MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

SOUTH SAN FRANCISCO CONFERENCE CENTER

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JAMES F. PETERS, CSR, RPR
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD

Mr. Jim Aguila, Manager, Substance Evaluation Section

Mr. Lynton Baker, ARB, Air Pollution Specialist

Mr. Jim Behrmann, Office of Health Advisor

Mr. Robert Krieger, Air Pollution Specialist

Mr. Peter Mathews, Office of Health Advisor

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. George Alexeeff, Deputy Director, Scientific Affairs

Dr. James Collins, OEHHA, Staff Toxicologist

Dr. Melanie Marty, OEHHA, Chief, Air Toxicology and Epidemiology Section

Dr. Mark Miller, OEHHA

Dr. Andy Salmon, Chief, Air Risk Assessment Unit

Dr. Bruce S. Winder, OEHHA, Associate Toxicologist

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION

Ms. Mary-Ann Warmerdam, Director, DPA

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PROCEEDINGS

CHAIRPERSON FROINES: We can officially open the November 30th, 2004, Scientific Review Panel meeting.

And at the outset I want to make two brief announcements. One is, when traffic permits the new Director of the Department of Pesticide Regulation is going to attend our meeting. And I'm going to introduce her and she's going to make a couple of remarks. So since she's had traffic problems coming down from Sacramento, she's running a little late.

So we'll stop, Melanie, the silica presentation -- presumably she'll be here during the discussion during that -- and give her chance a to say hello to the panel.

So that's very nice gesture on her part to come to this meeting even though we're not taking up a DPR pesticide.

The second announcement is -- and her name, by the way, is Mary-Ann Warmerdam. And so -- but we'll introduce her when she arrives.

The second item is, we now have for the first time in a few years -- and Peter or Jim probably knows how long it's been. But for the first time in a few years we have a complete panel. There are two members of the panel who are not here today, Gary Friedman and Roger Atkinson.

But our new member of the panel, who we would like to welcome is Dr. Charles Plopper from the University of California at Davis.

And so I think it might be useful if we just went around the room and each person introduce themselves to Charlie and said where you are from.

PANEL MEMBER BLANC: Could we just Go around the table? Would that be okay?

CHAIRPERSON FROINES: That's what we're doing.

PANEL MEMBER BLANC: Instead of the whole room.

CHAIRPERSON FROINES: Did I a say the room?

(Laughter.)

CHAIRPERSON FROINES: No, the room can relax.

(Laughter.)

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Charlie knows me. USC. I studied carcinogenesis and mutogenesis. We also went through similar branches of the Army together a long time ago, right? And have sat on review panels together.

PANEL MEMBER GLANTZ: I'm Stan Glantz. I'm a Professor of Medicine at UCSF. And I'm in the Cardiology Division and do a lot of work on tobacco.

PANEL MEMBER HAMMOND: I'm Kathy Hammond at University of California Berkeley, School of Public Health, Environmental Health Division. And my research is

particularly focused on exposure assessment -- epidemiologic studies.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: Craig Byus, University of California Riverside, Biomedical Sciences Program, work on cancer-related change expression.

PANEL MEMBER BLANC: Paul Blanc, UCSF, Occupational and Environmental Medicine.

CHAIRPERSON FROINES: Roger, as you probably know, is an atmospheric chemist. And Gary Friedman is of course our epidemiologist.

So that we have a full panel. And I think it's in some respects the best panel we've ever had. Not taking away from any previous incumbents.

So the first item on the agenda, unless somebody has something else, is the continuation of the discussion of the toxicity and chronic reference exposure level for respirable crystalline silica.

And, Melanie, are you going to make a presentation?

(Thereupon an overhead presentation was Presented as follows.)

SUPERVISING TOXICOLOGIST MARTY: Yeah, I'll just introduce -- Jim Collins will make the presentation. But just a couple introductory remarks.

Today we're going to review the changes made to the chronic reference exposure level in response to the Panel comments.

The Panel reviewed and discussed the crystalline silica chronic REL on the May 19th meeting. And there were a number of comments made by the Panel regarding the percent of dust that was crystalline silica in the epidemiologic studies and also the particulate matter fraction to which the REL should apply.

So with that I'm just going to hand it over to Jim.

DR. COLLINS: Next slide.

CHAIRPERSON FROINES: Jim, before you get started.

Charlie, just for your information, this chemical has two lead persons that took responsibility for working with the agency to try and ensure the best product as the document comes to the panel. And the lead for silica was Paul Blanc and Kathy Hammond. And in general we have historically always identified lead persons on a particular chemical. So when the -- I'm sorry. I apologize. So when the presentation is finished, Paul and Kathy will be the first two people to comment on the silica document. And then we basically go around the room and hear from each panel member.

DR. COLLINS: Okay. I'm Jim Collins. I'm a toxicologist with the Air Section of the OEHHA.

The silica chronic REL was discussed at the may 19th meeting. We used a standard benchmark concentration with USEPA BMDS software. We used a well conducted epidemiology study of white gold miners in South Africa conducted by Hnizdo and Sluis-Cremer. And our chronic REL is supported by several other studies of silicosis: In South Dakota gold miners by Steenland and Brown; in diatomaceous earth workers by Hughes, Checkoway and others; and Chinese tin miners by Chen, et al., with assistance from NIOSH.

Next slide please.

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DR. COLLINS: This study was published in 1993. It consisted of 2,235 white South African gold miners who were exposed in their work place. Three hundred thirteen of the minors had silicosis, that is, a disease of the respiratory system as then ILO classification of 1 over 1, which is definite silicosis.

Go to the next slide and we'll come back to this.

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DR. COLLINS: Here is a plot of the incidence data, the dose of the cumulative dust exposure of the miners on the X axis, and on the Y axis is the fraction of

the miners affected with silicosis.

Go back now.

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DR. COLLINS: From using the probit model with the log dose of the concentration, we obtained a BMC01, that is, the lower bound expected to cause 1 percent incidence of silicosis, 2.1 milligrams per cubic meter-years of cumulative dust exposure, which is equivalent to .636 milligrams per cubic meter-year of silica. That BMC is basically at the same level as the low -- as the NOAEL observed in the study. These miners were exposed eight hours per day roughly, five days a week. We assume they took in half their air concentration while they were working. The average exposure was 24 years. The range was from 10 to 39 years.

Okay. Next slide.

This is the plot. And then the next slide.

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DR. COLLINS: From this 636 microgram per cubic meter-year average exposure, we divided by 24 years, the average time of exposure, and we came up with a number of 26.5 micrograms per cubic meter as the average worker exposure. And this is equivalent to a continuous environmental exposure of 8.75 micrograms per cubic meter.

We then added several uncertainty factors. We

did not need a LOAEL UF because you don't need one in the BMC approach. We did not need a subchronic uncertainty factor because the chronic exposure of 10 -- of 39 years. We did not need an interspecies uncertainty factor because we were looking at humans.

We did insert an intraspecies factor of 3 because although a large number of men were studied and some of them would be sensitive, there were no women or children exposed. So we put in an intraspecies uncertainty factor of 3, which means the total uncertainty factor was 3.

And the chronic REL, 3 micrograms per cubic meter of respirable crystalline silica.

And whereas previously we included that as the PM10 fraction based on panel comments, it's now -- the occupational standard is measured by NIOSH, and the NIOSH method depends on the ACGIH.

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DR. COLLINS: So one of the major comments of the panel was that we should use the respirable silica particle size as defined occupationally. And in response we did that. We changed the document and the proposed REL were changed to reflect that comment.

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DR. COLLINS: The second comment, Dr. Blanc asked us to include additional studies on slate workers in Wales. We did that, Glover, et al., 1980. We also found data on slate pencil workers in India; two references on that. And it was suggested that we remove the study of coal workers because they had very high exposures, and it was at least relevant to the REL.

We made those changes. We also added a study of black South African gold mine workers. The blacks actually make up a majority of the workers in the gold mines. That study was published since the last meeting. So we included that study as well as an earlier study doing autopsies of black gold miners.

Next slide please.

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DR. COLLINS: There were a variety of Editorial changes and clarifications that were made. And if they were made too tersely, it was probably my fault. If they were made extensively, it was due to Andy's work.

Next slide please.

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DR. COLLINS: The final comment that we addressed was that we further investigate the issue about silica content of the dust in the study by Hnizdo and Sluis-Cremer raised in the comments by Gibbs and the

American Chemical Council.

Next slide.

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DR. COLLINS: Basically the comment is the silica content of acid-washed mine dust is 54 percent, not 30 percent.

And quoting from Gibbs' -- Du Toit's 2002 paper: "With many uncertainties we estimate that the quartz exposures of South African miners derived from past theoretically based conversions from particle number to respirable mass underestimate the actual quartz exposures by a factor of about 2."

Next slide please.

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DR. COLLINS: We reviewed the independent reporting of the underlying data by Page-Shipp and Harris. Page-Shipp and Harris basically published Beadle, who did most of the surveying. After Beadle died, Page-Shipp and Harris went over his work. An analysis by OEHHA staff, in this case Dr. Salmon, indicated that Hnizdo and Sluis-Cremer used the correct silica content of 30 percent, despite a confusing, in fact erroneous, statement in footnote to Table 2 of their paper.

We sent our analysis to Hnizdo, and she agreed that our analysis was clear to her and she thought she

agreed with it.

These calculations are now displayed in Table 18 of the chronic REL summary.

--o0o--

DR. COLLINS: Our next step, we need to be sure we've addressed the Panel's comments, respond to any further comments. And then after the panel approval, the OEHHA director will adopt the chronic REL for use in Hot Spots risk assessments.

That's the end of our presentation.

CHAIRPERSON FROINES: Okay. Thank you.

Paul.

PANEL MEMBER BLANC: There was a question that I had at the previous meeting which had some bearing on the mathematical calculations. And that's the presumption that even white miners in South Africa in the time period studied would have worked eight-hour shifts only five days a week. Did you --

DR. COLLINS: If you go to the -- is it Table 19 now? Let me see.

Yeah, do we have a -- it's in the text, Table 19. I'm sorry. Table 19 of our revised document shows in -- I don't know if we have an overhead projector.

SUPERVISING TOXICOLOGIST MARTY: We do.

DR. COLLINS: Oh, okay.

It's now Table 19 of the document. If you go to the first line in that, it shows that different people had different shift hours. And so that has been accounted for, we think.

PANEL MEMBER BLANC: And that was five days a week? They had two days off in South Africa?

DR. COLLINS: As far as we know, based on discussing this with Hnizdo. We showed her our analysis, and she --

PANEL MEMBER BLANC: Can you just double check that other question? It sounds like you've gone the extra mile in terms of the hours. But --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The claim is it's been normalized to, you know, an eight-hour shift five days a week basis. But we will certainly double check that and make sure that our understanding is correct.

PANEL MEMBER BLANC: Aside from that --

PANEL MEMBER HAMMOND: I think that that's what Page-Shipp have done in their paper. I think that they actually say they've normalized it, downshift.

PANEL MEMBER BLANC: Okay. The terms of the general issue, the what is the correct calculation of the percentage of silica, which has become such a focal point of debate because obviously it would upshift your --

DR. COLLINS: -- three to five.

PANEL MEMBER BLANC: -- from three to five. I found your arguments far more convincing now than they were before. I thought they were a little bit -- they weren't rigorous. And I think it's quite rigorous now. I think that, although it may be beyond -- somewhat beyond your charge, I think it would be very helpful in the scientific literature in general if Dr. Hnizdo could author or coauthor a letter to the journal in which your paper was originally published clarifying this point in the peer-reviewed literature.

The issue -- the second issue, which seems to -- well, let me ask you a question about Churchyard. One of the I things as I read the revision is I wondered why it was not possible also to do a calculation with the Churchyard data.

DR. COLLINS: We'd have to contact him. He has a figure with bar charts and showing a response. The thing is, I don't -- he doesn't share the raw data. So we'd have to contact him. And I can do that and see.

PANEL MEMBER BLANC: Because it would certainly strengthen the section wherein you have -- which was in the previous document, where you have sample calculations with their papers.

DR. COLLINS: Right. But I would really need to

get ahold of the author, because it's just -- it's like a percent silicosis. I don't know what the different -- with each exposure group, what the numerator and denominator are.

PANEL MEMBER BLANC: Well, if it's possible -- I mean since it's a recent paper, the person should be contacted --

DR. COLLINS: Oh, yeah, his E-mail's in the paper and --

PANEL MEMBER BLANC: And I would say that if you can't get the data, you might want to say explicitly we were unable to do this calculation with Churchard's data because we -- the data weren't presented in a form that allowed you to do it. Because it's -- it's sort of one expects seeing it now. Then you say, "Well, that sounds like a pretty rich recent data set." So --

CHAIRPERSON FROINES: What's the percent silica in the Churchyard paper?

PANEL MEMBER BLANC: What's that?

PANEL MEMBER HAMMOND: Twenty percent.

PANEL MEMBER BLANC: It's similar to the --

PANEL MEMBER HAMMOND: No, 12 percent. Excuse me.

PANEL MEMBER BLANC: -- the -- I mean it's within range of the other estimates. It's reasonable.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Most of the more modern studies actually report lower percentages of silica than the Hnizdo and Sluis-Cremer data.

CHAIRPERSON FROINES: Can I interrupt, Paul, just for a second if you'll defer.

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: That was a question that I had for you.

If you took the study that you used primarily with the 30 percent estimate of silica and said, based on the current literature as we understand it, what would you -- what would you conclude is the percent silica that you're seeing?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The range we see is something between 12 and -- 12 at the low end and 30 at the upper end for whole dust.

CHAIRPERSON FROINES: Because in Vermont we had used 9 percent for granite sheds. And so it's 9 percent as far as I know to -- what was the upper bound?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, the upper value that we have in the range in fact is the 30 percent, which Hnizdo reported. That may reflect conditions in the mine. It may also reflect that the more modern methods which depend on things like

x-ray defraction, which is, you know, a more certain identification of silica, in fact are saying that the earlier methods somewhat overestimated the amounts of silica in the dust.

CHAIRPERSON FROINES: Yeah, it's always been a problematic issue to relate particle number, et cetera, to particle mass. And so that always has been -- Bill Burgess always taught me that one couldn't trust those kinds of measurements. And so I understand that x-ray defraction method clearly is superior.

So you would argue then, you're talking as a central tendency, somewhere around 20 percent, is that reasonable?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

CHAIRPERSON FROINES: Sorry, Paul.

PANEL MEMBER BLANC: No, no. And I think that just underscores why -- if you could do the Churchyard data, it would reinforce the entire argument, I think.

