANOVA: In asbestos, it normally, even at
10 occupational levels, never gets above that theoretical
11 overload level. So asbestos is doing -- it is inherently
12 a toxic material or a pathogenic material.

13 DR. ABRAHAM: [Off microphone]

14 THE COURT REPORTER: Microphone, please.

15 DR. ABRAHAM: Excuse me. Even under the very heavy-
16 exposures instance in the animal studies that Dr. Roggli
17 mentioned a while ago, there was still a very rapid
18 clearance of chrysotile, though probably those were under
19 overload conditions.

20 DR. CASTRANOVA: Yes. Those are under overload.

21 DR. ABRAHAM: The clearance still works, but it slows
22 down.

23 DR. WHEELER: There's something that I don't
24 understand about this clearance thing that's always
25 bothered me; and that is, that longer fibers seem to be

1 more toxic because they're not cleared from the lungs as
2 fast. And so you're talking about the most toxic fibers
3 don't get cleared, so even if you've inhibited clearance,
4 it doesn't change the amount of fibers that are toxic
5 there. So how does inhibiting clearance of fibers that
6 aren't going to be cleared anyway increase the toxicity?

7 DR. CASTRANOVA: Well, the assumption you're making
8 is that the shorter fibers do not have any effect on the
9 disease. Certainly, the longer fibers are more
10 pathogenic. But my argument would be the shorter fibers
11 lead to an inflammatory background that would add to the
12 potential for disease.

13 DR. ABRAHAM: Also, it's not absolute. The longer
14 fibers have some clearance, and under anything -- overload
15 or smoking or anything that impairs clearance -- more of
16 those would be retained as well. So nothing is 100
17 percent retention.

18 DR. HOLGUIN: We have a couple of questions from the
19 audience. Would you mind saying your name and
20 affiliation.

21 DR. JOHNSON: Mark Johnson with ATSDR again.

22 A question has to do with the variability in the
23 clearance rate in the human population concerning
24 children, those with predisposing conditions like asthma.
25 That would need to be factored into an estimate of what

1 level of exposure could lead to overload.

2 DR. ROGGLI: I think there is a natural variation in
3 alveolar clearance level, and that there's some people
4 that have very poor alveolar clearance. And for those
5 individuals, you end up chasing your tail as far as trying
6 to determine exposure level that's going to -- that's
7 going to prevent disease in 100 percent of the population.

8 And I think that there's probably a continuous
9 distribution of clearance levels, and you're talking about
10 the people on the real small end of the clearance. And I
11 don't think we have good, noninvasive, reliable ways of
12 identifying who those people are at the present time.

13 But those people are certainly going to be the ones
14 who are at risk of accumulating the lungs more than the
15 usual amount of fiber for a given exposure level. And
16 that's maybe one of the differences that we see a
17 distribution in, for example, mesothelioma risks. We see
18 distributions in lung cancer risks for smokers and lots of
19 other diseases; distribution of silica, a risk from
20 exposure to silica. That's part of the problem there.

21 DR. HOLGUIN: Victor, are you aware of any -- of a
22 study of highly exposed populations of -- using -- I know
23 it's not specific to the source. But using, for example,
24 exhaled nitric oxide to monitor airway inflammation and
25 disease progression? Has that ever been done? Is anybody

1 aware? I mean, I know we use it a lot for asthma and
2 other diseases, and it tends to sort of parallel disease
3 activity. I mean, if you suddenly inhale airway particles
4 and they cause airway inflammation.

5 DR. CASTRANOVA: Most often, it's used for
6 conductant-zone inflammation and not alveolar
7 inflammation.

8 DR. WEISSMAN: Most of the NO is made by airway's
9 epithelial cells.

10 DR. HOLGUIN: But that's the -- you know, nowadays
11 you can actually partition alveolar from airway nitric
12 oxide using some modeling techniques that are not very
13 complicated. So nobody's looked at that with asbestos?

14 DR. CASTRANOVA: No; not that I know of.

15 DR. ABRAHAM: It would be easy enough to do a search.

16 DR. HOLGUIN: Somebody bring apartment, please.

17 DR. CASTRANOVA: To address the question about
18 clearance rate in asthmatics, to my knowledge, there's no
19 data one way or the other. One would expect that's an
20 upper airway disease and it's not affecting alveolar
21 clearance rates at all.

22 DR. HOLGUIN: I would be a lot more concerned in
23 clearance in people who have elevated left-end diastolic-
24 ventricular pressures or things like that.

25 DR. ROGGLI: In fact, it's possible from -- there's

1 some evidence to indicate that diseases like asthma might
2 even be protective because there's some evidence that
3 individuals who, for example, are smokers are less likely
4 to get silicosis for a given exposure than those who are
5 nonsmokers. And the theory about that is because
6 cigarette smoking increases the thickening of the mucus
7 blanket, decreases the diameter of the bronchi, and so
8 you're less likely to get peripherally deposited silica
9 particles for a given dose in that circumstance.

10 Interestingly, those individuals have more silicotic
11 changes in their lymph nodes and less in their lung.

12 So for example, with asthma, then you might expect it
13 could be protective possibly. We don't know for sure, but
14 I don't think there's any correlation between asthma and
15 the poor alveolar clearance that I mentioned earlier that
16 anybody's ever identified.

17 DR. WEISSMAN: Essentially, for nonasthmatics who are
18 silica exposed, it's an additional risk factor, if you
19 smoke, for silicosis. People who smoke and are exposed to
20 silica are more likely to develop x-ray changes.

21 DR. ROGGLI: That's different from the study from
22 South Africa where they found that smokers had less
23 radiographic disease for a given dose than the nonsmokers.

24 DR. CASTRANOVA: Again, it depends on the levels and
25 the years of smoking. What would normally happen with

1 smoking is you'd get increased mucus initially, and that
2 might increase trapping in the conductant zone. Then with
3 longer-term exposure to smoke, you would get a decreased
4 clearance. You could see both of those results, as a
5 matter of fact.

6 DR. HILLERDAL: And, of course, if you look at the
7 chest x-ray, it's well known that if you are a smoker --
8 and smokers who have never been exposed to asbestos will
9 have a certain amount of early, so-called asbestosis and
10 changes on their chest x-ray. And, of course, they don't
11 have asbestosis. These are the early x-ray changes,
12 unspecific for smoke specific. And the heavier the
13 exposure, the less importance has the smoking for it. So
14 there is no difference with the high degrees of asbestosis
15 and whether you smoke or not.

16 DR. HOLGUIN: We have a question from the audience.
17 Name and affiliation, please.

18 DR. KOPPIKAR: Aparna Koppikar from ORD, EPA. Going
19 back to overload burden about silica, you know, there is a
20 case in Hawk's Nest, as it's called, in West Virginia
21 where sandblasting was done to divert the river. And what
22 happened was that the workers were exposed to high, very
23 high, level of silica. And in them, they found acute
24 silicosis occurring in six months, rather than 15 to 20
25 years later. Is there any type of information available,

1 something like that, that asbestos exposure is to that
2 high level?

3 DR. HILLERDAL: No; not to my knowledge has anything
4 like that been described in asbestosis. But that's why I
5 asked about this overload, what it is for asbestosis.

6 DR. KOPPIKAR: That's where the overload question was
7 coming from.

8 DR. HILLERDAL: Yes; yes.

9 DR. ABRAHAM: But in animals with really heavy
10 exposure by installation, I believe, you can produce
11 alveolar proteinosis with the asbestos exposure, which is
12 the same reaction produced with acute silicosis. You get
13 a -- that disease wasn't really described until 30 years
14 later, after the Hawk's Nest episode. But it's in the
15 pathology of the Hawk's Nest cases.

16 DR. ROGGLI: In the geology of the Hawk's Nest
17 because my understanding that Gaulley Bridge creation --
18 that what they were cutting through was almost pure quartz
19 and that the exposure was extremely high to very fine
20 quartz particles, and so you end up with hundreds of
21 people getting acute and rapidly progressive or
22 accelerated silicosis as a consequence.

23 DR. GUNTER: And poor ventilation.

24 DR. ROGGLI: And there is -- I agree with Dr.
25 Hillerdal. I don't think that there's anything identified

1 -- a similar situation for asbestos that I've ever heard
2 of.

3 DR. WEISSMAN: I mean, the other place where we see
4 overload is in coal miners, really, who were exposed to --
5 you know, in the old days were exposed to extraordinarily
6 high concentrations of coal dust and, you know, on the
7 orders of tens of milligrams per meter cubes. You know,
8 so the exposures that we see in communities are nothing
9 like that.

10 DR. ABRAHAM: Maybe during dust storms.

11 DR. HOLGUIN: More comments? No? Should we go to
12 the next question?

13 (No audible response)

14 DR. HOLGUIN: Number 4 it is; right?

15 (Reading) "Would results of fiber burden analysis by
16 autopsy, BAL, or sputum differ depending on the mineralogy
17 of amphibole asbestos, similar to the differences between
18 chrysotile and amphibole?"

19 DR. GUNTER: When you say "mineralogy," do you mean
20 chemistry or structure or morphology or all that?

21 DR. DYKEN: I was talking about the different types
22 of amphibole asbestos.

23 DR. GUNTER: So then, basically, you're talking about
24 chemistry?

25 DR. DYKEN: Basically.

1 DR. ROGGLI: My understanding of what data is
2 available for humans is there's no difference in the
3 clearance or disappearance of the lungs for the amphibole
4 types, whether it's tremolite or amosite or crocidolite or
5 actinolite or anthophyllite. The persistence and clearance
6 rates are similar for similar length distributions of
7 fibers that are inhaled.

8 DR. CASTRANOVA: I agree with that. In the in-vitro
9 dissolution studies, I don't know of any difference in
10 dissolution rate with the various different amphiboles.

11 DR. ROGGLI: And it's very, very slow.

12 DR. CASTRANOVA: It's very, very slow.

13 DR. GUNTER: I'm sure there are differences in
14 dissolution rates, but it would be on the order of tens of
15 thousands of years probably before it would ever be --
16 they're not -- there would be insignificant differences in
17 dissolution rates based on the chemistry, but not based on
18 morphology.

19 DR. HOLGUIN: Dr. Dodson.

20 DR. DODSON: In the ATEM, the definition is
21 established on morphology, x-ray dispersive analysis, and
22 selected area diffraction, which the last one is an
23 important variable for distinguishing fibrous talc from
24 anthophyllite. But when I read that, if you make the call
25 as to type, whether it's chrysotile or one of the

1 amphiboles, it's done on one of those three parameters,
2 and that's the distinguishing factors.

3 I would just add that in chrysotile, particularly
4 fibril, it is possible that the beam damage to the
5 fibrillar unit that makes it look like it's been thermally
6 reacted with some external environment that had nothing to
7 do with anything other than someone used a very hot beam.

8 DR. HILLERDAL: There are size differences. If you
9 go back to this question, there are size differences
10 between different amphibole fibers. So I would imagine,
11 depending on which technique you use, you would find many
12 more -- many more fibers in a crocidolite case than you
13 would in an anthophyllite case, or am I wrong?

14 DR. DODSON: Why?

15 DR. HILLERDAL: Because the anthophyllite fibers are
16 bigger, larger.

17 DR. DODSON: Oh, oh. You're talking about diameters
18 and the likelihood of inhaling something.

19 DR. HILLERDAL: Yes.

20 DR. DODSON: That depends on the exposure, but the
21 logic is certainly there, what you just said. Sure.

22 DR. ABRAHAM: And via the analysis --

23 DR. DODSON: For viability.

24 DR. ABRAHAM: The analysis method of magnification
25 would determine what fraction of the thinner fibers you

1 detect as well.

2 DR. HILLEREDAL: Yes.

3 DR. DODSON: Right.

4 DR. GUNTER: We're currently doing some dissolution-
5 rate experiments on different amphiboles that have
6 different chemistries. But, again, they're geologic
7 inclusive and not thermal.

8 DR. HOLGUIN: Any more comments?

9 (No audible response)

10 DR. HOLGUIN: (Reading) "How do fiber dimensions
11 change over time after deposition in the lung? Is there a
12 correlation with exposure fiber dimensions on which risk
13 models are based?"

14 That is Question 5. Anybody want to --

15 DR. DODSON: Small things clear more readily than big
16 things (laughter).

17 DR. HOLGUIN: Does that answer your question?

18 DR. CARBONE: Next question.

19 DR. DYKEN: If you have a fiber that's retained in
20 the lung though, however, how will its dimensions change
21 over time? I know some fibers get broken down into small
22 fibril units.

23 DR. CASTRANOVA: Well, but the amphiboles provide a
24 persistence of the long fiber is certainly within the
25 human lifetime, so I would suggest it doesn't change.

1 DR. ROGGLI: Our studies show that over time that the
2 average length of the fibers in the lungs from amphibole
3 exposures increased, and that's because the short fibers
4 were being removed. Long fibers were being retained.
5 There was no change in the diameter which we could
6 identify for the amphibole fibers.

7 So the current concepts are that once amphibole
8 fibers are deposited in the lungs, they do not change in
9 their dimensions, either length or diameter, to a
10 significant degree over time in human lung tissue samples.

11 And with regard to the second part of the question,
12 the risk assessment's been done. Berman and Crump have
13 done that analysis based on fiber dimensions and
14 correlation with risk models. And that data's available,
15 and you can use it or not.

16 DR. CASTRANOVA: Now, the Berman and Crump data are
17 only on lung cancer.

18 DR. ROGGLI: And mesotheliomas.

19 DR. CASTRANOVA: But not on fibrotic changes.

20 DR. ROGGLI: That's true.

21 DR. ABRAHAM: But they're not based on lung burden
22 data. They're based on exposure data.

23 DR. DODSON: Correct.

24 DR. ABRAHAM: To comment just a little bit more on
25 the fibers in the lung, several labs have shown for

1 chrysotile that bundles of fibrils can dissociate, and
2 they're splitting longitudinally. I don't know if you see
3 that in the lung with amphiboles, but I see amphibole
4 bundles in the lungs sometimes that have frayed ends, but
5 I don't know if that progresses during the time in the
6 lung or not. I can't tell from a single point.