The other substantive issue that the comments seem to be concerned with are whether or not the mathematical calculations, even if correct, yield a result which is biologically plausible, because of this argument about sometimes air levels of ambient silica have approached this value.

And although I think that you address that, I think perhaps the document is still a little sheepish in that regard. And I wonder if there are ways of presenting the argument more forcefully. I mean you have two arguments, one of which I think is not necessary and not convincing, which is that there may be undetected environmental silicosis. I mean I think that there may be some undetected silicosis, for example, in agricultural jobs which end up exposing people to pretty high levels of silica that's not appreciated.

But the point is not that. The point is that in fact your value is intended to be a value at which were someone to be exposed lifelong at this value or above all the time, that's the point at which you would -- above which you might start to see an appreciable risk. So if sometimes people have detected values that may be near this for presumably transient periods, it in fact in no way suggests that this is not a biologically plausible cut point.

Now, you try to say that. But I think you should go back over it and really look, because I think you -- because if in the same breath then you start to say well maybe we're missing some cases silicosis, you're undermining your own argument, I think.

Is it really true that the only -- you only have

one citation that you could make of anybody ever doing ambient environmental silica levels? I mean you quote these three samples all done in one study in one part of Santa Barbara County. So nowhere else in the world?

DR. COLLINS: There were some. But we felt that was the most reliable thing. The EPA 20-years ago had some measurements, but --

PANEL MEMBER BLANC: And no one else anywhere has ever --

DR. COLLINS: -- find getting it published is the trick.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: One of problems is that there haven't -- really haven't been very many measurements of real background levels. For instance, the EPA measurements that Jim referred to, most of those actually are I think what you would characterize as near-source type of background measurements rather than real backgrounds.

PANEL MEMBER BLANC: And how high do those ones go.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Some of them go, I believe -- 6 or --

PANEL MEMBER BLANC: And those are near source?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, they're in the -- you know, they're sort of

the general vicinity of things that were going on kind of measurements. The trouble is people have tended not to be terribly interested in --

CHAIRPERSON FROINES: Kathy, did you want to make --

PANEL MEMBER HAMMOND: Yes, but were those PM10 measurements, the EPA measurements? They almost certainly were PM10 or total suspended particulate, right?

DR. COLLINS: I'm not sure. I'd have to --

PANEL MEMBER HAMMOND: Yeah, I mean they weren't doing PM2.5 twenty years ago. So dollars to donuts, it's either total suspended particulate or PM10, in which case it overestimates the respirable. So I think that that's also important, and all those environmental measurements, to be very clear what that size fraction is.

PANEL MEMBER BLANC: Is that Also true of the Santa Barbara measurements?

PANEL MEMBER HAMMOND: Those are probably PM10.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Those were PM10.

PANEL MEMBER BLANC: Well, then that --

PANEL MEMBER HAMMOND: That needs to be clear in the document.

PANEL MEMBER BLANC: Yeah. But then in fact the statement that ambient levels have been near these levels

is not true, because these ambient levels were significantly lower.

So I would just say that it's not -- this is a comment somewhere -- somewhere in between style and content. I mean I think it's an important content question because it uses an argument to say this is in the biologically plausible end result that you have. And I think that that is an important question to ask oneself.

For example, we've had previous documents that we've looked at where the calculations in the NK values which seem in a range that is not plausible, because were that to be the case, we should be seeing more diseases.

So I think it's not a weakness of your calculation. It's simply you don't put the best, most coherent argument on it.

So those are the major things.

A couple of minors things. One is that when you do your ILO category, Table 1, you're citing the paper that I did with Gordon Gamsu -- you know, that 0 over 1 is possible silicosis. The citation for what the ILO criteria should be should be the ILO criteria document, not a secondary analysis question, because that's what we based on. So that's just slightly sloppy.

And, you know, thanks for putting in sandblasting as a source of ambient silica, because I think that is

relevant. I guess I think sandblasting is a pretty important occupational source too. And it's really not in the first list, unless you mean sandblasting when you talk about as an abrasive. If that's what you mean in that phrase, then I would put e.g., sandblasting.

And then I think you're -- you've tried to expand your human health effects list to be a little bit more inclusive and I think that's good. That being said -- and also your sort of theoretical model of the path of physiology of it. I think that there should be some kind of nod to acute silicosis, even though it's not relevant to what you're doing here, since you're being fairly exhaustive in your list of human health effects. Since acute silicosis, which is pathologically the same as pulmonary alveolar prognosis.

And, secondly, I think that you need to state that -- as you get beyond the part about silica particles are engulfed by macrophages, I think you have to say something like "The generally assumed pathological model is" or something like that. I mean you state this as if this was, you know -- I mean these are constructs and data support it, but it's still the presumed -- you know, based on experimental evidence.

So those are I think the main things that -- the two main things. But I think that in general, the

document is considerably stronger by taking head-on the issue of the sampling and what your standard refers to, I mean how it would have to be interpreted.

And the inclusion of the more recent data and some of the relevant older data. And then the analysis related to the silica content.

And in particular, the part where if you did the calculations with the 30 percent, it comes out to the exact numbers that someone else had having worked with the data independently. That doesn't seem like that would be likely to be due to chance.

DR. COLLINS: It might be incidence, according to Dr. Gibbs.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We don't believe in coincidences.

PANEL MEMBER BLANC: Well, can I ask: Were these numbers like -- I mean these were to the two digits past the decimal point, right? So is that -- do you feel you've said that as clearly as you can at that point in the document?

SUPERVISING TOXICOLOGIST MARTY: We can go back and look and see if we can make that clearer.

PANEL MEMBER BLANC: Because to me that was the -- the whole thing was logical, but that was sort of the coupe de grace as I read it. But it wasn't -- I mean

I think it would be clearer that the -- it can't -- it's not an artifact because this person went back -- had gone back to the original data, all right, as I understand it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER BLANC: So I'm done.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: First, I would really like to commend OEHHA for tackling this incredibly difficult problem of this percent silica and what was going on. And I was -- read through your materials and the supporting materials and the papers. And that was real detective work, a lot of work. And so that was really good. And, like Paul, I found it very convincing in the end. But it was a lot of work. And in the end of course the fact that the author, the original key study felt that that was appropriate I think is very important. I think that's nice you were able to contact her.

I think there are a couple of other things. Even though you don't deal with it in the document, but -- you know, in the Gibbs paper, he -- the authors, Gibbs and Du Toit, say over and over that there's like a twofold or a fourfold decline over time and underestimate of exposures, and they go through that. But when I went back and looked actually at the data, like their Table 2, the historical

data does not bear out what they were saying. It's true that from the first year they have in the study, 1931, to the end, there looks like to be a twofold change. But that change almost entirely occurs in the first three years before people entered the study.

So if you take the time when people entered the epidemiologic study and you looked at that change over time, there's very little change. In fact I would argue there's no discernible change.

So if you go over 1940, or even from 1934 to 1967, there's virtually -- you know, there's no -- certainly no significant change, particularly if you go to their Table 5, and from which they do give -- it's not in Table 2 unfortunately. And there's no indication of the precision of these numbers. And there's actually a very wide variation, as we expect in the occupational setting. So if you look at this coefficient of variation, Table 5, which is not calculated, but I did calculate, you know, for the very first measures of coefficient of variation was 50 percent. But after that the coefficient of variation is basically 80 to 90 percent. You know, there's a pretty huge curve.

So that to be sitting there given that and saying in Table 2 that when you go from 118 -- actually the total overall in 1941 was 118 -- you go to 128 in 1967, that's

hard to say that's a decline. I think that by itself is an increase. But, you know, the 118 could be 139 to 128, given the microscope differences.

But, you know, this -- I actually see an amazing evidence of stability and very little change. It probably does go up and down with production. So I know that comes with detail, but I think it's part -- it's part of that history. Because as an industrial hygienist too I'm used to thinking that there have been huge changes over time. That's my first thought. We often look at threefold and fourfold and fivefold and tenfold changes over time. And these are actually amazingly stable over time. And I think that's actually noteworthy to the degree we have any data.

And actually they also mention in the paper the two main reasons the levels are relatively low and stable are that from 1911 they've been using wet mining procedures, as opposed to the dry methods often used. So that suppresses dust.

And they also, because it's so deep -- the mines are so deep, they're very hot, they have to have a lot of ventilation. That reduces the dust. So I thought that was actually very interesting to see.

So all of those things in combination with all that you have done convinced me that those numbers are

correct.

The other question about the percent of silica in the dust, actually as I looked through the various data, including -- this was -- a lot of it as summarized in the Churchyard data, I actually see a lower percentage than 30 percent. In fact, 30 percent's the only place I see it, is in the key study. And as I look at the data, the Randall data and all the data that's been cited, I see numbers between 10 and 20 percent and nothing above 20 percent, which would actually imply just the opposite problem from what Gibbs is talking about.

So if there's any error, I think it's running the other way. And I would just comment on that. But, you know, you have to make the --

CHAIRPERSON FROINES: Well, the implication of that is that REL is too high.

PANEL MEMBER HAMMOND: Right.

PANEL MEMBER GLANTZ: Well, wouldn't -- going back to the early discussion about 30 percent versus 20 percent versus 9 percent. If you were to take the central estimate of 20 percent, wouldn't that push the REL up?

PANEL MEMBER HAMMOND: No, down.

PANEL MEMBER GLANTZ: I meant down.

PANEL MEMBER HAMMOND: Well, see, the trouble is Gibbs is saying it should be 54 percent. That's the other

number in the mix. But, I mean, it just doesn't fit any other data.

And I think the other piece is that, as far as I can tell -- and I would actually like to have the table -- I think I mentioned this to you earlier -- a little clearly on the methodology. But as far as I can tell, it's only the Churchyard data that has x-ray defraction for the silica. And that's the one that has the lowest number -- well, among the lowest, 12 to 16 percent was what they found. So I tend to take that particularly seriously. And then there's no evidence of change from when they started listing data from '77. It was 10 to 20 percent in '77, '87 to '88 it was 10 to 20 percent, '92 to '94 surveys were 15 percent -- 12 to 16 percent. So it just looks like it's in that 10 to 20 percent range. And 20 percent's the upper end of that.

CHAIRPERSON FROINES: I mean going back to Gauley bridge, if you want -- Paul and you will at least know what that was -- you know, the percent silica was very, very high. So that there are historical examples of --

PANEL MEMBER BLANC: Would you say that G-a-l-l-e-y?

CHAIRPERSON FROINES: What?

PANEL MEMBER BLANC: Galley Bridge, G-a-l-l-e-y?

CHAIRPERSON FROINES: G-a-u-l-e-y.

PANEL MEMBER BLANC: G-a-u-l-e-y.

PANEL MEMBER HAMMOND: Hawks Nest.

PANEL MEMBER BLANC: Thank you for the spelling.

PANEL MEMBER HAMMOND: So, anyhow --

CHAIRPERSON FROINES: But my point is in general what one has found has been lower than those values, not higher.

PANEL MEMBER HAMMOND: Yeah, in the miners.

Now, the second -- my second major point is the Churchyard study, which I know came out since your first assessment -- and I'm not sure just what the appropriate way to include this is, but I would just like to comment on it -- I found that study very sobering when I read it. I mean it's just really quite sobering. And it's notable both for the quality of the exposure assessment in the study, although they have some of the best data included in the x-ray defraction data, and for the magnitude of the effect that's seen. And so they actually collected respirable dust, weighed it gravimetrically, and then analyzed it by x-ray defraction.

So they didn't deduce it, which was done in the other methods. And all of the deductions and subtractions, I think most of the errors would lead towards overestimates of percent silica. So if you just were to look at the directions of errors, they would lead

to an overestimate, which I suspect the 30 percent numbers are in the other studies.

They also have documented very little change in the overall exposure during the relevant time period for the people in the study.

And there are two major epidemiological -- well, first of all there are about 20 percent of the workers -- it's a cross-sectional study. The workers average age 46, and 20 percent of them have silicosis by the ILO 1 over 1. And I would defer to Paul or someone else about the significance. But half of those have two or three. You know, so that's a more severe silicosis, right?

So that seems rather sobering to me that at a relatively young age, on 21 years of exposure, they have that effect.

But, furthermore, because it's a cross-sectional study, it has two limitations:

The first is that any people who got sick or even were out on sick leave for a cold or for any other problem were not included in the study. The cross-sectional measurement of this just excluded people who are out on sick leave or who might have left work because they'd gotten sick already. So that already depresses -- that will underestimate any effect.

And, secondarily, because it doesn't have -- this

isn't the follow-up after all these years of exposure. We all know, as you well cited in the document, the internal dose continues for silica, that everyone knows that those particular category of workers will have a higher rate of silicosis ten years out than what's seen at this point. And that's already 20 percent.

So with even those problems, I found it a pretty sobering study.

Also the silica exposures averaged 53 micrograms per cubic meter, half of the standard -- the current OEL's in most of the world. And they said that 90 percent of the workers had average exposures between 29 and 75 micrograms per cubic meter. So these people had a low -- in the world of what the standards were, relatively low exposures, and 20 percent of them as an underestimate had this already.

So I found that a rather sobering study. And if there were a way to incorporate it without leading to a lot of difficulties, I would encourage you to. But I don't think that should slow down the process. And if that slows down the process, we could just note the importance of the study that came out after the main documents.

CHAIRPERSON FROINES: Have you done a calculation of what that would lead --

DR. COLLINS: We can't do it because of the way the data's written. It's a bar graph with percent silicosis. And all we can find out are the numerators and denominators from the authors.

PANEL MEMBER HAMMOND: That's who they'd have to contact, the authors.

CHAIRPERSON FROINES: Well, that wouldn't be a terrible idea. This isn't -- this is a very important chem --

PANEL MEMBER HAMMOND: Yeah, I think the study itself was a very important one.

Then the other issue which we spent so much time on last time was the metric to use, the size. And I commend you in terms of scientifically going to the respirable as defined in the occupational method, which is the way in which the sampling was done for the critical studies. And I think that that's totally appropriate.

I think it's better to refer to it as the ACGIH method or the ACGIH/ISO method for definition of respirable, because NIOSH just refers themselves to the ACGIH.

I think that in the documents still there are some points of confusion. I mean you point out that in the environmental community, people often use the term "respirable" meaning PM10. So I think that maybe having a

paragraph early in the document, that just is very clear, that says, "This 'respirable' term is myth. It has these multiple meanings. In this document we are going to use respirable" -- and maybe italicize it -- "always meaning" you know, with the occupational definition, go through what that is, and say that instead of -- even though PM10 is referred to as respirable, just call it PM10, because there's a name for it -- another name nor it. And use PM10 throughout. And I would just suggest you do a search and just check for all words "respirable" and keep that very clear throughout to do that.

And as I mentioned earlier, I think it's important to clarify the size distribution that was used for the ambient measurements that were taken. My guess is they're either TSP or ambient -- PM10.

I think the recommendation for the REL, it's there, but I think it needs to be very clear. As I understand what you're suggesting is that this REL, as you said here, is for respirable particles as defined in the occupational setting. And you can go through that.

And the PM10 samples can be taken as a screening tool, because they over -- they'll overestimate. They shouldn't be seen as a problem, but tell you where you need to do more. And I think that's in your document, but not always clear to all the readers.

And like page 33, the first two lines are kind of confusing, whether you're saying -- I think at one sentence you're using respirable for ACGIH and one sentence it's about PM10.

And then I have a series of just tiny little comments. Occasionally -- most of the places you've got it corrected, but occasionally you're still -- there's a mention about the ACGIH definition relating to respirable as being a deposition. But it's actually a penetration of particles of a certain size to the lung. So just kind of check some of those.

The WHO recommendation that you cite, is that for occupational or environmental, the 40 micrograms per cubic --

DR. COLLINS: I think -- I'm pretty sure that's occupational.

PANEL MEMBER HAMMOND: Occupational.

And then what particle size were they -- did they specify --

DR. COLLINS: I don't remember right now.

PANEL MEMBER HAMMOND: I think it should be in the document. If you could just put that -- and those are small things. But just -- if you're going to cite it, I think given those things we need to say to whom it applies and what size range.

Oh, and I guess one other -- and, again, I would defer to some of the physicians here. In the American Chemical Council statements, they said that idiopathic small irregular opacities of non-occupational populations have been reported in the literature of the pool prevalence 1.3 percent in North America. That's in their comments.

Does that mean that there is a --

PANEL MEMBER BLANC: Well, I think they do attempt to go back. And there is a section in the revised document where they have an expanded discussion of the very low prevalence of opacities which could be graded by ILO criteria. And you cite the Castellan study. And it's quite low. And almost all of what is seen as a sort of background prevalence is 1 over 0, not 1 over 1.

PANEL MEMBER HAMMOND: Oh, okay.

PANEL MEMBER BLANC: So they're, you know --

PANEL MEMBER HAMMOND: That's what they meant by -- I just was curious. I wasn't sure about it in --

PANEL MEMBER BLANC: And Much of it's not -- much of it's irregular and not rounded.

In any event, I thought there was enough it and I thought there was enough of a discussion there, now in the expanded version, as you --

PANEL MEMBER HAMMOND: But I think that you've

done a great job on this document. A lot of work has gone into it.

Thank you very much.

DR. COLLINS: Thank you.

CHAIRPERSON FROINES: So having heard from the two leads, why don't we go around the room and give other comments. I have some comments, but I'll defer.

Stan.

PANEL MEMBER GLANTZ: Well, I have one -- I read it through. This is not my area of total expertise. But I had one small question.

(Laughter.)

PANEL MEMBER GLANTZ: And then I had a comment based on the discussion so far. And let me just -- this is a very picky point. But somewhere here --

CHAIRPERSON FROINES: We understand that when you say this is not your area of expertise, everybody starts to shutter.

(Laughter.)

PANEL MEMBER GLANTZ: Why?

CHAIRPERSON FROINES: Because we don't know what's coming next.

PANEL MEMBER GLANTZ: No, it's a very small thing.

If you just look on page 26, you have a P value

by a Fisher exact test. And I think you should specify if that's one or two tails. Hopefully it's two tails. You should use the two-tail test there. But a lot of programs report one-tail tests without telling you. That was my highlight subjectively.

The question I had based on the discussion -- I mean I also thought you did a very nice job of responding to the comments and dealing with this 30 percent issue. And I came in here all happy about that. But now listening to the conversation, I'm wondering if you shouldn't be using 20 percent.

PANEL MEMBER BLANC: No.

PANEL MEMBER GLANTZ: No. Okay.

So you're happy with the 30 percent?

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER GLANTZ: Okay. Then I'm happy too.

PANEL MEMBER BLANC: I think it's fine enough to say that, if anything, it's conservative, it's not radical. But I don't think that there is a scientific basis for presuming it to be lower than what -- to doing the calculations a little bit lower. I think they should stick with what they have.

CHAIRPERSON FROINES: I'm not sure Kathy would agree with that --

PANEL MEMBER HAMMOND: Yeah, I guess I don't. I

mean -- the thing is, every other -- the better the data are -- any place one looks at the data, the better they are, the more it looks like it's between 10 and 20 percent. And the only place I see 30 percent is when it's this very crude way they did it. You know, where you just --

PANEL MEMBER BLANC: But you have to use the --

PANEL MEMBER HAMMOND: -- you kind of -- you acid wash it and you kind of heat it up to see what's --

PANEL MEMBER BLANC: Well, then if you don't believe the data, then you shouldn't use the study. I mean if you're going to say, okay, we're going to use the study with its strengths and with its weaknesses, then you use the data that you have. And then that's why they have these other calculations from other studies. I guess it's -- we didn't specifically comment on the important revision in that section, which is that when you use the Hughes study in this revision, you have gone from yielding a value of 10 to yielding a value of 3, which is again matching what you've gotten. And that was based on the fact that the author's no-effect level was really a lowest-effect level.

And then you say, "See below." What's the "below" supposed to refer to?

DR. COLLINS: I'm pretty sure that it was a --

because of some of the extra discussion, it goes further down. And the second supportive study, Hughes, is all down. In this case the silicoses is the lowest exposure group. And then we basically say we believe it's a LOAEL, not a --

PANEL MEMBER BLANC: I know. But where is the "see below" -- where is the reader supposed to look below --

DR. COLLINS: Oh, oh, yeah. Yeah. Okay.

PANEL MEMBER BLANC: What is it that you're referring to?

DR. COLLINS: There's a paragraph --

PANEL MEMBER BLANC: On the next page?

DR. COLLINS: Well, no it's actually after Table 20. It's second -- it actually got moved a lot because we had put in this new section. Maybe that's what makes it --

PANEL MEMBER BLANC: Yeah. So I think that needs to be --

SUPERVISING TOXICOLOGIST MARTY: We'll fix that.

PANEL MEMBER BLANC: -- reedited. And I think that that -- you know, it's a major issue.

SUPERVISING TOXICOLOGIST MARTY: I have a suggestion for revision to deal with this issue of percent silica. We can, I think -- you know, we feel we need to

stick with the study. But it seems clear to me that we should be making a statement that this is in no way an overestimate of the REL based on methods to look at percent silica in the dust. And then note what Kathy has noted herself, that the better the methods and the newer the studies, the lower these percents seem to be. At least what we would be doing is pointing out that perhaps --

PANEL MEMBER BLANC: No, no. And I would support that. I think that's a reasonable thing to do. Because, again, you're talking about the -- in this case not the biological plausibility, but the sample.

CHAIRPERSON FROINES: Yeah, I want to go on record basically agreeing with Kathy, that I think that the estimates of 30 and certainly 54 percent seem to me to be high. But I think that we shouldn't necessarily change the study that we're relying on. I think that the -- that language that Paul and you were talking about would make sense.

PANEL MEMBER BLANC: I guess one other -- no, never mind.

Well, let me just ask the question. In the Chen study of tin miners, it was also based on the ILO-graded x-rays, I assume?

DR. COLLINS: I think it was -- it was based on

the Chinese system, which is similar.

PANEL MEMBER BLANC: Since tin causes radiographic opacities, how did they account for --

DR. COLLINS: They didn't mention anything about tin or stenosis anywhere in the study. I went through it and I couldn't find any references to that.

PANEL MEMBER BLANC: Because I had asked about this before and --

DR. COLLINS: Yeah. I couldn't find anything.

PANEL MEMBER BLANC: Then how do use that study? I mean does that cause the same problem as the coal miner study?

DR. COLLINS: I don't think so, because it was -- they had lots of -- they had lower levels. They had a whole gradation of levels of exposure. But I mean as far as is there a one-to-one correspondence between the Chinese system and the ILO, I'm not sure. They said it's a similar system. And they were collaborating with the people from either -- I think NIOSH on it. So it wasn't just -- they had input from people that would be familiar with the American system.

PANEL MEMBER BLANC: Yeah, that's not my point. I mean you could use the ILO -- they could have used the ILO too. But if you use the system where you're looking at radiographic opacities in people who are tin miners,

which is another cause for having radiographic opacities -- remember, the whole point of the ILO system is radiographic opacities which can be consistent with pneumoconiosis. It's not a diagnostic system you've revised, to make that clear.

DR. COLLINS: I went back and looked at that tin miner study. And there was no mention of any disease caused by tin. The only thing they discussed was silicosis. And, now, should they have? I don't know. But I could not find any reference to anything other than silicosis.

SUPERVISING TOXICOLOGIST MARTY: I think at a minimum we need to in the description state that tin exposure can also cause radiologic opacities, when we discuss that study. Whether or not the authors themselves make mention --

PANEL MEMBER BLANC: Well, I mean I just wonder whether there are -- whether if there are certain questions about it that can't be clarified, I don't think you should drop the study from the document. But should it be one of the studies that appear as the four studies -- the three other studies which are supported? Because the problem with it is it could go either way. You could be overestimating or underestimating silica effect, because of the people who had higher tin exposure

had lower -- if there was a systematic -- weird systematic relationship that could lead you to overestimate the silica effect or underestimate the silica effect, depending, right? I mean I can't predict how it could confound a relationship.

CHAIRPERSON FROINES: Stan?

PANEL MEMBER GLANTZ: That's all I had.

CHAIRPERSON FROINES: Good. I'm glad you raised that point, but it actually took us to a somewhat better place on this issue.

Joe?

PANEL MEMBER LANDOLPH: I think Kathy and Paul did a fantastic job and everybody else. And I think that we all did a fantastic job leaving that -- but I'm satisfied with the document.

CHAIRPERSON FROINES: Charlie, I don't know if you've had a chance to look at this.

PANEL MEMBER PLOPPER: I did.

CHAIRPERSON FROINES: You did.

PANEL MEMBER PLOPPER: I thought it was an excellent document. The only concern I had is that it was underestimating the risk based on the percentages. But that sounds like it was everybody else's concern also.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: I have nothing to add.

1 That's very nice. And you've dealt with all the comments
2 very effectively.
3 CHAIRPERSON FROINES: I have a couple questions.
4 It won't take long.
5 First, I was interested in your references,
6 because there are two references to a fellow I worked with
7 in Vermont years ago named Jack Craighead. And so I've
8 been through the document and I can't find -- there are
9 references to Craighead, but I can't find any discussion
10 of his work.
11 The reason I raise the issue is Craighead was one
12 of the first people who showed actual pathologic changes
13 in the lung associated with very relatively low levels of
14 silica exposure. We got autopsy victims and took out
15 lungs and looked at people who had very low silica levels
16 at that point, people who had worked in industries where
17 the silica was well controlled. And Jack saw and wrote
18 papers about what he found in terms of changes.
19 So I think that in terms of going to the issue --
20 there's this issue that, as we all know, that John Peters
21 has argued for some time that one sees lung function
22 changes before radiographic changes. And so if
23 one measures -- if one develops standards based on lung
24 function changes, you would have perhaps different
25 numbers. Craighead argued that you see level -- you see

changes at very low levels as well.

And so there are some other ways people have looked at the issue. And so the fact that there's the references but no discussion of those kinds of questions seems to me -- I mean either take out the references or put in some text is what I think you need to do.

DR. COLLINS: I remember distinctly, one of the Craighead references he had studied 12 slate-exposed people and found some changes in the lung, but wasn't sure it was pneumoconiosis. But it was a lung effect due to slate exposure.

CHAIRPERSON FROINES: Well, there's some other literature, I think.

DR. COLLINS: That may well be.

CHAIRPERSON FROINES: I don't -- I think what you've done is -- as everybody agrees, is more than sufficient. But having worked regulating the granite industry in Vermont, the issue of lung function changes, and pathologic changes at low levels is still a matter of interest to me. So I -- but I don't think you need to go back and put that in. I think what you have is sufficient.

I had one question about a response that was written that talks about the USEPA -- this is on Culver 4. "The USEPA defines a reference concentration as an

estimate, with uncertainty spanning perhaps in order of magnitude of a daily exposure," and so on and so forth. "OEHHA uses a similar definition. The 'order of magnitude' statement can be taken as a confidence level."

Now, I found that sentence -- this sentence to be -- I don't know what you're saying. And if you're saying that --

DR. COLLINS: Did we say it or we -- we said it in our response.

CHAIRPERSON FROINES: This is in your response.

If you're saying that you accept -- that you assume that you have an order of magnitude confidence -- rather uncertainty spanning an order of magnitude, then I suspect that should be in your main document, if that's what you're saying. But I don't think you're really saying that.

It's Culver 4. And it says that "the 'order of magnitude' statement can be taken as a type of confidence level. OEHHA uses a similar definition for chronic RELs in the technical support documents," so on and so forth. And so you're essentially acknowledging EPA's order of magnitude uncertainty value. And I think Dale Hattis just rolled over dead, you know, from a statement like that.

The point being that -- well, that point's obvious.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It seems like we need to rephrase that.

CHAIRPERSON FROINES: Well, I think you need to rephrase it simply because I don't think you mean it. And I think that if you're going to talk about the magnitude of uncertainty, then that ought to be appear in your full document.

PANEL MEMBER BLANC: What did you mean?

DR. COLLINS: Probably I -- I copied the EPA's definition, and should have put that sentence after the EPA's definition rather than after ours.

SUPERVISING TOXICOLOGIST MARTY: The EPA makes that statement. And it's really -- it's really not based on any kind of statistical analysis. It's more of a gestalt about the database available to do any of these kinds of assessments. In the case of crystalline silica, we have some very good data on which to base a REL. In a lot of cases we have pretty poor data in terms of: What toxicological endpoints were actually evaluated. Did they look at exposure early in life? And what other -- you know, what exactly are the studies you have to use to do any type of quantitative estimate?

So that statement appears in EPA's documents just to give the idea that these types of calculations are not perfect by any stretch. But I don't think anybody means

it in a statistical sense of a confidence bound or --

CHAIRPERSON FROINES: Yeah, unfortunately it says that it's found in here as a confidence bound. And so I don't think you're really saying that your values should -- could be in a range of .3 to 30.

SUPERVISING TOXICOLOGIST MARTY: No.

CHAIRPERSON FROINES: And I don't think that's what you're saying.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: No.

CHAIRPERSON FROINES: So I think you ought to take a look at that and maybe improve on it.

I want to go back to this issue that we debated so long and hard last time, because I -- and this gets us a little beyond the issue of risk assessment. But I think it's an issue that's come up.