7 DR. DODSON: That's a very important point with
8 chrysotile and bundles. Just add the one other variable
9 that that means not only do they have that potential in
10 the lung, but there's also a technique of preparative
11 involvement that is of grave concern. If you induce
12 traumatic processes to them and the more direct method of
13 manipulation, then you can create more of them because
14 they will dissociate through the processing, which has
15 nothing to do with how they were in the lung or -- should
16 we say also in the pleura, which is where meso occurs.

17 DR. CASTRANOVA: And that also reflects the in-vitro
18 dissolution data that chrysotile does have a measurable
19 dissolution while amphiboles don't in -- not in geologic
20 time.

21 DR. HOLGUIN: Do you have a comment?

22 MR. DEN: Yeah. Arnold Den, EPA, San Francisco.
23 Most of our studies involve sports activities, let's say,
24 in El Dorado or in CCMA. And we're making the assumption
25 that most of them will be mouth breathers, so they would

1 be inhaling, let's say, the amphiboles. Maybe thicker
2 fibers would get stilled down into the lung because
3 they're mouth breathers. And will those still stay there
4 over time? The thicker fibers. And they were amphiboles,
5 let's say, is the question.

6 DR. ROGGLI: I don't know that that's the case that
7 for mouth breathers you'll get more thicker fibers
8 deposited in the distal lung. It may be that the
9 bypassing of the nasal hairs, which you would get from
10 mouth breathing, simply means that those are going to be
11 deposited higher in the bronchial bifurcation trees and
12 then removed by the mucociliary escalator. I don't know
13 of any evidence that you'll get from mouth breathing of
14 thicker diameter fibers deposited in the peripheral lung.

15 MR. DEN: Okay. I raise that because the peer
16 consultation expert panel on the Berman-Crump method did
17 make that comment about mouth breathers and suggested that
18 the diameter be changed for the Berman-Crump method
19 because of that.

20 DR. ROGGLI: Well, of course, Berman and Crump is
21 looking not just what gets in the peripheral lung but what
22 gets deposited in the airways because of lung cancer risk.
23 And if you consider that, then you maybe get more
24 deposited in the bronchial tree, which then can migrate
25 across the epithelium and then cause damage which may

1 later lead to lung cancer at that site.

2 MR. DEN: Then the other question is we looked at
3 mostly young children. Are their deposition and their
4 retention going to be different than, let's say, an adult?

5 DR. CASTRANOVA: To answer your first question, there
6 are models for deposition curves for mouth breathing and
7 for respiratory rate. So you can get the particle
8 diameters at different areas of the lung and what the
9 deposition rate would be: mouth breather versus nonmouth
10 breather, rest versus exercise, that sort of thing.
11 That's available.

12 A child would have smaller airways, so the deposition
13 would be affected by the smaller airways.

14 DR. ROGGLI: Which way? More or less?

15 DR. CASTRANOVA: Well, you would have more deposition
16 in the conductant zone because it would trap the larger
17 particles.

18 DR. CARBONE: But if the data that Peter published
19 are correct that there is no difference in the incidence
20 of mesothelioma at least, regardless of when you start
21 your exposure, then all this difference account for
22 nothing biological.

23 DR. CASTRANOVA: I think you're right because the
24 fibers we're talking about are very thin, so their
25 aerodynamic diameter is very small, and so a change in the

1 conductant zone diameter wouldn't have much of an effect.

2 DR. HILLERDAL: The only thought that I would really
3 have on child exposures are from Turkey from those
4 villages and from other villages where you have endemic
5 exposure, and it seems that these people who are born in
6 those villages, they end up getting mesotheliomas when
7 they are about 50. So it doesn't seem that they get it
8 quicker than other people.

9 They have about the same latency time for their
10 changes as other people have. So I don't think there is
11 any fundamental difference in inhaling and retaining
12 asbestos fibers in small children.

13 DR. ROGGLI: I think one of the questions that I'll
14 just throw out some information about that it address is
15 that -- you might ask why is it that longer fibers are
16 retained and shorter fibers cleared more rapidly. And the
17 rapid clearance is probably macrophage-related clearance.
18 So what is it about long fibers that interfere with rapid
19 macrophage clearance?

20 And it's interesting. In some studies that one of
21 the people who worked in my lab, Pat Coin, did for both
22 chrysotile and for amphiboles, the clearance rate within
23 the parameters of our study for fibers that were greater
24 than about 16 microns in length was zero. It was
25 undetectable clearance rates.

1 Of course, if we follow chrysotile longer, we would
2 have seen the dissolution effect that occurred after that
3 period of time. But for the short period of time, you
4 can't show any clearance for the longer fibers. And I
5 suspect that what's going on there is the dimension of the
6 fibers because that size is similar to what we have
7 independently identified as the size of fiber that seems
8 to trigger the coating mechanism, which is, as discussed
9 yesterday, I believe around somewhere between 16 and 20
10 microns in length that triggers the coating mechanism.

11 And the -- our understanding of how that was -- that
12 was one of the questions addressed earlier this morning by
13 the ATSDR members of the mechanism of asbestos body
14 formation. That has to do with macrophages coating the
15 fibers, and it seems to be triggered when the macrophage
16 cannot completely phagocytize the fiber. In other words,
17 it's too long for the macrophage to encompass the entirety
18 of the fiber that triggers the coating process.

19 That may then theoretically -- and I don't know if
20 this has actually been studied -- inhibit macrophage
21 movement if they can't completely encompass the fiber, and
22 that may be one of the reasons that these long fibers are
23 cleared.

24 In terms of asbestos body formation, which was a
25 question earlier today, it turns out that we see asbestos

1 bodies showing up about three months after an exposure in
2 experimental animals. We believe it's about the same in
3 humans based on finding asbestos bodies in children's
4 lungs. And by six months, they're fully formed from an
5 exposure.

6 And although it's been pointed out here -- and I
7 think that we criticized using asbestos bodies because
8 they don't measure well chrysotile exposures and because
9 there's no predictable correlation with the fiber burden
10 for an individual patient. I think it's important to
11 point out that there are several studies from our
12 laboratory and others that show that in the population
13 basis that asbestos bodies correlate very well and
14 significantly with long amphibole fibers in the lung
15 tissue samples.

16 And that was shown also by Morgan and Holmes' study.
17 So that for a population -- even though you can't predict
18 what the fiber count is in an individual patient based on
19 the asbestos body counts because of the scatter of the
20 data for a population, you can say that asbestos body
21 counts correlate very well with the burden of long
22 amphibole fibers in the lung.

23 DR. CARBONE: Victor, where did you study? In what
24 model did you study the clearance of the long fibers? How
25 did you do that?

1 DR. ROGGLI: That was by inhalation studies. Pat
2 Coin did that by inhalation of chrysotile and by
3 inhalation of amosite, and the animals were sacrificed at
4 different periods of time and looked at the -- an absolute
5 calculation of the numbers of the various fiber sizes that
6 were present. And over time, the absolute numbers of the
7 fibers longer than 16 microns did not change.

8 DR. CARBONE: And these were in mice?

9 DR. ROGGLI: They were in rats, white rats.

10 DR. CASTRANOVA: It's very interesting that you came
11 up with 16 microns --

12 DR. ROGGLI: Yes.

13 DR. CASTRANOVA: -- in length. We did size-separated
14 fibers in rat macrophages in culture and showed that at 17
15 micrometers we got illustrative phagocytosis. So that's
16 amazingly good correlation.

17 DR. DYKEN: Do you think that length would hold for
18 humans as well?

19 DR. CASTRANOVA: Human macrophages are larger, and so
20 when we did it with human macrophages, it's more like 20
21 micrometers.

22 DR. ROGGLI: Which is about the size where you start
23 seeing intact asbestos products.

24 DR. DYKEN: Okay.

25 DR. GUNTER: It's sort of a silly analogy, but when

1 you started telling that story, I was imagining, like, an
2 inner tube, going down a river, where the river is fairly
3 narrow and you've got things hanging out of it, like your
4 feet hanging out, and banging into the sides. It would be
5 the exact same analogy is what you're saying.

6 DR. ROGGLI: I don't know if it's a physical or if
7 it's a functional effect that fibers sticking out of the
8 macrophage and its ability to complete its cytoplasm over
9 may trigger some functional effects on what the macrophage
10 can do. I don't know.

11 DR. CASTRANOVA: What it does is it inhibits the
12 ability of the macrophages to move. They can't deform the
13 membrane because their membrane's deformed by this long
14 fiber spearing.

15 DR. CARBONE: Well, what you can see sometimes is
16 spears of cells. It looks like a spear. It gets four or
17 five cells together, which is dangerous talk, the topic of
18 the length of the fibers, where I don't want to get in.
19 But certainly, the longer the fiber, the least likely it
20 is that this fiber is going to go to the pleura.

21 So this is something that has to be kept in mind
22 because we are talking about the toxicity, which is not
23 the same thing as carcinogenicity. And if this fiber has
24 to cause mesotheliomas, then how is it to get to the
25 pleura? And if this fiber is so long that it gets stuck

1 with the macrophages, it's going to be very unlikely that
2 these very long fibers are going to go to the pleura. So
3 without entering into the debate of chrysotile and
4 crocidolite -- God save me -- the fact is that these very
5 long fibers are unlikely to do the job.

6 DR. ROGGLI: Except that Boutin has shown that the
7 long fibers do, in fact, get to the pleura in hot spots
8 that correlate precisely with the location of early
9 mesothelioma, which is the stomata in the lower -- lower
10 and lateral parts of the parental pleura.

11 DR. CARBONE: Yeah. That's the only single paper
12 that I know that has done that, and some -- I mean,
13 obviously, these are interesting things to study, but
14 somebody should explain me how is it that this long fiber
15 cannot get out of the lung but can get to the pleura. I
16 mean, either it can't go anywhere or it can go everywhere.

17 DR. ROGGLI: They can get to the pleura. We've shown
18 that in studies where animals inhale crocidolite asbestos,
19 and within three weeks of an inhalation exposure, by
20 simply lavaging the pleural space, we found long
21 crocidolite fibers greater than 10 microns in length
22 already present within weeks of lavage.

23 DR. CARBONE: So they must get out too.

24 DR. ROGGLI: So they get through. They penetrate
25 right through the visceral pleura, and from there, it's

1 just simply a potential space between the visceral and
2 parental pleura.

3 DR. CARBONE: See, but then they should also get out.

4 DR. ROGGLI: Well, they go as far as they can, but
5 the mode of exit's from the parental pleuras through the
6 stomata of the lymphatics, and those stomata have a
7 diameter of about 5 microns. And so the longer and larger
8 the fiber, the more likely it is to be hung up in the
9 stomata.

10 DR. CARBONE: So you think that they get all the way
11 down and make kind of a mechanical passage into the pleura
12 and then get picked up into the lymphatics by macrophages;
13 right? Or by themselves?

14 DR. ROGGLI: Either way; probably by themselves, but
15 we don't know.

16 DR. CARBONE: By themselves because if they are
17 picked up by microphages, these microphages --

18 DR. ROGGLI: Can't go anywhere.

19 DR. CARBONE: -- wouldn't move; right? So they can't
20 go there.

21 DR. ROGGLI: Exactly; but the fibers -- I mean, the
22 point is the fibers do get there. They've been identified
23 in those locations by several studies, including Dr.
24 Dodson's.

25 DR. DODSON: We did not have as homogeneous

1 amphibole-exposed group as the one you referred to. In
2 his follow-up paper, in the correlation with changes in
3 those regions, cytologically did not determine there was a
4 relationship. They were present, but no correlation with,
5 as I understood it, with changes in the mesothelium. Is
6 that incorrect?

7 DR. ROGGLI: Well, yeah. That wasn't the purpose of
8 the study: to look for changes in mesothelium. They
9 didn't -- that would take a much longer progressive -- in
10 fact, you need to do that in animal studies if you were
11 going to try to --

12 DR. DODSON: I'm speaking of his second observation
13 where he did not correlate that with the potential site
14 for mesothelioma to development. Nevertheless, you are
15 totally correct that some longer fibers can reach those
16 sites.

17 In that case, that was with the predominant type of
18 fiber in the lung was. And we showed some, but very much
19 of a minority of the total burden, and they were pretty
20 unique because they were very thin, just as the short
21 fibers were thin.

22 DR. HOLGUIN: Any more comments?

23 (No audible response)

24 DR. HOLGUIN: Do we have time for another question
25 before?

1 DR. DYKEN: Yeah.

2 DR. HOLGUIN: Okay. I think this question has been
3 partly discussed at some level.

4 (Reading) "Would serum biomarkers be useful for
5 populations/communities exposed to asbestos and other
6 similar asbestiform fibers, particularly amphiboles, like
7 in Libby, Montana?"

8 DR. ROGGLI: I think the answer to that would require
9 a vote around the panel of yes or no.

10 DR. CASTRANOVA: Well, at this point in time, we
11 don't know what -- we don't know what cytokines or growth
12 factors to look at, so I think, as it came up before, it's
13 not ready for prime time to do a serum biomarker for
14 disease of asbestos.

15 That's why I keep bringing up if you're going to do
16 BAL, this is the time to do research to find out if there
17 would be one. So I think you ought to take that
18 advantage. But right now, I wouldn't know of a serum
19 biomarker that is ready for a screening at the moment.

20 DR. CARBONE: It depends what the question is that
21 you want to answer. I mean, that's the answer. It
22 depends on what you want to do. If you want to treat
23 patients, no. If you want to do research and you want to
24 develop data that they can become useful in the near
25 future, yes.

1 DR. WEISSMAN: And I think that's really the key.
2 That's the key point is if by useful, you mean, you know,
3 that you're doing research and you're developing knowledge
4 on how did the test perform, that's one thing.

5 If by useful, you mean assessing levels of exposure
6 in the population, you know, probably not. And then, you
7 know, with regard to osteopontin, you know, there's the
8 concern about the rather -- about it being unspecific and
9 having 14 percent of your population with the high level
10 and then the problem of knowing what to do with them.