And, for example, here you say -- on IDPA 5 you say, "CARB and the air districts have regulatory approaches designed to provide the best possible protection for public health, taking into account the specific features of each individual situation."

PANEL MEMBER BLANC: Are you talking about a response somewhere?

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER BLANC: What page are you on?

CHAIRPERSON FROINES: IDPA 5.

And so, Melanie, the issue I still am concerned about is we no longer are talking about PM10 as the operative sampling method for identifying silica. And you talk about using the NIOSH respirable method. But I don't know -- I don't understand -- and this may be me and not you -- but I don't understand then what ARB is going to use to measure silica, because the NIOSH sampling method is not what they're going to use. So the NIOSH definitions -- and Paul's spoken to that issue -- is something that one can acknowledge in the context of the risk assessment.

But what's the practical significance of that at this point? What are you going to do? You've got this wonderful table in here showing cutoffs with various sampling devices. And so how is one going to determine what the -- you know, when you've gone to Santa Ana and Santa Monica and the winds blowing 30 miles an hour across the beach, you know, how are you going to monitor for those silica levels that are obviously quite high?

SUPERVISING TOXICOLOGIST MARTY: Well, I'm going to speak for ARB now, which is probably not the greatest thing. And maybe -- I know Lyn was in the audience earlier. He might talk about this.

CHAIRPERSON FROINES: Well, Lyn's sitting right

there.

SUPERVISING TOXICOLOGIST MARTY: We've had some preliminary discussions. And we think we need to set up a working group to address this issue. Because, as you note, ARB has standard methods for PM10 and now PM2.5, but not something that's exactly analogous to the ACGIH method.

So I don't know if Lyn wants to add anything to that. But it's a good question.

ARB AIR POLLUTION SPECIALIST BAKER: Hi, Dr. Froines. Lyn Baker with the Air Resources Board.

We've talked with Melanie and OEHHA staff about this issue a few times, as Melanie mentioned. And we do not have a method for measuring PM4. You could use the -- the studies have been done with a cyclone personal sampler. It's a little device attached to a person's vest or whatever. It measures PM4 at a very slow flow rate. But it's designed for an occupational setting. And it has not actually been validated for concentrations below 25 micrograms per cubic meter. So with the chronic REL proposed at 3, if you used this in an ambient setting you'd have to do some validation work to make sure it was even a valid method. But currently we'd have to do some side-by-side work with PM10 samplers or other samplers if we were going to try to come up with a ratio or to design

a different sampler.

PANEL MEMBER BLANC: Well, I guess a couple comments. And this echoes back to the discussion at the last meeting. And now with the corrected language with the document, in fact the response that John is referring to on IDPA 5 is probably imprecise, because the OEHHA staff realizes that the proposed REL is close to levels that have been obtained with PM10, which is -- you know, which would overestimate. So actually in fact we don't have any evidence that there are ambient levels measured consistently with what the REL is stated as that would be close to 3. That's one point.

But the second point to being more -- less bureaucratic, based on the size cutoffs it does seem that ARB could at least develop an algorithm wherein if the PM10 measurement is below 3, then based on the size cutoff certainly the ACGIH-based sampling method, which NIOSH concurs, would have to be also below 3. If you did side-by-side monitoring and the -- both the PM10 and the PM2.5 were above 3, then you know you're above 3 with -- you would be above 3 with NIOSH.

And the problem would be -- or where you would need an algorithm for doing additional sampling would be if you had a value which was above 3 on the PM10 and below 3 on the 2.5. That's the situation where you actually

would not know. You could have some algebraic, you know, guestimates on -- you know, Dumont Carlo estimates or something. But even -- I think you'd have to come up with an alternative sampling method. But at least that would be a useful screening algorithm.

ARB AIR POLLUTION SPECIALIST BAKER: It would. And we've also thought about that, that it would probably be pretty site specific. Or if that ratio in a --

PANEL MEMBER BLANC: Now, whether it's useful in this document to say -- in this section wherein you talk about what these various words, how they're used. But I think if you wanted to say that if a sample -- you know, the implication of the figure -- this figure on page -- is it -- it's in the main document, right? The figure -- yeah, the last figure. The implication of that figure on page 34 in fact is that if a value with a -- if a PM10 value were below 3, then the NIOSH value has to be below 3. And I think that would be a useful statement.

PANEL MEMBER HAMMOND: One thought I had is you could actually modify this figure a little bit and just have the PM10, PM2.5 and the occupational respirable curves, and actually shade the areas between some of those lines to emphasize this is the degree of overestimate -- of potential overestimate and of underestimate. But without knowing the full particle size distribution -- and

not only the full particle size distribution, but the composition could change with particle size. So I think you have to be extremely careful. I don't think you can use an algorithm. I think you have to do a measurement. And I think you're absolutely correct, Paul, that you could do --

PANEL MEMBER BLANC: -- screening?

PANEL MEMBER HAMMOND: The screening that you outlined would work.

CHAIRPERSON FROINES: I think you'd have to do a PM2.5.

PANEL MEMBER HAMMOND: But I would actually point out as well that there -- you're right, that there are these small personal sampling cyclones. But there are also high volume cyclones that yield respirable dust, you know. And I have one that's over 20 years old. I mean they're not new. There are plenty of those out. So there are ways to do respirable sampling. I know that they're not in the standard repertoire of ARB. But you're not limited just to the, you know, 1.7 liters per minute nylon cyclone. There are other options that will go up 400 liters, you know, 430 litters and things like that.

CHAIRPERSON FROINES: And, Lyn, I agree with you, that I think that the percent silica is going to be -- is going to be changing quite considerably, depending upon

where you are.

So that I don't know if you want to -- I don't know. What does the Committee think about whether or not this discussion needs to be in this document? Or this is something that we can do something at ARB, and OEHHA will deal outside the scheme of this review and this Committee.

PANEL MEMBER HAMMOND: I think the document stands as a scientific document as it is. But it does present some pragmatic challenges to ARB. But I don't know if those are too difficult to --

PANEL MEMBER BLANC: Well, but it is true -- you could make a couple -- it is true, I'm not wrong in saying this, that if a PM10 was below 3, then by definition you would be below the standard, because that's --

PANEL MEMBER HAMMOND: Well, I think that's what I was saying in my earlier comments. I was saying that we need to make that -- I think that this document needs to be very clear. Bring all those comments together in one place and say the REL is three microns per cubic meter, defined as this respirable by the ACGIH standards. A screening can be done with PM10. If the PM10 is under 3, by definition you'll be under the 3. I think that should -- but this has to be in one place on the one little box, one paragraph, clear.

CHAIRPERSON FROINES: Well, I just want to be

differ from the two of you a little bit. I think that the issue isn't the upward bound, the way Paul is describing it, because I think there are going to be lots of cases where it will be above 3. Remember, that the -- you know, a particle that has one micron diameter is -- a ten micron diameter particle weighs a thousand times more. So a PM10 measurement is weighted heavily.

PANEL MEMBER BLANC: Oh, no, I think in the same -- well, in the same sentence you can say if a PM10 value is above 3, it does not necessarily mean, however, that you --

CHAIRPERSON FROINES: But the issue is you're going to -- what I'm saying is you're going to find I think a number of values, depending on where you measure, that will be above --

PANEL MEMBER BLANC: Well, maybe. But they haven't cited any examples.

SUPERVISING TOXICOLOGIST MARTY: Can I just insert a little thought into the discussion about exposure -- or about dealing with exposure and measurement. We have not typically done that in the REL documents. We've just presented basically the toxicologic, epidemiologic side of things.

And in the Hot Spots program it's even a little more complicated because most of those exposures are

estimated rather than measured. In talking about silica sources, we have been talking about, well, they need some help in estimating. And the only way you're going to get help is if you actually go out and do some measurements so you can tell them how to estimate. So it's a real issue. I don't think we can resolve it within this document.

CHAIRPERSON FROINES: But I just want to -- I understand what you just said and I agree with you. But I also think that the reason this discussion is coming up here -- and if we were dealing with hexachlorobenzene or something else, it wouldn't be coming up. You know, I mean it's -- we're talking silica is unfortunately a hot ticket item. But, you know, without a trace on Channel 2 last Sunday they were talking about exposures to silica on the television program. So it's not an issue that's not in the public eye. And there are people who worry about their kids being in sand boxes. I mean so that what we have is something that has a high public interest associated with it.

So it means that we have to be very careful on this sampling question, I think. And we can defer to you -- the two agencies to resolve the issue, and I'm quite comfortable with that. But I think it's an issue that needs to be clearly addressed, because I don't think this is an abstract question by my means.

SUPERVISING TOXICOLOGIST MARTY: Can we have a little bit of discussion in this REL document to that effect?

CHAIRPERSON FROINES: If you want to --

SUPERVISING TOXICOLOGIST MARTY: I think that would be really reasonable to do.

CHAIRPERSON FROINES: If the panel thinks that would be appropriate.

PANEL MEMBER HAMMOND: You mean about the screening that we were just talking about?

SUPERVISING TOXICOLOGIST MARTY: Yeah, the screening and the fact that, you know, it's not standard procedures to look at that size fraction for ambient measures.

PANEL MEMBER HAMMOND: I think that would be helpful to the readers.

CHAIRPERSON FROINES: I would argue that there is sufficient agreement with the document that that would -- that that agreement and the other things that people have suggested would not preclude our moving forward on the document, but we'll take that up in a second. But I think it -- I think it's in your best interests to address it up front rather than saying we're simply going to establish a work group. That's less satisfying to the person reading the transcript who has an interest in

silica.

So let me go back then. Given the changes that people have suggested, is the Panel comfortable going forward with a vote on this document as such? Or do you want to have Melanie come back again?

Paul, Katharine?

PANEL MEMBER HAMMOND: I think we've been pretty clear about I think the very specific things. This is going to -- I think this might be the first document that I've been party to, and so I don't know the whole procedures. But my sense is that they're pretty clear things we've said; they're not major -- issues that take conversation. So if there's a way that we can say, given certain changes and someone checks it out on the panel, then I think we could -- then we could go forward.

CHAIRPERSON FROINES: I don't think there's any substantive disagreement. In fact I think there is agreement with that.

PANEL MEMBER HAMMOND: Right. So I think -- to my mind, then I think, you know, assuming that those changes can be made, I think we could -- I would think we could accept this way to do that.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I want to give the OEHHA a little bit of wiggle room here.

If you send an E-mail tomorrow to Churchyard and if Churchyard sent you the data and if you did the calculations and if they came out to be 3 again, then I don't see there being an issue. But if they come out to be, you know, 1 or .05 or something, is -- you know, what would you do in that situation -- or if they came out to be 6?

DR. COLLINS: I think that's always a possibility with any of the chronic RELs, that better data can come out.

PANEL MEMBER BLANC: Right.

DR. COLLINS: The problem we have with that study, it is a cross-sectional study, so we know it's going to underestimate the ultimate REL. But I doubt that it's going to come out at .1 or .0 --

PANEL MEMBER BLANC: No, I know. I think it's unlikely too. But I'm just asking. In other words the two options are that we tentatively approve the document presuming that the changes that -- the actions that we've asked for do not lead to substantive changes. But I'd like you to be able -- if you find in your review that in fact the actions that we ask you to take lead to what you view as potentially substantive changes, that you would notify us of that. So that the wording of the resolution somehow builds that into it so that you have some option.

I don't want you locked into -- or us locked into approving a document which is in some ways substantively different.

CHAIRPERSON FROINES: Well, I think that should be almost a generic statement, that if we approve something -- tentatively approve something, but in going back you find substantive changes, then in fact I think it's incumbent upon you to bring it back to the panel.

PANEL MEMBER BLANC: So I would move that the panel approve the document pending the modifications discussed today, and presuming that there are no scientifically substantive changes to the findings.

CHAIRPERSON FROINES: Is there a second?

PANEL MEMBER LANDOLPH: Second.

CHAIRPERSON FROINES: Any further discussion?

All those in favor?

(Hands raised.)

CHAIRPERSON FROINES: Unanimous, 6 to -- 7 to 0.

This is a very interesting compound. I think we won't hear the last of it.

Let's take a break.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Mary-Ann, why don't you come up and have a seat. I would have you sit next to me, but there's no chair. So maybe if you could sit at the

table.

This is a real pleasure for me. Everybody in this room knows that historically there has been some tension between the DPR and this Panel. And so I'm really happy to introduce Mary-Ann Warmerdam.

How do I pronounce it correctly?

DPR DIRECTOR WARMERDAM: Well, in the old country we'd say Varmerdaum, but here it's Warmerdam.

CHAIRPERSON FROINES: Warmerdam. Okay.

Mary-Ann is the new Director of DPR. And we've been exchanging E-mails. And she asked to attend a meeting and introduce herself. And I think it -- we've just had a very nice conversation. And I won't characterize it in terms of Stan's role, but --

(Laughter.)

CHAIRPERSON FROINES: But in any case, we're looking forward to working with her. And I think it's going to be very positive in the future.

Welcome.

DPR DIRECTOR WARMERDAM: Well, thank you, Dr. Froines. And thank you, Panel members. I did ask if I could come by and just spend a moment with you to introduce myself.

I was appointed Director of DPR about a month ago -- well, close to six weeks ago now, have been on the

job a month. So there's much that I don't know about the Department's functions. But I'm absolutely delighted to be with the Department.

And I want to start out by thanking you all for spending your time doing the scientific work. I am not a scientist by training. I am a policy person. I've spent most of my professional career working on either agricultural or water, natural resource policy. And so coming to a panel like this is really quite illuminating, and I do appreciate the work that you've done.

As Dr. Froines said, we've had a sometimes checkered history, "we" being DPR, with the Panel. But this Governor has been very clear in his direction to -- at least to me, and that we want to have transparency, we want to have economic growth, and we want to have environmental improvements. And to the extent that we can effectively do that together, I look forward to working with you all in reaching those goals on behalf of the Governor.

And with that, if there are any questions any of the panelists would like to ask. Otherwise I'll leave you to your next discussion item.

CHAIRPERSON FROINES: Thank you.

Any questions?

DPR DIRECTOR WARMERDAM: Thank you very much.

PANEL MEMBER HAMMOND: Thank you for coming.

DPR DIRECTOR WARMERDAM: You're welcome.

CHAIRPERSON FROINES: Okay. We are trying to figure out what we're going to do about lunch.

PANEL MEMBER GLANTZ: I think we should work through lunch.

CHAIRPERSON FROINES: That would take us to about 2 o'clock. Is the panel --

PANEL MEMBER GLANTZ: No, I mean get lunch and eat while we're talking.

CHAIRPERSON FROINES: Is it possible, Peter? Can we -- is the Panel agreeable to having lunch brought in and continuing till 2?