11 DR. CARBONE: Yeah. But that's a single study of
12 which I was a co-author. So that needs to be verified,
13 and the specificity needs to be defined.

14 DR. WEISSMAN: And your point is well taken. I mean,
15 what we need to do is research to -- do research to better
16 understand these things.

17 DR. ROGGLI: And if you collect that data now, then
18 you'd have to have very careful informed consent of the
19 individuals to let them know that we're simply measuring
20 these levels, that there's a wide level of scatter in the
21 population. We don't know what it means, and we don't
22 recommend that you take any particular action based on any
23 particular finding.

24 DR. HOLGUIN: (Reading) "Would osteopontin be useful
25 as a marker of exposure in exposed communities, as a

1 research tool or to correlate with pleural disease absence
2 or presence?"

3 I guess this comes back to the same answer.

4 DR. CASTRANOVA: Same answer.

5 DR. ROGGLI: Good research question.

6 DR. CASTRANOVA: It is.

7 DR. ROGGLI: Find out what the answer is, but don't
8 promise any results to the people.

9 DR. HOLGUIN: I think we have time for one.

10 (Reading) "Please comment specifically on carbon
11 monoxide diffusing capacity as a clinically useful means
12 of evaluating restrictive disease."

13 DR. CARBONE: You know, when you talk about not
14 promising anything to people, I agree. But don't promise
15 anything to people whatever you do because then if you
16 find asbestos in the lung of somebody means nothing. The
17 likelihood that that person gets sick is nil and so on.

18 So none of the techniques that are going to detect
19 asbestos in somebody means anything, so the same informed
20 consent that you suggested to be done for osteopontin --
21 the same one should be done for asbestos determination
22 because, certainly, you don't want to do anything based on
23 the fact that somebody has some asbestos in his sputum.

24 So all this information allows you simply to
25 determine if a population has been exposed to asbestos.

1 Now, the osteopontin part is used as marker for exposure.
2 The mesothelin part is used mostly as a marker of disease,
3 and there I see your point in saying, "Let's not do a
4 thoracoscopy because you have a very high level of
5 mesothelin."

6 But when you're talking about the way that it was
7 phrased -- the osteopontin question and detecting asbestos
8 bodies, these are not done for diagnostics or for
9 therapeutic process. They're only done to identify
10 populations that we believe are exposed to asbestos.

11 DR. ROGGLI: I agree with you on that up to a point,
12 the difference being that the literature clearly states
13 that finding asbestos in bronchoalveolar lavage fluid is a
14 marker of exposure, not of disease. Harvey Pass' article
15 suggests if you have very high osteopontin levels, you
16 have an increased risk that you have the disease
17 mesothelioma. And so that is the difference, and I think
18 that that's what would have to be addressed in informed
19 consent.

20 DR. HOLGUIN: That's going to require a lengthy IRB
21 process.

22 DR. WEISSMAN: Diffusing capacity -- it's a good
23 test.

24 DR. HOLGUIN: Diffusing capacity; yeah.

25 DR. WEISSMAN: It's simple to perform. It's

1 noninvasive. In a number of studies, it's correlated very
2 well with early findings of fibrosis by high-resolution
3 CT. In fact, DLCO, in some studies, has been associated
4 with exposure to asbestos even without radiologic changes.

5 And another issue with DLCO is that in one large
6 longitudinal study in Australia, a decline
7 over time in asbestos-exposed individuals was
8 demonstrated. SO DLCO is a really useful part of the
9 clinical tool chest. The one thing I would say about DLCO
10 is that it's technically more complex than spirometry.
11 And from the standpoint of standardizing the instruments
12 that are used to do DLCO, the ATS has recommendations in
13 terms of, you know, having a panel of people with known
14 DLCOs that you routinely, you know, run through your
15 instrument to, you know, make sure that your instrument
16 stays stable over time.

17 There's another instrument that's available from Hans
18 Rudolph, which is a DLCO calibrator. That's the only
19 external calibration machine that I know of that you could
20 apply to making sure that your instruments are giving
21 accurate responses and that there's not drift over time.
22 And I think in a big study that is something that one
23 would have to give a lot of attention to is accuracy of
24 the test.

25 The other issue is prediction equations for DLCO.

1 Prediction equations for DLCO aren't based on as large
2 populations as the prediction equations for spirometry, so
3 the prediction equations for spirometry are much better
4 established and, for DLCO, you know, maybe not quite as
5 good, not based on as big populations. So following
6 people over time in DLCO, that doesn't really impact on.
7 But interpreting normal, you know, abnormal, it's not
8 quite as robust a thing as for spirometry, but it's an
9 excellent test.

10 DR. CASTRANOVA: The only caution with DLCO would be
11 is that you would expect a decrease in DLCO with
12 emphysema, which is an obstructive disease and not a
13 restrictive disease. So you would have to have smoking
14 history to make sure that that might not be a confounder.

15 DR. WEISSMAN: Sure.

16 DR. ROGGLI: Yeah. I agree with that point. You
17 have to look at what is DLCO measuring. It's measuring
18 diffusion capacity for carbon monoxide, and there are a
19 number of determinants of that, which include the blood
20 volume of individuals, so you have to correct for
21 hematocrit. There are corrections, prediction equations
22 for the age, sex, height, and weight of the individual.

23 It also measures the thickness of the alveolar
24 membrane and how far the gas has to diffuse to get from
25 the alveolar space to the capillaries, and that's where

1 interstitial lung disease comes in, and it's a good, early
2 detector for that. And it's also related to the cross-
3 section of the -- cross-sectional area of the blood
4 supply, the capillary bed in the lung. And that's what's
5 destroyed in emphysema.

6 So as you destroy your cross-sectional area of the
7 capillary bed, if a proportional amount of emphysema is
8 present, you're going to reduce the DLCO, and so that has
9 to be kept in mind: exactly what you're measuring and what
10 other diseases can confound the finding of the results.

11 DR. HOLGUIN: One problem that I see is feasibility
12 in the field because you need a tank of carbon monoxide
13 and helium, and so you have to have a lab set up. It's
14 not something you can take on the field with you. It's
15 complicated to do on large epidemiological scale studies,
16 I guess.

17 DR. WEISSMAN: I mean, there are relatively -- you
18 know, the current modern machines are small enough that
19 they could easily be put into a van or something like
20 that, but it's not a trivial thing. I guess one other
21 correction, in addition to hemoglobin, that's useful is
22 carbon monoxide back pressure, you know, and there are
23 corrections that are available for that too, especially if
24 you're looking at people that are smoking.

25 DR. ROGGLI: What does that correlate with? Does

1 that correlate with the loss of the capillary bed cross-
2 sectional area?

3 DR. WEISSMAN: Well, if you have a hemoglobin that's
4 already bound up with carbon monoxide, then you'll
5 obviously have less uptake.

6 DR. HOLGUIN: I mean, we do a ten-second DLCO
7 maneuver which is very standardized and is very stable, so
8 it gives good results. Then you have to take the absolute
9 diffusion capacity and adjust it for alveolar volume. You
10 get interesting results.