Any problems?

Okay. We're off and running.

My assumption is that we're going to spend most of the next three hours going through the presentations. And then in January 6th, we will have a full panel discussion and hopefully we can get through the document at that time.

PANEL MEMBER BLANC: Well, the only other agenda item -- and this is going to be a question more for Peter -- is whether or not there should be some discussion here of future dates that would narrow down the blocks. I find it difficult to respond to the last date request,

because basically it was like "Tell me your availability for the rest of the year." And that's somewhat tedious. I would rather respond to, you know, "Of the last two weeks of," you know, "March when are you available?" Or something a little bit more focused. So I think having some time set in the meeting to talk about when it is you want to meet after the January meeting would be helpful to me.

CHAIRPERSON FROINES: Well, let me ask the question then a little differently than you just said it.

We are meeting here November 30th and we have a meeting January 6. So it's a little bit more than a month difference between the meetings.

Given people's schedules, how long after January 6th would you be comfortable holding a meeting? Do you want a month? Do you want two months? What's your --

PANEL MEMBER GLANTZ: Well, I think it sort of depends on what happens at the January 6th meeting, because I'd like to not have this document drag on for a really long time. So what you might want to do is schedule -- I mean the other thing is what else is on the agenda?

CHAIRPERSON FROINES: The other item on the agenda --

PANEL MEMBER GLANTZ: I mean for the future.

CHAIRPERSON FROINES: And Mary-Ann I think left. But we have sulfurofluoride coming up.

PANEL MEMBER GLANTZ: And when will that that be ready?

CHAIRPERSON FROINES: It's ready.

PANEL MEMBER BYUS: No, no, no, not exactly.

CHAIRPERSON FROINES: Close.

PANEL MEMBER BYUS: I'm having them rewrite part of it. There's been some additions which they've just got back to me.

CHAIRPERSON FROINES: Well, what's your guess?

PANEL MEMBER BYUS: It should be ready in January, hopefully. It depends. I haven't actually read all that they have written.

CHAIRPERSON FROINES: So let's assume January. So let's assume that it's going to be available after the first of the year.

PANEL MEMBER BYUS: Right.

CHAIRPERSON FROINES: Just as a touch point.

So, Stan, I agree with you that we don't want this document to -- we want to move this document along. At the same time, this is a major document, and we want to have a very clear record, a thorough review and analysis. And so I think we have to take the time that it's going to take.

PANEL MEMBER GLANTZ: No, I agree with that. It's just if the -- especially if you're saying that most of the meeting today is going to be the presentation rather than discussion, I mean I would -- it might be that the thing to do is to try to schedule another meeting at -- I mean we may finish it with the January 6th. I would worry that we might not.

So then I would suggest, especially if there's another document coming down the pipe, that you schedule a couple of more meetings like in about a monthly interval or something.

PANEL MEMBER BLANC: I would sort of take a middle ground. And what I would suggest --

PANEL MEMBER GLANTZ: You can always cancel them.

PANEL MEMBER BLANC: Well, even taking that into account, what I would say is that it would probably be helpful for us to schedule an early March meeting, which if we don't need, we can cancel. I don't think I would be very happy about a January and a February meeting.

CHAIRPERSON FROINES: Can I ask one question about that?

I'm going to China for three weeks because we have a lung cancer project.

PANEL MEMBER BLANC: And when are you leaving?

CHAIRPERSON FROINES: About the second week in

March. So I'd like to -- if we could do it, I'd like either the last week of February or the first week in March.

PANEL MEMBER BLANC: First week in March would be I think a good compromise, wouldn't it?

PANEL MEMBER GLANTZ: Well, I think -- why don't we say -- why don't we agree to the last week of February or the first week of March and see what date works for the most people.

CHAIRPERSON FROINES: Charlie, are you okay?

PANEL MEMBER PLOPPER: Yes.

CHAIRPERSON FROINES: Craig?

PANEL MEMBER BYUS: (Nods head.)

PANEL MEMBER GLANTZ: Because we are going to have -- in addition to finishing the ETS document, we're going to have this other one. And it's very hard for me to believe we could get through two things at one meeting on January 6th and do it well.

CHAIRPERSON FROINES: I had a meeting with Secretary Tamminen about a month ago. And one of the things that we discussed was how's the panel functioning. And Secretary Tamminen is no longer Secretary of CalEPA. He's now in the Governor's office. But the one thing that we agreed to was that we are going to, at some point next year -- and I say next year, so nobody needs to be

worried -- is have a half day or a day long workshop on what are the kinds of chemicals that should be coming before this Panel in the long term. So it's a long-term planning meeting, not a short-term planning meeting. And it doesn't have to occur until December 2005. But it's one of the things that we'll have on our agenda for the future.

PANEL MEMBER BLANC: Well, then rather than belabor this more now, Peter, can you follow up for this meeting, circulate it E-mail, but focused on the last week in February, first week in March?

MR. MATTHEWS: I will.

CHAIRPERSON FROINES: We'll work it out.

Kathy and I have a conflict in the first week in March.

PANEL MEMBER LANDOLPH: I'll be gone 28th of February 1st and 2nd of March.

CHAIRPERSON FROINES: Yeah. Paul was making that suggestion so we would avoid exactly what we're getting into. So let's not get into individual schedules.

PANEL MEMBER BLANC: Plus we have tow people that aren't here today, so we'd need to here from them.

CHAIRPERSON FROINES: And I think today one of the reasons I'm hoping that we spend most of the time on presentation is I think it's very, very important to have

a fully prepared Gary Friedman as our epidemiologist for the January meeting. So that the discussion on various epidemiologic studies I think is -- I'm going to work with him, and I think OEHHA can work with him, to make sure that over the holidays and everything he's well prepared for that January 6th meeting.

PANEL MEMBER GLANTZ: Yeah, just one last thing. I just was looking at Joe's calendar. And the last -- february 28th is a Monday. So just to be precise, I would say that you try to get a meeting scheduled between the 21st of February and the 4th of March or maybe the 11th of March.

CHAIRPERSON FROINES: We'll move ahead, unless -- Paul is looking at his calendar -- and says those don't work.

PANEL MEMBER BLANC: No, no, no. I'm fine.

CHAIRPERSON FROINES: Okay. Jim, let's go.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Very good.

Well, good morning to Dr. Froines and the rest of the Panel. Appreciate your consideration of our report this morning.

My name is Jim Aguila. I'm the Manager of the Substance Evaluation Section within the Air Resources Board. And our group was responsible for developing the

exposure assessment, and will also be the primary group that takes us through the legal rulemaking process for eventually identifying environmental tobacco smoke as a toxic air contaminant.

This morning's strategy, what we intend to do is tag team with OEHHA in our presentation today. And actually one of my staff will be giving our presentation on the exposure assessment. And then we'll turn it over OEHHA for their part.

So with that, I'll go ahead and introduce Robert.

CHAIRPERSON FROINES: Can everybody see okay? It seems to me a little light. And should we move this over? How are you?

PANEL MEMBER GLANTZ: Okay. It's fine.

PANEL MEMBER BLANC: If your okay, then we're okay.

MR. KRIEGER: Thank you, Jim.

As Jim mentioned, my name's Robert Krieger. I'm staff lead for the proposed identification of ETS as a TAC.

(Thereupon an overhead presentation was Presented as follows.)

MR. KRIEGER: Today we'll be providing you with a summary of the SRP version of the draft report proposed identification of the environmental tobacco smoke as a

toxic air contaminant.

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MR. KRIEGER: Developed by the Air Resources Board and the Office of --

CHAIRPERSON FROINES: Just for Dr. Plopper. People -- most of this discussion will occur at the January 6th meeting. But keep in mind that people always break into to the presentation for questions. So there's no problem.

PANEL MEMBER BLANC: Just like he's doing now.

MR. KRIEGER: Thank you. Good example.

The information presented in this report will serve as the basis for its identification as a toxic air contaminant.

I will be giving an overview of the ARB's exposure assessment evaluation, followed by Dr. Melanie Marty of the Office of Environmental Health Hazard Assessment, who will provide a presentation on OEHHA's health assessment report.

Included in each presentation will be a summary of comments and responses to these comments we received on the respective parts during the public comment period earlier this year on the initial draft report dated December 2003.

Our presentation will conclude with a slide

describing the next steps of the process.

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MR. KRIEGER: State law requires that ARB assess exposures to a substance suspected to cause adverse public health effects for people in California. The law also requires the OEHHA to evaluate health effects of the substance and to determine if the threshold of the significant adverse health effects exists for that substance.

SB 25 established the Children's Health Protection Act of 2001. Specifically for air toxic identification it requires that health risk assessments include an analysis of children's exposure and health impacts from each substance. We have addressed these requirements in the public report.

Next slide.

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MR. KRIEGER: This slide shows the definition -- legal definition of a toxic air contaminant, which is: "A toxic air contaminant is defined in California law as an air pollutant which may cause or contribute to an increase in mortality or in serious illness or which may pose a present or potential hazard to human health."

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MR. KRIEGER: This chart shows the toxic air

contaminant identification process we follow to ensure that any regulation we propose will be based on good science. The process provides for publicly review and complies with all the applicable administrative requirements.

Initially, the ARB undergoes a process to prioritize substances of concern to determine if they should be selected for evaluation.

Once we have entered a substance into the identification process, we work with OEHHA to develop a report which will serve as the basis for the identification. OEHHA develops the health effects portion of the report, while ARB develops the exposure data. The report then undergoes public review, with a public workshop held generally towards the end of the comment period.

The Scientific Review Panel on toxic air contaminants then conducts peer review of the report and provides its findings to the ARB. At that point, the ARB initiates the rulemaking process with the public release of the staff report, which contains the staff's proposal to list ETS as a toxic air contaminant. The public is given a 45-day comment period on the initial statement of reasons. And the process culminates with a board hearing to consider identifying by regulation ETS as a TAC.

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MR. KRIEGER: This slide presents a chronology of ETS-related work that brings us to where we are today.

In February of 1992 a collaborative agreement between the ARB and OEHHA was reached to initiate a report on the health effects of ETS, as requested by the Scientific Review Panel.

The final draft of this report was reviewed and approved by SRP in 1997. Subsequently the National Cancer Institute recognized the importance of the report and incorporated it into their smoking and tobacco controlled monograph series in 1999.

In June 2001 ETS was formally entered into the toxic air contaminant identification process, given its significant health risks to the public, particularly children.

In December of last year, the draft ETS identification report was released for public comment.

In March of this year, a public workshop was held to discuss the report.

We responded to public comments on -- report this past October.

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MR. KRIEGER: Now on to our Part A, Exposure Assessment.

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MR. KRIEGER: With that background I'll now review the Part A, Exposure Assessment.

The exposure assessment meant incorporates information from Chapter 2 of the 1997 OEHHA report. However, much of our exposure assessment was information that was not presented in the original OEHHA report.

As with other identification reports, our report addresses the areas required by law. They include information on a substance's chemical and physical characteristics, sources and emissions, a measure of an estimate of ambient concentrations, indoor and total exposure, children's exposure, and a substance's persistence in the atmosphere.

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MR. KRIEGER: ETS is well established that it is a complex mixture of gases and fine particle emitted primarily by the burning of tobacco products and from smoke exhaled by the smoker. Other minor contributors are from the smoke that escapes while the smoker inhales and some vapor phase-related compounds that diffuse from the tobacco product.

Many of the substances found in ETS have known adverse health effects. For directly emitted side-stream smoke and mainstream smoke, most ETS particles can range

in size from .01 to 1 micrometer.

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MR. KRIEGER: Since smokers are the origin of ETS emissions, smoking prevalence provides a helpful indication of how ETS exposure is generated and by whom. According to the California tobacco survey data collected by the California Department of Health Services, smoking prevalence among adults and adolescence has decreased over the past decade.

Since the passage of Proposition 99 in 1988, adult per capita cigarette consumption decreased by over 16 percent in California. In 2002, California adult smoking prevalence was 16 percent and lower than the rest of the nation. Credit here should be given to the California anti-smoking laws and programs that help with smoking cessation.

In 2001 the California Students Tobacco Survey was adopted by the Department of Health Services as a more accurate survey to measure adolescent smoking behavior. The CSTS utilizes in-school surveys, which are expected to be much more accurate as opposed to the random phone calls performed under the original CTS.

The Latest results of the survey showed 16 percent of California adolescent population smokes.

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MR. KRIEGER: This slide shows ARB's estimated total statewide emissions for some of the pollutants commonly associated with ETS. The basic calculation is straightforward: Emission factors times the products consumed. We repeated the calculation for both cigarettes and cigars and added the results to obtain the total.

Sales tax information from the Board of Equalization, emission factor studies, and the California tobacco survey were used to estimate statewide and county-by-county emission estimates.

Staff then adjusted -- had applied an adjustment factor to account for the fact that smokers generally burn about 90 percent of tobacco column.

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MR. KRIEGER: How do we measure ETS exposure? There are a number of components associated with determining ETS exposure due to its complex mixer such as the ability to determine the appropriate marker that represents ETS as a whole. Several components of ETS have been used as markers: Nicotine, solanesol, 3-EP, iso-anteisoalkanes, PAHs, and RSP.

Nicotine has been the most widely used marker because its unique to tobacco smoke.

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MR. KRIEGER: Two published studies measured

outdoor concentrations of ETS:

Rogge in his study measured fine particles of ETS in a range from .28 to .36 micrograms per cubic meter.

Eisner used passive benchmark to measure nicotine concentrations over a 7-day period. The results show an average concentration level of .025 micrograms per cubic meter of nicotine.

To fill the gap in California's ETS ambient exposures ARB also collected data through ambient ETS air monitoring study. ARB monitored nicotine concentrations at several outdoor smoking areas in California. The results showed a range of concentrations from .01 to 3.1 micrograms per cubic meter for an 8-hour period and .039 to 4.6 microgram per cubic meter for a 1-our period.

PANEL MEMBER BLANC: The Eisner study is not a pure outdoor nicotine study and you can't use it in the way that you're citing it here.

MR. KRIEGER: Is that --

PANEL MEMBER BLANC: It's a 7-day integrated indoor/outdoor, to wherever people --

MR. KRIEGER: You're correct. It is an integrated study. They do provide an outdoor number, but it is integrated.

PANEL MEMBER BLANC: It's not an outdoor by nature, but there are outdoor hours of self-reported

exposure. And you could probably take the average outdoor hours as a percentage of total hours and multiply it. Although I think that that would presume that the concentration was the same, which you can't do. So I don't think you can cite that here for the purposes that you seem to be trying to site it, which is as a measure of outdoor --

PANEL MEMBER HAMMOND: I think there was a part of that -- I think -- I agree with that part. But I think there's a part of that study where some of the people in the study were only exposed outdoors. And I didn't --

PANEL MEMBER BLANC: Yes. But I don't --

PANEL MEMBER HAMMOND: They had no indoor exposure.

PANEL MEMBER BLANC: Yeah. But I don't know if there was a separate calculation done in that study. You can look.

MR. KRIEGER: I believe there was a separate calculation in there. But I can --

PANEL MEMBER HAMMOND: And this may be that number.

PANEL MEMBER BLANC: And is that what you're using?

MR. KRIEGER: That was the one we were using the separate calculation for that. But I know it was an

integrated study and I --

PANEL MEMBER HAMMOND: I thought some people reported it only exposures that --

PANEL MEMBER BLANC: Okay. If that's true, that's okay then. I just want to make sure that --

MR. KRIEGER: I mean there --

PANEL MEMBER BLANC: Just double check if that's what you did.

MR. KRIEGER: Well, we'll double check that and make sure. But I believe that was the one. That was the number that we used for the study. But like I said, there's not too many outdoor --

PANEL MEMBER BLANC: No, I understand.

MR. KRIEGER: Oh, and our last number -- bullet there, our last was to provide a perspective on general exposure. And we did the -- the ARB staff estimated statewide annual average annual concentration for ETS particulate and nicotine to be .02 micrograms per cubic meter an .0025 micrograms per cubic meter, respectively.

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CHAIRPERSON FROINES: How was that arrived at?

MR. KRIEGER: That was taken into account for emissions inventory and emission factors for ETS from cigarettes themselves. So we merely did a simple calculation of it: What's the inventory of ETS

particulate in California and ETS nicotine in California, taking into account the number of cigarettes smoked in California, the number of cigars smoked in California as well? And the fine PM inventory in California and taking a percentage of that.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Actually --

PANEL MEMBER HAMMOND: But is there an underlying assumption then that the ETS is equally distributed throughout the state?

MR. KRIEGER: Yes, there's a big assumption there.

PANEL MEMBER HAMMOND: And that's probably an inaccurate assumption.

PANEL MEMBER BLANC: And then how did you arrive at how much of the cigarette consumption was consumed outdoors?

MR. KRIEGER: We're assuming that all of the cigarettes consumed indoors makes it outdoors. We have a number of assumptions here that we used.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, it was a total estimate.

MR. KRIEGER: It was a total estimate.

CHAIRPERSON FROINES: That's a very questionable estimate.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Basically what we wanted to do is to provide some perspective in the case where you would have concentrated smokers and have -- is it possible to estimate some kind of a background level? And we had -- as Robert mentioned, we had PM10 emissions inventory data, and then we used that with emission factor studies to correlate the RSP from tobacco smoke, and were able to determine these background numbers based on the existing inventory PM10.

CHAIRPERSON FROINES: But if the -- if much of the smoking that you're actually estimating comes from indoor smoking -- tobacco smoke is sticky stuff. And so whether or not that ever has a slightest change to occur outdoors, but that could be a very misleading estimate.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, that's one of our underlying assumptions, is that the smoking occurs outside.

PANEL MEMBER BLANC: But don't you know from other survey information how many cigarettes people smoke outside? I mean the California Tobacco Survey is quite detailed.

Stan, do you know if they --

PANEL MEMBER GLANTZ: I don't remember if they asked the question, "Do you smoke inside or outside?" But I think that there are probably good data in the

literature on that.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, we found literature to indicate that most of the smoking, you know, occurs outside. But we didn't have an exact number or percent.

PANEL MEMBER GLANTZ: In California that may be actually getting true because of all the smoke. I don't know if that would be true nationally. But in California most smoke -- you know, a lot of the smoking is now outside.

PANEL MEMBER BLANC: Well, I think it would be worth incorporating some fractional discount in your number that says, "Okay, we are going to conservatively assume that on average," you know, one out of four cigarettes that are smoked are smoked outside. Or here's the range if we assume that it's one out of four and here is if it's three out of four --

MR. KRIEGER: Okay.

PANEL MEMBER BLANC: -- or something. Because otherwise the face validity of the exercise seems too dubious.

CHAIRPERSON FROINES: The other problem is that the -- it's not clear what you want to use a number like that for. And that number will be get quoted everywhere in every newspaper when it covers this kind of issue. And

so there will be an assumption that there's some significant validity to the number. And so we just want to be careful not to give misleading information for which we don't really have a reason for that.

PANEL MEMBER HAMMOND: Well, and I'm equally concerned or maybe even more so about the geographic distribution. In other words, almost certainly there's more emitted where there are more people living. And there's going to be more -- so that concentration of that area will be higher and the exposures of people who are outdoors in that area where most of the population is will be higher.

So for two ways that underestimates exposure to spread it through the entire study.

MR. KRIEGER: Those are good comments.

Okay. Now, on Indoor study --

PANEL MEMBER GLANTZ: Just one other comment on this.

You know, the way I sort of think about the outdoor exposures is more like a hot spot rather than a broad ambient exposure. And so you might want to be thinking about it in those terms too.

MR. KRIEGER: Yeah. And --

PANEL MEMBER GLANTZ: And that certainly would fit with the way you did this -- you know, the studies

you're probably going to talk about that you guys did, which are in the appendix Part A, I mean those are really kind of hot spot studies rather than broad ambient studies.

MR. KRIEGER: And I think that's -- yeah, that's a good point. I think Dr. Glantz has a good point. And I know we speak on the next proceeding slides, where we focus our attention on the scenarios that we've done, which incorporates the hot spot exposure. Because ETS is localized and that's more of a hot spot issue versus the statewide population layer, any kind of estimate that we have.

--o0o--

MR. KRIEGER: Several studies that measured ETS concentrations indoors, in different environments using primarily nicotine and RSP as markers for ETS, an exposure. Indoor concentrations of nicotine are estimated to range from .5 to 6 microgram per cubic meter in the home environment, and 2.2 to 8 micrograms per cubic meter in offices or public buildings where smoking is allowed, and less than 1 microgram per cubic meter in public buildings where smoking is prohibited.

As also indicated, certain work places such as free-standing bars in betting establishments that do not comply with California's work place smoking ban would

likely have higher levels of ETS.

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MR. KRIEGER: As we talked about just briefly, a scenario-based approach is used to characterize the range of the public's exposure to ETS in this report. We believe this approach provides more informative estimates of public exposure to ETS than population-weighted outdoor ambient exposures calculated for previous TAC exposure assessments. This approach takes into consideration that cigars and cigarettes, the primary source of ETS, are small sources that emit pollutants near people and that these exposures are localized.

The scenario-based exposure method uses the results from ARB's nicotine air monitoring study, available indoor ETS concentration data, and activity patterns to estimate exposures under different conditions for various segments of our population.

The results of the different scenarios indicate that exposures to ETS can vary in many different situations. Daily exposures for individuals living in nonsmoking homes and having only brief encounters with smokers are estimated to be less than 1 microgram per cubic meter. Individuals living in homes with indoor smokers and experiencing other ETS exposures throughout the day may result in higher exposures of about 3

micrograms per cubic meter. For some of the population outdoor smoking can contribute from virtually 0 to 100 percent of an individual's exposure to ETS.

--o0o--

MR. KRIEGER: Another method for estimating human exposures to ETS is through the use of biomarkers. Cotinine, the major metabolite of nicotine, has emerged over the past 20 years as a widely used biological marker for most field exposure studies. Cotinine is sensitive enough that its concentration can reliably distinguish between non-ETS exposed persons and ETS exposed non-smokers with low, moderate, and high levels of exposure.

Nicotine in hair is an emerging biomarker that may be as effective as cotinine in predicting levels of ETS exposure.

Other biomarkers of exposure such as DNA and protein adducts of ETS link ETS exposure directly to carcinogenic metabolites.

PANEL MEMBER BLANC: Doesn't that list also need to include some of the other nicotine metabolites that people like -- which we're starting to look at? I mean this is just a table you're presenting. But in the document, do you at least allude to that even if they're not ready for prime time?

DR. WINDER: Well, there is some discussion of other biomarkers and their relative effectiveness compared to the cotinine in nicotine. And the conclusion being that these two at this point in time are the best we have.

PANEL MEMBER HAMMOND: I think the purpose of these biomarkers is to evaluate the exposure of a population. And to that degree, it has to be established by the markers as opposed to the research level. Is that correct -- a correct interpretation?

PANEL MEMBER BLANC: And you feel you're clear enough about that.

And there's a sufficient discussion of the shortcomings of -- the timeframe shortcomings of cotinine, or limitations in terms of it being a fairly recent ETS exposure marker and how as we start to look at populations with intermittent exposures, which only occur in ambient hot spot areas, a urinary cotinine measure is likely to be a poor assessment tool in that regard as compared to more integrated cumulative measures. In other words, even if I -- if I was exposed heavily to ETS every Friday, and you sampled my urinary cotinine every Wednesday, you would have -- you would think I wasn't exposed at all. But if you had a more integrated measure, you would catch the fact that every Friday I go to Bingo and have this heavy exposure.

I mean do you feel that that's adequately discussed as a limitation in your --

DR. WINDER: Well, there's a discussion in several places in the document regarding the time period over which both serum and urinary codeines are appropriate and the limitations with respect to short-term exposure.

Your suggestion with an integrated marker is a point well taken. But it's not something that's occurred at least in many studies.

PANEL MEMBER BLANC: But it does tend to mean that some of the estimates you have will be underestimates of precisely the kind of exposure scenarios which are most important to the document, and that all the bias is towards underestimation. Isn't that correct? Or am I -- is that a fair -- to the extent that someone's exposure is regular indoor. I live with a smoker or I work with smoker in an indoor environment, the latter being now taken largely out of the mix in California. Then for those kinds of populations cotinine is not such a bad marker because your sampling issues are -- the day-to-day variability is, although present, is not huge.

But to the extent that someone's exposure is predominantly ambient and, by definition, predominantly hot spot with peaks and valleys that are intermittent, then the cotinine tool becomes more and more prone to

missing the exposure and, therefore, falsely categorizing somebody as underexposed, and will only categorize them as exposed when you catch them the day after one of these events.

MR. KRIEGER: Well, that's a good comment, Dr. Blanc. We'll certainly go back and take a look at what we have in the report and revise that to our -- and strengthen that section to talk about the variability and the sampling.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: I think we should add some text to qualify basically the point you're making, Dr. Blanc.

CHAIRPERSON FROINES: Can I make one comment.

This last statement of DNA and protein adducts less useful in quantifying exposure. Is there going to be a discussion presumably by OEHHA at some point about the biomarker issue or --

PANEL MEMBER HAMMOND: You mean as a risk estimator as opposed to --

CHAIRPERSON FROINES: Well, you see, the trouble with DNA adducts is that people use them for various reasons. And I think that often there's a lot of confusion specifically with respect to timing, that if you measure DNA adducts, you're measuring -- in fact the BAP, for example, is bound with a DNA at that particular

timeframe. And so it's -- so people use them because they think they have mechanistic significance. They use them as potential for linkages with epidemiology and they -- but in fact what it is is a measure of exposure. And we need to be sure we're clear on some of these studies that -- because there are a lot of studies that have looked at APB and BAP and what have you.

So at some point during this process, we need to have a discussion about the nature of biomarkers I think.

SUPERVISING TOXICOLOGIST MARTY: This is Melanie Marty.

There are a few studies that looked at DNA adducts and tried to correlate that with, for example, breast cancer risk. And I think most of those studies the authors themselves recognized the difficulty of trying to make those types of correlations, because of differences in individual variability and metabolizing the carcinogen to the DNA adducting ultimate carcinogen and just kinetic issues. So there's some discussion about that.

CHAIRPERSON FROINES: Well, there's a temporal issue --

SUPERVISING TOXICOLOGIST MARTY: Right, the temporal issue.

CHAIRPERSON FROINES: You know, a latency issue.

Are we going to talk about that at some point?

SUPERVISING TOXICOLOGIST MARTY: Just a little bit when we talk about the breast cancer. But there's more discussion in the document.

CHAIRPERSON FROINES: Yeah, I know there's discussion in the document. And that's what primed me to raise this, because I think there's -- there is some misunderstanding about the nature of these.

PANEL MEMBER BYUS: It's exposure versus mechanism is really the question with the adducts.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: That's right.

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MR. KRIEGER: The constituents of ETS undergo independent atmospheric reactions. In general, gaseous chemicals of ETS can react in the atmosphere with other pollutants and sunlight to form new chemical species.

Nicotine, the principal alkaloid in tobacco, which is most commonly found in the gas -- environment. In the ambient air nicotine may react with hydroxyl radicals to have a half life of approximately one day. ETS particles are subject to deposition and atmosphere transformation of species adsorbed to the particles. One chamber study showed that these particles can persist of up to five hours.

CHAIRPERSON FROINES: But there's the other

category that we've been looking at in terms of air pollution and, that is, when those hot vapors come out of the cigarette, don't you have also some volatile particle formation as well?

PANEL MEMBER HAMMOND: There's evaporation.

CHAIRPERSON FROINES: Well, there's evaporation, but there's also --

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: There's a number of things.

CHAIRPERSON FROINES: -- in the wintertime you're going to get condensation and you're going to form particles. We see that -- that's what happens when things come out of the tailpipe. They form particles by condensing.

MR. KRIEGER: Yes.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Like aerosols.

CHAIRPERSON FROINES: What?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Forming aerosols or --

CHAIRPERSON FROINES: Yeah. Vapors can evaporate and vapors can condense. And both things happen. And so you're going to have some particle formation as -- and they're going to be very volatile particles relative to what Kathy's talking about which is the evaporation of

organics and things off the particles.

So my sense, and I don't know the literature on this, is that you may have some particle formation that also occurs.

PANEL MEMBER BLANC: I fear to ask this question in front of an industrial hygienist.

When you say particle here, do you mean both solid particulates and liquid aerosols? Is that what you mean by particulate here?

MR. KRIEGER: Well, from my understanding that's what the literature says.

PANEL MEMBER BLANC: And that's your intent?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, we recognized that there are components that are being formed from VOC's. Likewise, there's also particulates that sublimate mate too and --

MR. KRIEGER: And we also recognize the vapor -- you know, the vapors coming off can form particulates, especially when it cools, any particular temperature really. But we recognize that too as well. And there are some literature that shows that as well.

PANEL MEMBER HAMMOND: I think it -- it's pretty complex. I mean I don't know whether -- I think it's important either not to try to attempt to do this or to do a really thorough review. I think to do it superficially

would be a mistake, because there's also a lot of literature about volatilization, especially as there's less concentration and particle size is getting smaller, rather -- you know, especially I would think outdoors.