11 DR. WEISSMAN: And probably from the standpoint of,
12 you know, the unadjusted DLCO versus the KCO, the
13 unadjusted DLCO is probably the number that one would
14 actually want to use in terms of looking at the total
15 ability of the lung, you know, to take out carbon monoxide
16 as a measure of gas exchange. The KCO, there are issues
17 with that.

18 DR. ROGGLI: And then once you've corrected for all
19 of that and decided that you're dealing with a restrictive
20 disease, then you've got to decide whether it's asbestos
21 or one of the hundred other fibrotic lung disorders that
22 can cause restriction.

23 DR. HOLGUIN: It's not specific at all.

24 DR. ROGGLI: It's not specific, so you have to keep
25 all those things in mind in using it. If you've got a

1 heavily exposed population of workers with asbestos, then
2 the pretest probability that you're dealing with
3 asbestosis goes up and the usefulness of the carbon
4 monoxide diffusing capacity for detecting disease goes up
5 as well. But if you're dealing with a population that has
6 low-dose exposure, a very low likelihood of having
7 asbestosis, then there's going to be so much noise that
8 the diffusion capacity is not going to be helpful, as
9 would be the case for any other pulmonary function test.

10 DR. KAPIK: Just a follow-up question for David. The
11 back pressure issue, the CL binding to hemoglobin is
12 related primarily to smoking?

13 DR. WEISSMAN: Well, practically, what you do is you
14 measure exhaled CO on an individual before doing your
15 DLCO, and then there are correction factors that allow you
16 to -- in the same way that you can correct for hemoglobin,
17 you're correcting for the presence -- the fact that some
18 of your hemoglobin is already bound up with carbon
19 monoxide is going to decrease the amount there in uptake
20 that are taken up from the inhaled breath.

21 DR. CASTRANOVA: That's another possibility. If this
22 person were a garage mechanic, it's possible he can have
23 high blood CO from that as well. So you would need to --
24 and it's because the equations for calculating the DLCO
25 assume that the blood CO is essentially zero.

1 DR. HOLGUIN: I think we're going to break for lunch
2 now, and we're going to come back, and there's some
3 questions that would like to be addressed as well as the
4 final conclusions and key recommendations. So we'll see
5 each other at 1:30.

6 (Whereupon, a recess of approximately 127 minutes was
7 taken.)

8 DR. HOLGUIN: Let's get started because people have
9 to go to the airport. For the remaining of the session,
10 what we'll do is ATSDR will give a brief summary, a wrap-
11 up, regarding the discussion of the CT scan earlier today.
12 And then each member of the panel will have the
13 opportunity to give their overall wrap-up of key
14 recommendations, and then I think Dr. Carbone -- or
15 Carbone will give a brief presentation of some slides of
16 his work in Turkey.

17 DR. DYKEN: That will be after the end of the panel.

18 DR. HOLGUIN: At the end of the panel.

19 DR. DYKEN: But we'll try to finish early enough so
20 that everybody will have time.

21 DR. HOLGUIN: All right. So the mike goes back to
22 you.

23 DR. KAPIL: I think -- thank you. I think we've
24 probably already -- repeat this pretty much, but I'll just
25 briefly summarize what I heard at least about the CT scan

1 discussion.

2 We talked about excellent sensitivity and actually
3 good specificity as well. We talked about the ability to
4 detect pleural changes in many cases at a very early
5 stage. I think there was some concern about what those
6 early, early pleural changes mean, especially when not
7 correlated with spirometric findings and not in
8 conjunction with other changes on the CT scan. And there
9 was, I think, some suggestion that those may or may not be
10 clinically significant changes and may need to be followed
11 over time.

12 There was also discussion of some of the sort of the
13 downside of using CT especially in screening populations.
14 The issues that were discussed there primarily were
15 potential increased radiation exposure through the
16 technique and then also the issue of very high
17 sensitivity, meaning the potential for false-positive
18 results and the implications for those -- those positive
19 findings. In some cases, not really false positives, but
20 they're positive findings. But they need further
21 evaluation, such as biopsies or thoracoscopy, perhaps even
22 other more significant procedures and the related risks of
23 those procedures.

24 So I think that's sort of in a nutshell what I heard
25 about CT scanning. If others on the panel feel that I've

1 missed something important related to CT, please jump in
2 because we want to try to capture the essence of the
3 discussion.

4 (No audible response)

5 DR. HOLGUIN: So I guess we will ask each member of
6 the panel to provide a brief comment on the key
7 recommendations or a wrap-up of the session. I'm going to
8 start on my right with Dr. Jerrold Abraham.

9 DR. ABRAHAM: [Off microphone]

10 THE COURT REPORTER: Microphone, please.

11 DR. ABRAHAM: My microphone? Okay.

12 My comments will be very brief. Basically, I thought
13 the one thing missing here is putting something on the
14 record as to what to give to the community, how each
15 member of the panel feels. And I'm not asking anybody to
16 say things exactly the way I do, but I would just say that
17 based on the information I have about the occurrence of
18 amphibole asbestos fibers in the areas around El Dorado
19 and based on the results of the EPA sampling and based on
20 the results of the dog- and cat-tissue sampling we've
21 done, it's convincing to me that there's more exposure
22 there than there would otherwise be, and it's putting
23 people at increased risk that we can't exactly quantify:
24 risk of long-term -- risk for asbestos-related disease
25 such as mesothelioma.

1 And that if I had a choice of buying a house in that
2 area versus one where there wasn't that exposure, it would
3 be a very easy decision for me, all other things being
4 equal: price and convenience to where I worked. That's
5 all I really wanted to say.

6 DR. HOLGUIN: Thank you. Dr. Carbone.

7 DR. CARBONE: I was not ready for this one. I think
8 that the community that you have described, the Libby,
9 Montana, one and the few other ones that I can't remember
10 the name that you have described here in the United States
11 where there is a higher level of exposure and so there is
12 a higher risk that they can develop mesothelioma possibly
13 or other asbestos-related disease.

14 You offered us the opportunity to do something, not
15 only about these communities, but more in general to
16 understand the phenomena that we have under our eyes
17 because the fact is that mesothelioma -- that's, for
18 example, continue to increase.

19 I just remembered that it was in 1994 that I was in
20 Joe Framini's [phonetic] office and he showed me that the
21 peak of mesothelioma had already passed and was going
22 down. And by the 2000, he showed me this curve was going
23 down definitely because the exposure to asbestos
24 diminished. And the fact is that I keep seeing all these
25 papers where these peaks go down, but the peaks don't.

1 So we have a high incidence of mesothelioma, and
2 something needs to be done about that. And therefore, I
3 think that these communities that you described give us
4 the opportunity not only to help the people in these
5 community but also to use what we learn by studying this
6 community for the overall program of mesothelioma. That
7 is a serious problem.

8 As I suggested before, it is important not to focus
9 only on the problems. It's important to recognize the
10 problems that we have, but then we have to see what we can
11 do to try to overcome those problems. And so if we can
12 synergize different techniques, as the ones that have been
13 described today, to get a better answer to the question, I
14 think that that's the way that we should do.

15 And novel techniques, of course, always come up with
16 a lot of uncertainties, but these communities give us the
17 possibility to verify the validity of these new
18 techniques. And if, in fact, they are valid, they can
19 have a higher and general impact on the entire population
20 in the United States, not just in the community that we
21 are studying.

22 My experience with the community that I study in
23 Turkey is that if you want to gain their support and if
24 you want to work with them, you need to offer them
25 something. And so I think that it would be very important

1 to develop in addition to detection strategies in which
2 you simply tell people, yes, you have been exposed, which
3 is something that they usually -- the human being is not
4 particularly interested. He wants to know what are you
5 going to do about it now.

6 And so that we -- together with the detection
7 strategies that we are trying to improve, we also plan to
8 offer -- to think what we can offer these people, if we
9 can offer something. I think we can. We have discussed
10 the role of chronic inflammation in promoting asbestos-
11 related diseases, but I think that is very important to go
12 in parallel and offer then some clinical trials,
13 experimental clinical trials, that, of course, should not
14 be toxic to see whether we can diminish the possible
15 increase in disease that they have.

16 If you parallel the two things, then I think that it
17 is going to be much easier to work with these communities
18 and we will also will learn a lot. And what we're going
19 to learn is not going to be limited to the relatively
20 small community of Libby, Montana, but will have a general
21 impact on the entire population of the United States and
22 on this increasing problem of mesothelioma.

23 DR. CASTRANOVA: My comment is somewhat similar, in
24 that you were talking about biomarkers of exposure. And
25 there was some interest in looking at fiber counts in

1 accident victims, looking at BAL to look at fiber counts.
2 What I would encourage is -- we have a research
3 opportunity to gain a lot of knowledge -- that while you
4 have the tissue sample to do the fiber counts also look at
5 maybe cytokine expression, RT-PCR for cytokine message,
6 et cetera. And when you have the BAL, also look at
7 cytokine expression for inflammatory factors, growth
8 factors, et cetera. And this may -- it may not pan out,
9 but it may lead to a biomarker of effect that may be
10 elevated in the serum, and so you have learned something
11 down the road.

12 DR. HOLGUIN: Thank you.

13 DR. DODSON: I guess the -- what has concerned me
14 appreciably during these discussions is we've had some, I
15 think, in-detail concepts presented by various assessment
16 mechanisms. They, in point of fact, in many instances,
17 require exposure and don't speak to prevention, and I'm
18 not sure that I have a comfort zone that once a number of
19 fibers have been defined in whatever we define it in that
20 we've talked about at this stage what intervention might
21 be provided or what offering we would have for the people
22 that may have had such an exposure.

23 To me, as a scientist, that's obviously very
24 frustrating. But I do appreciate the opportunity to be on
25 this panel and the privilege to be with this distinguished

1 panel in discussing these issues.

2 DR. HOLGUIN: Thank you.

3 DR. GUNTER: I'd like to echo that feeling of really
4 appreciating being asked to serve on this panel. I think
5 many times we might feel frustrated about what does or
6 doesn't -- doesn't get accomplished in something like
7 this. We realize we all get to meet each other and
8 there's possible research interest that we can all have in
9 the future to answer some of these questions. So my
10 knowledge in this biomarker thing has grown considerably,
11 seeing as though I didn't know much about it to start
12 with.

13 But my contribution to this, I hope, can be somewhat
14 in the mineralogical end. Hopefully, through some of the
15 comments I've made and some of the work we're doing, some
16 of you might realize that there may be a more complicated
17 mineral reactions in the lung, that certain minerals may
18 dissolve. Certain minerals may transform to others, and
19 that might explain some of these diseases. It might very
20 well have nothing to do with it, but it's an area to look
21 in.

22 I'm interested in trying to bring some of the
23 terminology from the mineralogy field more into these
24 fields with the terms of calling some of these materials
25 particles and then the discussion of asbestiform versus

1 nonasbestiform. Defining them may be better on shapes;
2 again, trying to get away from some of the regulatory
3 language maybe, to get more into the
4 mineralogical/morphological definitions, which might help
5 us find some of these causes of disease in these.

6 As you know, I despise the word that I can't even say
7 -- naturally occurring whatever it is. And I would like
8 to see that -- I think I probably said that enough. But I
9 would like to see it called environmental amphiboles --
10 I've said that enough? Okay -- free-range amphiboles or
11 whatever because I think it really confuses the public.

12 I guess in the end, as I've said several times today,
13 my whole theme in life is the only thing we'll ever do is
14 worthwhile is to help other people. That's my sort of --
15 what I live by. And I'm afraid many times we hurt other
16 people when we start using some of these terms that may
17 make sense to us but not to the public. So I'm really
18 concerned about the public risk and the fear we put into
19 the public on some of these things when we use certain
20 words. I'd like to try to be careful on that.

21 Again, how can we intervene to help in some of these
22 things? I think possibly in some of the chrysotile
23 exposures in America, as I've already said, comparing this
24 to some of the Quebec, showing people what life is like in
25 Quebec where these mines are and looking to some of the

1 diseases there. As you mentioned, the exposure rates are
2 ten times as high, but possibly the diseases don't occur
3 there; again, maybe reduce some of the fears.

4 I think also the thing that's come around in this is
5 that exposure and possibly getting an idea of air
6 sampling, what's in the air, and then trying to determine
7 some risks from that is a meaningful thing to do.

8 And again, I'd just like to thank everyone because I
9 most certainly have enjoyed meeting you all and having
10 some of the discussions and look forward to working with
11 you all in the future.

12 DR. HOLGUIN: Thank you. Dr. Hillerdal.

13 DR. HILLERDAL: I don't know what more to add to
14 this. I think it's -- the Libby group is one thing, and I
15 think that is a big problem, and the El Dorado thing is
16 also another thing. And I think the El Dorado is a big
17 problem because, for sure, there is exposure there, and we
18 don't know what that means, but that it does mean an
19 increased risk of -- mainly of mesothelioma because I
20 don't think the exposure is anywhere near high enough to
21 become -- to give asbestosis or anything like that.

22 And it's also very strange when you look on the
23 United States a few years ago when you had this big
24 fighting about asbestos in schools and all those millions
25 of dollars that were put down to tear down asbestos in

1 schools with the risks that were much lower than I think
2 they are here in El Dorado.

3 So the problem is really to somehow get this
4 information to the people living in these areas and how to
5 diminish those risks. Of course, we can go on. We can
6 make lavage. I think that's very good. That should prove
7 even more that people really are exposed. Screening the
8 El Dorado people now, today, I think is not going to give
9 any good results. It could actually -- because the
10 latency time is so small still, so you wouldn't find very
11 much and that might even work in the other direction.
12 People go around and they have a normal chest x-ray and
13 they say, "So what? This was nothing anyway, so we don't
14 have to do anything about it." So I think you have to be
15 very careful there. It's a big information gap.

16 Having said that, I think it's still possible, you
17 know, by paving roads and by really marking hot spots and
18 maybe stopping exposure there by planting grass and trees
19 and whatever. I think that's the way we have to go. But
20 I think it's very difficult. This is psychology more than
21 science really.