But I don't know. Is that something you want to go into in -- I think you'd need to choose whether to go in-depth or to just to -- but I wouldn't do it superficially.

But then, again, they can react with other things that are in the atmosphere, that aren't in a house maybe, but they're outdoors.

PANEL MEMBER BLANC: Well, clearly the ARB has a lot of experience in talking about engine emissions. Is there some corollary here that you could summarize briefly that would put it in that context? Since part of what the exposure document is trying to do is put ETS on the same footing of other airborne pollutants, right?

MR. KRIEGER: You're right, yeah.

PANEL MEMBER BLANC: And the model of having to deal with non-stationary internal combustion emission mixes is not so very different, is it?

MR. KRIEGER: No, it's not. And, for instance, diesel exhaust, you know, a complex mixture, it's the same sort of deal. I mean you have different sources obviously in different locations. It's not as localized. But you

still have the complex mix coming out of the tailpipe and eventually ending up into the atmosphere. And you're having different reaction products over the vapor phase and the particle phase, all those different reactions. And we addressed it in diesel exhaust, I know. We briefly mentioned on the gaseous components and the particle components just like we did here. We didn't go in-depth.

I mean we could go in-depth for every, you know, reaction and the different reactions that happen in the atmosphere with the different radicals and reactions within themselves, the organics playing with each other to form particles.

We didn't go in depth in this. And certainly we could. But we felt for this identification report -- the law specifically tells us to address this comment. But as far as the details with all the minutia, we didn't -- we chose not to do this. Because, like Dr. Hammond suggested, there's a number and it can -- it's overwhelming at times for the amount of information.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Would it make sense to expand the discussion of particulate component and reaction to include aerosols -- aerosol component reactions? That seems like it would be more comprehensive, to be more clear in our report that we're actually talking about both, not just VOC related

but the solid particulates too.

CHAIRPERSON FROINES: Well, I should say that we have just published about five papers on particle formation from vapors that have never been published before. And so the question is -- and we find very different particles formed by condensation of vapors. And so we can give you those papers. And then you can think about whether or not this has any relevance to environmental tobacco smoke.

But this isn't -- this is not in the literature. This is new findings. For example, we've just done a major study at the Caldecott Tunnel, and so on and so forth, so that -- the issue is the particles that are formed from vapors may have significant toxicity that is not generally understood when you have a traditional kind of soot particles that you're referring to.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: I think that would be very helpful, Dr. Froines, to get those papers.

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MR. KRIEGER: In summary, ETS is a complex mixture of gases and particles, many with known adverse health effects. Tobacco smoke contributes several tons per year of nicotine, fine particles and carbon monoxide into the California atmosphere. Most ETS particles range

in size from .01 to 1 microgram.

Although most of the non-smoking public's exposure to ETS is low, in certain cases outdoor exposures can be significant, ranging up to 4.6 micrograms per cubic meter in nicotine. Indoor ETS nicotine concentrations may range from .5 to 76 micrograms per cubic meter.

Use of biomarkers are a good predictor of ETS exposures.

And daily exposures to ETS nicotine concentrations can range from less than 1 to 3 micrograms per cubic meter.

PANEL MEMBER BLANC: What do you mean when you say significant?

MR. KRIEGER: Oh, significant, when we referred to the outdoor concentration of 4.6?

PANEL MEMBER BLANC: Yeah, what does significant mean in that sense?

MR. KRIEGER: Significant means that -- from our standpoint, significant is an exposure level that's equal to some concentrations that are found indoors. The 4.6 is significant compared to an outdoor of low exposure.

PANEL MEMBER BLANC: So when you say the sentence, what you really mean is indoor -- I'm sorry. So the point -- is that supposed to be indoor ETS nicotine --

MR. KRIEGER: Yeah, indoor.

PANEL MEMBER BLANC: Okay. So that's supposed to say indoor, right?

CHAIRPERSON FROINES: Which one are you on?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, the third bullet from the bottom?

PANEL MEMBER BLANC: So then why are you going from outdoor to indoor? Why wouldn't you go from indoor to outdoor, for example? Is the argument -- what's the logical argument here?

MR. KRIEGER: I'm looking at the -- oh, we're talking about the fourth bullet down, right?

PANEL MEMBER BLANC: The third bullet from the bottom, "Indoor ETS nicotine concentrations present significant exposures ranging from .5 to 76."

MR. KRIEGER: Oh, the "significant" would be actually the upper end of that range. It would be the 76.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah.

PANEL MEMBER BLANC: So then you're saying that the bullet before that, the significance of the outdoor is not significant because it doesn't get up to 76?

MR. KRIEGER: No, I think we -- we need to clarify that point. Actually the 4.6, the outdoor concentration, is significant, is compared to those concentrations generally found indoors. The slide before,

the table, indoor concentrations on average had .5 to 6 micrograms per cubic meter.

The 76 micrograms per cubic meter for the indoor concentration was -- basically the betting established those of the priors. So that's the very high end of the range.

But the 4.6 outdoor concentration is significant that it falls right in between the middle of the indoor exposure --

PANEL MEMBER BLANC: So it's not that the word is not "significant". In the bullet before then what you mean is that outdoor exposures can be substantive and fall within a range that is commonly found indoors. Is that what you mean?

MR. KRIEGER: That's correct, that's correct.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: That's the point we're trying to make.

CHAIRPERSON FROINES: I think we have a tendency to overuse the word "significant". And probably leaving the word "significant" out would -- and let the data stand on its own, or if there's some explanation to explain it. But I think the word "significant" tends to mean different things with different people.

PANEL MEMBER BLANC: And I think you need to reverse the order here, because if you're building up the

argument that the reason it's substantive is because it approaches the indoor levels, then you should tell us what the indoor levels are first. It's not a logical sequence here.

MR. KRIEGER: Okay.

PANEL MEMBER BLANC: I mean I understand this is a slide for us. But assuming that this somehow may appear in some other summary recitation.

MR. KRIEGER: Okay. Good point.

Next slide.

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MR. KRIEGER: Before we go on to OEHHA's presentation, we have summarized a few of the major -- or the major comments that we received on the Part A exposure assessment. In general they fall into four categories.

First, we have several comment letters in support of our report and the identification of ETS as a TAC.

Next, in the exposure assessment portion of the report, a comment centered around the contention that the draft report does not address the specific exposures that cause adverse health effects. Our response is that we believe there is sufficient evidence presented in the report to show that ETS is admitted into the ambient air in California and that there are adverse health-related impacts to exposures to ETS.

Another comment suggested that short-term exposures are inadequate to assess long-term population-weighted exposures. As we talked about before, we used a scenario-based approach to estimate daily concentration for a range of subpopulations. Since ETS sources are localized, we felt it better to estimate a measure of daily exposure. A population-weighted assessment would not adequately address the public's exposure, especially those subgroups that are being exposed to higher ETS concentration levels.

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MR. KRIEGER: The next category of comments address ARB's monitoring study. A commenter mentioned that ARB's monitoring study did not measure exposure duration and its use of nicotine as a marker has problems. Again, the purpose of our monitoring study was to estimate exposures near smoking sources. We took one-hour and eight-hour samples to estimate more realistic daily exposure scenarios.

The use of nicotine in the outdoor environment has been done before, and we believe this method used to collect the samples was accurate and reliable.

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MR. KRIEGER: Next comment. The staff should consider the personal monitoring results from the 16-city

study done by Jenkins.

We added the personal exposure results to this study into our indoor section of the report.

The next comment. The commenter suggests that cotinine is not a particularly quantitative indicator of a person's nicotine exposure.

At this time the scientific community accepts the basis that cotinine and nicotine are reasonable indicators of a person's relative degree of exposure to tobacco smoke. Several studies referenced in Part A exposure assessment used cotinine as a sufficient indicator of ETS exposures.

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MR. KRIEGER: The last major comment focused on our authority to identify ETS as a whole since its makeup changes over time. We believe that it is reasonable to consider ETS holistically as a toxic air contaminant as it is emitted from a common source. The ARB used this approach in the past when evaluating diesel exhaust as a toxic air contaminant. They included information on the atmospheric persistence of the ETS compounds because it is important to point out that a chemical nature of ETS has a temporal effect.

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MR. KRIEGER: Now, before I turn it over to

Melanie for OEHHA's presentation I would like to go over the next steps in the identification process, as shown in this slide.

If the Panel is still deliberating about the ETS report after today's meeting, a second meeting will be needed.

If you approve the report at the next meeting, you would prepare and send findings on the report to the ARB.

Once we receive the SRP findings, the ARB initiates the rulemaking process with the public release of the hearing notice and the staff report, which contains the staff proposal to list ETS as a TAC. The public is then given a 45-day comment period on the initial statement of reasons.

And the process culminates with the Board hearing to considering identifying by regulation ETS as a TAC.

And that concludes my presentation.

Any questions on that before we go to Melanie?

CHAIRPERSON FROINES: I think it would have been useful to have seen in your presentation some of the data that you actually collected. It seemed a little thin in terms of the presentation to me.

PANEL MEMBER BLANC: Well, they did present some of the data at a previous meetings, isn't that correct?

The actual sampling data from Sacramento. You might want to just have just perhaps more -- at our January meeting you may want to just remind us of some of the key original studies that you did. So I think that's what you --

CHAIRPERSON FROINES: Jim, can you make a note of that, to follow up on that?

MR. KRIEGER: We can do that.

PANEL MEMBER BLANC: And is there a -- forgive me for asking certain questions, which betray a lack of total familiarity with the draft document. But remind me, is there a table in your exposure document which lists the known constituents which are already designated as TACs? That's in there, isn't it? We talked about that before.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: That's in there.

PANEL MEMBER BLANC: So that addresses the one -- also doesn't that address one of those -- the critical comments that you received?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yes.

CHAIRPERSON FROINES: Is there a table -- and I'm sorry. I apologize for the same reason. Is there a table that looks at the size distribution of the particulate?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: There is, as a matter of fact.

CHAIRPERSON FROINES: And I just don't remember. And I didn't want to take time to look. I'll have to worry about it.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yeah, there's actually a table that summarizes some of the key studies that we looked at. And then there was also a graph from a Morasco study, kind of indicates --

CHAIRPERSON FROINES: That's fine.

Peter, where are we in terms of lunch?

MR. MATTHEWS: It's soon coming.

CHAIRPERSON FROINES: Is that -- could you check and see if the person peaking through the door is lunch.

MR. MATTHEWS: They're coming in.

CHAIRPERSON FROINES: Because if the lunch is here, we could take a short break and then we can get started with Melanie and OEHHA.

MR. MATTHEWS: They're coming in.

CHAIRPERSON FROINES: They are?

Well, let's take a break, get some sandwiches, and come back and Melanie will get started.

I think -- unless there are more questions for ARB right now.

No?

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Is everybody on the Panel

here?

Before we continue I want to make one statement basically for the record. And, that is, that the Panel has received a letter dated November 16th, 2004, from an attorney representing R.J. Reynolds Tobacco Company. In the letter the company claims that panel members qualified as pathologists or oncologists must also be medical doctors; and that Drs. Glantz and Hammond have engaged in certain professional activities which cast doubt on their ability to review the draft report objectively.

So I have consulted with SRP's legal counsel on this issue. And I have been advised that nothing in the R.J. Reynolds letter prevents the panel from moving forward on the draft report.

The Health and Safety Code does not require a medical degree for one to be qualified as an expert in pathology or oncology.

Further, the lawyer has concluded that Drs. Glantz and Hammond do not have conflicts of interest in the matter at hand.

I've spoken with Stan and -- Dr. Glantz and Hammond, and they both assured me that they will be able to fairly and objectively participate in the Panel's review of the draft report.

I'm satisfied with those assurances and believe

the Panel should move forward on the consideration of the report.

So we are going to reject the contentions of the R.J. Reynolds letter and we can move forward.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA DEPUTY DIRECTOR ALEXEEFF: Hi. This is George Alexeeff, Deputy Director of OEHHA. I just wanted to make a couple of comments.

One is we did a very extensive, thorough, comprehensive evaluation of environmental tobacco smoke over the last two to three years. It utilized probably up to about ten or more staff members in various ways. And we feel -- although it's been referred to or might be called an update, we feel it's a very thorough, comprehensive report. We're very proud of this report and think it has identified a number of very important scientific issues and public health issues. And so we're just -- we know you'll have a number of issues that you'll raise. But we feel very proud and very happy to bring this report to you today.

SUPERVISING TOXICOLOGIST MARTY: With that I'm going to start by going through the introduction to the document. And we do have a presentation on each chapter. Since time is sort of critical today, I will reserve the

right to skip some of the slides in the hopes of just giving a reasonable overview of the material that's in the document.

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SUPERVISING TOXICOLOGIST MARTY: The Children's Health Act of 1999 in California did amend the toxic air contaminant statutes mandating OEHHA to explicitly consider exposure patterns and special susceptibility of infants and children when developing health effects assessments of toxic air contaminants.

It's worth noting that ETS has a number of adverse health effects on infants and children, including sudden infant death syndrome, asthma induction and exacerbation, increased lower respiratory tract infections, and impacts on decrements in berth weight.

Therefore if the panel chooses to recommend that ETS be added as a TAC, we think it should be added to the list of TAC that disproportionately impact infants and children pursuant to Health and Safety Code Section 396669.5.

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SUPERVISING TOXICOLOGIST MARTY: The approach OEHHA used to updating our '97 health effects assessment focused essentially on epidemi --

CHAIRPERSON FROINES: Melanie, I'm sorry. I

don't mean to interrupt, and I'll try and be quiet.

But just as a matter of policy -- and this may be for George -- every time we now see a document from you, can we make that determination were the evidence to warrant it? In other words, we went through the five chemicals, and we listed another group of chemicals that didn't meet the requirements, didn't meet the -- have sufficient evidentiary basis. And so the point is: Is it as a matter of law and policy that we can with each chemical make that determination?

SUPERVISING TOXICOLOGIST MARTY: The law actually requires OEHHA to update the list. So if OEHHA makes the recommendation, then the list gets updated. I think the panel can weigh in as to whether that TAC should be on the list of those that disproportionately impact infants and children.

CHAIRPERSON FROINES: So this could be a method to update the list?

SUPERVISING TOXICOLOGIST MARTY: Correct.

OEHHA DEPUTY DIRECTOR ALEXEEFF: And --

CHAIRPERSON FROINES: Beyond five?

OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah. This is George Alexeeff again.

Of course this compound is being brought to you through the TAC process. So every compound brought

through the TAC process should be evaluated for its impact on children. Any recommendations you have regarding either endpoints or health issues that address that issue would be very helpful for us in terms of adding in the process. Since we haven't actually added one to the list by this process yet, we'll probably just be working it out with the Air Board once we add one. And then we'll know all the different particulars.