22 DR. HOLGUIN: Thank you. Dr. Roggli.

23 DR. ROGGLI: I also appreciate the opportunity of
24 being here and being invited for this presentation.

25 I believe that the questions that we've been

1 addressing, trying to answer the last couple of days have
2 basically been looked at. How do you approach these
3 communities for which there is a potential for
4 environmental exposure? And the paradigm which has been
5 described to us of measurements that are taken in the
6 environment, as the EPA and ATSDR have done, I think is a
7 very important and a valid one to do, to look at what is
8 measured in the air and what is measured in these areas.

9 What you do beyond that, I think, depends on what you
10 find and on looking for two things. One, can you further
11 validate exposure? And two, what are you looking for in
12 terms of disease? And in circumstances where you do find
13 that there is a level of exposure in the environment that
14 for your agency you believe is a concern, then you might
15 find further validation of exposure by looking at medical
16 examiner autopsy cases of young individuals from those
17 areas and by looking at bronchoalveolar lavage in healthy
18 volunteers. Again, that would be further confirmation of
19 a significant exposure.

20 In those communities where there has been long enough
21 duration of exposure that there is a potential for
22 asbestos disease to be manifested, in such communities, it
23 might be then worthwhile to add on screening of chest
24 x-rays to look for evidence of an effect of the asbestos
25 exposure and in some cases perhaps do CT scanning, not, I

1 don't think, as a screening procedure, but as an
2 additional procedure.

3 And perhaps I'm less enthusiastic about doing
4 spirometry, but that might also be useful at least in
5 terms of a baseline in those situations.

6 DR. HOLGUIN: Thank you. Dr. Weissman.

7 DR. WEISSMAN: Well, once again, I'd like to echo
8 what everyone else has said and thank ATSDR for inviting
9 me to come here and participate in the panel. I really
10 learned a lot myself in terms of the discussions that
11 we've had, and I've appreciated the opportunity.

12 And I've really come to appreciate the challenge that
13 ATSDR and EPA face in dealing with a situation where
14 there's exposed individuals who are at risk for a disease
15 which has a very long latency and those people have
16 concerns about what their risks are.

17 I think that one of the most important concerns
18 though is the one that was raised by Dr. Dodson, which is
19 how can we take our uncertainty about what to do for
20 primary prevention and change it into a situation where
21 there is greater certainty about what to do for primary
22 prevention. And I think that's where working with
23 biological samples to confirm exposures to a greater
24 degree can be helpful in terms of helping people have
25 greater certainty that actions to -- primary actions to

1 reduce exposures are useful.

2 So I do think that even though by measuring exposures
3 in things like lavage and sputum -- for those individuals,
4 we're talking about secondary prevention because they're
5 already exposed. That can feed back and help motivate
6 primary prevention, depending upon what the results are.

7 So I think this is all very challenging. I think
8 there are specific things that can be done. A lot of
9 careful thought has to go into study design and into doing
10 studies that will translate into greater certainty about
11 how to do prevention.

12 DR. HOLGUIN: Thank you to all the panel members.
13 John, I don't know.

14 DR. FORRESTER: I would like to thank all the
15 panelists. We're in awe of the knowledge in this room and
16 very pleased to have the opportunity to have had you here.
17 It makes us even understand more how difficult our job is
18 and all the knowledge we need to do to make the proper
19 decisions, and it is -- I have learned a lot today. This
20 has been a very profitable two days this year, so I'm very
21 pleased to have been here.

22 What happens next? The transcript -- there will be a
23 transcript of the proceedings, and there also will be a
24 final report. The report should be generated in the next
25 three or four weeks. The first review will be by the

1 ATSDR El Dorado team and EPA to look at the statements.
2 And then there will be a document for the panelists to
3 review, and then we will produce a final report that will
4 be available for the public.

5 And it will probably be published on our Web site as
6 well so it has national access. As to the El Dorado
7 community, we plan a special session where we go out to
8 them and present the report and the findings. It would've
9 been very nice to have this in El Dorado, but it was so
10 expensive to get this large group of people there that we
11 made it to fit the money we had for the panel. But we
12 really owe it to the El Dorado community to come back and
13 to talk to them about the findings of this panel, so we
14 will be doing that as well.

15 Furthermore, we will continue down our road to
16 address the health concerns at El Dorado. We have some
17 more consultative work to do on the air samples in the
18 greater El Dorado County. We're looking at the
19 feasibility of certain health studies and follow-up public
20 health actions. And as you heard from the gentleman from
21 Georgia today, this won't be the only place in the United
22 States that we will get petitioned to assist.

23 So as an agency, we need to look at a broader
24 perspective on how we're going to address these exposures
25 to -- what kind of asbestos? Not naturally occurring.

1 What do you want me to call it?

2 DR. GUNTER: Free range. Noncommercial is my
3 favorite.

4 (Indistinguishable and overlapping words from
5 panelists and audience members)

6 DR. FORRESTER: Free-range asbestos. So again, thank
7 you very much for your participation, and we're going to
8 formally adjourn the meeting. I'd also like to thank
9 Fernando for being our moderator (applause). He did a
10 great job. Thank you.

11 DR. HOLGUIN: I enjoyed it. Thank you.

12 DR. FORRESTER: We have one more common from the
13 panel, or do we have any more comments from the panel?
14 Feel free.

15 DR. HOLGUIN: Go ahead.

16 DR. ROGGLI: One additional comment based on your
17 summary is that there has been a lot of information
18 discussed and presented here in the last couple of days.
19 I can't speak for the entire panel, but for myself, I'm
20 sure that additional questions among ATSDR and maybe even
21 EPA members may occur as time goes on and they have time
22 to think about what we've talked about and processed here.
23 So for myself, I hope that either members of the EPA or
24 ATSDR will feel free to contact me to get additional
25 comments about questions that may arise after this

1 meeting.

2 DR. HOLGUIN: Thank you.

3 DR. FORRESTER: Thank you very much.

4 Okay. With that, we're going to formally adjourn the
5 meeting.

6 (Whereupon, the proceeding was adjourned at
7 approximately 2:26 p.m.)

D I S C L O S U R E

STATE OF GEORGIA)

COUNTY OF COBB)

Pursuant to Article 8.B. of the Rules and Regulations of the Board of Court Reporting of the Judicial Council of Georgia, I make the following disclosure:

I am a Georgia Certified Court Reporter. I am here as a representative of Nancy Lee and Associates, who was contacted by the offices of to provide court reporting services for this proceeding. I will not be taking this proceeding under any contract that is prohibited by O.C.G.A. 1514-37 (a)(b).

I have no contract/agreement to provide court reporting services with any party, any counsel, or any reporter or reporting agency from whom a referral might have been made to cover this proceeding. I will charge the usual and customary rates to all parties, and a financial discount will not be given to any party.

DATED: May 10, 2006.

DIANE GAFFOGLIO, CCR, CVR-CM
Nationally Certified Merit Reporter
Certificate No. B-2372

NANCY LEE & ASSOCIATES

C E R T I F I C A T E

STATE OF GEORGIA)

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.

DIANE GAFFOGLIO, CCR, CVR-CM
Nationally Certified Merit Reporter
Certificate No. B-2372

NANCY LEE & ASSOCIATES