But any -- as Melanie mentioned, we do have to update the list. And this would be, you know, a candidate for updating the list. Or it could be the next compound that updates the list, depending upon how the panel concludes its review and how the -- you know, the chemicals listed as a TAC.

SUPERVISING TOXICOLOGIST MARTY: To be noted, the list updates have to go through panel review. So we do have a significant role.

In our approach to updating the '97 health effects assessment we focused primarily on the epidemiology studies rather than the animal toxicology. So the chapters describe new epidemiology studies published since the previous document was written. And we did use animal toxicology information to support specific health outcomes.

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SUPERVISING TOXICOLOGIST MARTY: We conducted literature searches basically from '96 forward using a variety of search terms, including passive smoking, ETS, side-stream smoke and so on.

We described the more important epidemiological studies in each of the chapters.

Chapters 3 through 5 deal with developmental and reproductive health effects. Chapter 6 deals with the respiratory tract. Chapter 7 is carcinogenicity. And Chapter 8 is cardiovascular health effects.

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SUPERVISING TOXICOLOGIST MARTY: When we evaluated studies we focused on study quality, looking at thing such as: Sample size; the ability to ascertain exposure and associated problems with misclassification of exposure; and then potential confounding and how the studies dealt with that; and as well as sources of bias.

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SUPERVISING TOXICOLOGIST MARTY: As in the last evaluation, we used what we term a "weight-of-evidence" approach.

An effect is judged to be causal when positive associations between ETS exposure and effect is observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence.

We examined the body of the studies for:

Consistency from study to study.

For biological plausibility; and this is where the animal studies did play an important role.

And for bias and confounding as ways to explain the results.

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SUPERVISING TOXICOLOGIST MARTY: We did find that the evidence was sufficient to say there is a causal association between ETS and developmental effects including SIDS and fetal growth. We thought the data were sufficient for a number respiratory endpoints including acute lower respiratory infections in children, asthma induction and exacerbation in children and adults, chronic respiratory symptoms such as bronchitis in children and otitis media. And, finally, we looked at the carcinogenic effects. And we continue to believe the data are sufficient for a causal association between ETS and lung cancer and also nasal sinus and now breast cancer. Breast cancer is a new finding.

PANEL MEMBER BLANC: Melanie, can you go back to the previous slide for a second.

When you're -- you're not using the terms here. But you're clearly trying to be consistent with sort of classic Bradford-Hill criteria.

And one of the issues that comes up in various chapters or with various issues, although not consistently, is the issue of whether or not an effect which is consistent with direct cigarette smoking is evidence of a dose response. I mean it's a sort of implicit issue that comes up.

And in certain -- in responses to certain critiques you get into arguments about -- or discussions as to ways in which it might not be -- certainly not a linear dose response, and perhaps even not ordinal dose response.

Is that safe to say?

SUPERVISING TOXICOLOGIST MARTY: Yes, that's safe to say.

PANEL MEMBER BLANC: And yet it seems to -- the issue seems to come up in these context-specific ways, but not in a very general way at the same point in which you're discussing sort of the Bradford-Hill criteria. Would it not strike them -- the document even if it was somewhat competitive to have an overall discussion of the dose response -- of what dose response -- of the implications of the relationship between findings with active smoking versus findings with secondhand smoke in terms of dose response as an argument for causality.

SUPERVISING TOXICOLOGIST MARTY: Yeah, I think we

did try to do that. Wherever we had dose response formation we pointed that out.

PANEL MEMBER BLANC: But that's dose response within higher or lower ETS, isn't it? It's not dose response -- because for all of these things there are studies which talk about direct smoking.

SUPERVISING TOXICOLOGIST MARTY: Right. We did talk about direct smoking for most of the health endpoints, and whether or not there was an effect with direct smoking.

The one health endpoint where we don't think that dose response is particularly linear is with breast cancer. And we'll get into that in a few slides. So we did talk about dose response not being linear because of these other issues associated with active smoking. And those affect -- the effect of the act of smoking on breast cancer risk is various susceptible sub-populations related to antigenicity --

PANEL MEMBER BLANC: And I'm not saying you shouldn't have that discussion there. I guess what I'm saying is: Is there a global discussion that you should have?

SUPERVISING TOXICOLOGIST MARTY: You know, it almost didn't come up except for there, because --

PANEL MEMBER GLANTZ: Yeah, I think that the --

it also is an issue when you talk about cardiovascular effects and the trying to do a -- and that brings up the whole issue of what are people talking about in terms of so-called cigarette equivalence.

And I really think that's not a productive way to look at this, because there's so many different ways, so many different compounds in cigarette smoke, that what you get as your, quote, cigarette equivalent is highly dependent on what compound you're measuring.

So I think that the idea of dose response and trying to make the active smoking and the passive smoking stuff -- to kind of put them on the same scale would be very misleading because the secondhand smoke is a complex compound and it's different from the mainstream smoke.

PANEL MEMBER BLANC: But doesn't that argument -- if that's going to be the argument, doesn't that argument need -- isn't that I primal enough argument that needs to be made early in the document?

PANEL MEMBER GLANTZ: Well, you know, I guess. I mean I can't -- I've been through the document a few times and I know these arguments are in there somewhere.

SUPERVISING TOXICOLOGIST MARTY: Yeah, we could pull them forward.

PANEL MEMBER BYUS: Well, I also agree with Paul. And that was one of the -- you constantly go back and

forth between primary smoking and ETS. And you -- which is a good thing to do. Don't get me wrong. I think it's a good thing. But you really need to try and discuss what the limitations on that kind of association are, if there are any.

And then also dose response, I would disagree with you. I mean I think trying to -- establishing a dose response is the gold standard of establishing causality. And so you're referring to a constant -- you're repeatedly referring to dose response relationships between ETS and primary smoking is a good thing to do, except if there are limitations in the overall strategy. I think if you lay that out initially, as Paul suggests, that it would allow your arguments to be easier to follow as you go through the document.

SUPERVISING TOXICOLOGIST MARTY: All right. We'll put that into the introduction section and a little discussion bringing that forward. That's a good point.

PANEL MEMBER GLANTZ: Just the point I was trying to make -- I mean I think if you do find a dose response, that strengthens your argument. The issue I was trying to raise was trying to go between dose of active smoking and dose of passive smoking, that and the idea of having cigarette equivalent type things. And I think that's very problematic. I think within looking at active smokers or

passive smokers, if you see a dose response effect, that's a very -- that strengthens your argument. It's just trying to extrapolate from active smoking down to passive smoking, which is where I think you get into trouble, at least with some endpoints like heart disease.

PANEL MEMBER BLANC: So I think it would be -- just to clarify what it was that I implied in this discussion would be, if you couldn't lay out for the reader in general we -- you know, obviously dose response is a key part of our causal assessment, that we have certain general principles in terms of looking at active smoking as a dose -- in a dose response way that in -- pour out comes for which we have no reason to believe that it would not be an ordinal relationship, we will -- you will see that we will use it as an argument for dose response in situations where we believe it's ordinal.

But we have strong reasons to believe it's not linear where there may be a steep step up early on such as cardiovascular. We make that clear. In areas where we think in fact it's not even ordinal, because of anti -- you know, estrogenal -- anti-estrogenal effects that high exposure such as with active smoking, which may be relevant to endocrine-related malignancy and promotion, we will make that clear as we go forward. Because, otherwise, it's just odd not to be -- to be avoiding the

issue as head-on at the beginning.

SUPERVISING TOXICOLOGIST MARTY: Okay. So we also noted that we think the evidence is sufficient for a causal association between ETS exposure and the number of cardiovascular effects, including heart disease mortality -- heart disease morbidity and altered vascular properties.

And also there are a number of other health endpoints that we think there is evidence that there is suggestive associations between ETS exposure amongst other endpoints.

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SUPERVISING TOXICOLOGIST MARTY: We updated some of my attributable risk calculations where data permitted. And these are all presented in Table is 1.2 for a number of endpoints.

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SUPERVISING TOXICOLOGIST MARTY: And this is Table 1.2. And what we have presented is the excess number of cases attributable to ETS exposure for those health endpoints in California and then an estimate for the excess in the United States. And there's a lot of description in the document about how those numbers were calculated.

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SUPERVISING TOXICOLOGIST MARTY: I'd like to go through each chapter. What I want to do though is -- I may not do it in order. So I'm going to start with Chapter 3, which is perinatal manifestations of developmental toxicity. And depending on how time is moving on, we really should get through Chapters 6 and 7 today since they have the two endpoints that have jumped to conclusive.

CHAIRPERSON FROINES: Do those estimates that you've just showed on the slides, do they -- do they then meet the requirement for some estimate of risk, in your view?

SUPERVISING TOXICOLOGIST MARTY: That is how we approached --

CHAIRPERSON FROINES: The question was raised by one of the commenters.

SUPERVISING TOXICOLOGIST MARTY: Right. That is how we approached risk in the context of the ETS, rather than generating a universal factor or even attempting to do that.

CHAIRPERSON FROINES: Good.

SUPERVISING TOXICOLOGIST MARTY: The first slide of each of these chapter discussions is essentially the table in the beginning of the chapter. That looks at the health outcome; the number of studies that we reviewed for

the '97 document; the number of additional studies in the update; and whether we think there is sufficient evidence of causal association, is it suggestive, is it inconclusive or is it conclusive?

In this particular table we're describing ETS and pregnancy outcomes. And essentially we think the newest studies strengthen the conclusions of the '97 report regarding effect on low birth weight and birth weight decrement, pre-term delivery, and intrauterine growth retardation.

CHAIRPERSON FROINES: Can I just say that I thought this approach that you had consistently with each chapter starting off with that tabular presentation was extremely helpful.

SUPERVISING TOXICOLOGIST MARTY: Thanks.

This slide is designed to give you a bird's-eye view of the information reported in the literature on mean change in birth weight. The change is on the Y axis, and it's in grams. The X axis is essentially each of the studies that looked at that.

You can note that there are a number of studies which indicate a depression in mean birth weight in the ETS exposed groups in these studies relative to non-exposed. And that many of these are statistically significant; for example, the diamonds that are filled in

are statistically significant estimates.

In some of the studies, they broke out the groups by age. For example, Ahluwalia, which is in our update. It's that point -- where am I?

The 30 -- the greater than 30-year-old women actually had babies that were -- had birth weight decrements. But the younger-than-30-year-old women did not. So it kind of is an indication of susceptible sub-populations.

And there are a number of very well conducted studies that had all those small decrements in birth weight such as Marty Kharrazi's study here and Dejmek's study here. There were small but significant birth weight decrements.

And I think I should make a comment that these small birth weight decrements may be in and of themselves to an individual not especially important, unless they're already small babies and you're pushing them into the low-birth-weight high risk category and all of the associated health outcomes of low -- from having low birth weight.

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SUPERVISING TOXICOLOGIST MARTY: In addition, there were a couple of meta-analyses published.

Gayle Windham published one, in which she looked

at studies for North America. And these studies that she chose and the eight that she ended up choosing assessed multiple sources of exposure to the mother rather than just, "Does your spouse smoke?" And they also had adjusted for a number of important confounders. And she finds the birth weight decrement of 24 grams. That's statistically significant.

Peacock, et al., also published a meta-analysis along with her own original study. And she pulled estimates from 11 studies that had also adjusted for confounders and gets a birth weight decrement in a similar range. Also statistically significant.

And in both of these meta-analysis there was no evidence of paragenetics. So they thought they were dealing with a homogenous group of studies.

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SUPERVISING TOXICOLOGIST MARTY: This slide just shows an overview of the data on ETS and risk of low birth weight. So in this case we're looking at an odds ratio of having a baby that's less than 2500 grams, which is the standard definition of low birth weight. And, again, it's interesting to see that there appears to be some differences by maternal characteristics.

Ahluwalia again looked at women 30 years old and greater. And they had a very statistically significant

odds ratio of low birth weight compared to younger women in that study.

And Gayle Windham looked at whether you were -- what race you were. And if you were non-Caucasian, there was also a very significant risk odds ratio for low birth weight.

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SUPERVISING TOXICOLOGIST MARTY: So you can see that there are a number of studies that have elevated risks. Some are statistically significant. There was one meta-analysis published again by Windham. And she combined low birth weight and small for gestational age. She looked at 11 studies and got pooled risk estimates that were statistically significant and elevated. And then for three of the studies that she had determined had the best exposure and confounder adjustment. Their at the pool estimate was higher.

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PANEL MEMBER BLANC: Well, then this is another generic question that will come up throughout.

When you have a luxury of a meta-analysis that's been published in the interim, where do you count it when you talk about a number of additional studies in update? Is it in the total number of studies? Is it --

SUPERVISING TOXICOLOGIST MARTY: No, it's not.

It's not. Those -- the number of studies in the update I believe are just the original -- new original studies. In both those cases, Windham and Peacock, they did original study, and they also included a meta-analysis in their paper.

PANEL MEMBER PLOPPER: So you count it as an original study?

SUPERVISING TOXICOLOGIST MARTY: Yeah, so their -- we counted their original study.

PANEL MEMBER BLANC: As original studies.

That was in the same publication. They did a meta-analysis at the same --

SUPERVISING TOXICOLOGIST MARTY: Correct, right.

And I should note also that these slides, looking at an overview picture, these are the overall odds ratios. And some of those papers had separated out groups by other methods and had different odds ratios according to maternal factors.

In the case of Ahluwalia, she didn't do an overall. She did a greater than 30, less than 30. So that's why they're both up there on that slide.

PANEL MEMBER BLANC: But they're not counted as two studies?

SUPERVISING TOXICOLOGIST MARTY: No, it's not counted as two studies.

PANEL MEMBER BLANC: So in fact if you wanted to put a little asterisk and, say, below the table, this does not even include two meta-analyses, that will be put in later, I mean it does strengthen your -- there are two positive meta-analyses, right?

PANEL MEMBER HAMMOND: Or you can put another line down set met analyses data and put it on the graph.

SUPERVISING TOXICOLOGIST MARTY: Can put it on the graph, yes --

PANEL MEMBER HAMMOND: But it's a separate thing from the individual.

SUPERVISING TOXICOLOGIST MARTY: Okay. Put them on the graph.

Okay. This is an overview of some of the studies that looked at small for gestational age, which is generally identifies less than a 10th percentile of body weight for that gestational age. And most people use it synonymously with IUGR, intrauterine growth retardation.

And you can see that there are some suggestive studies that there is an effect, some of the risk estimates are elevated. A couple of them are even statistically significant. There is one more study which we didn't put on here because it was from India. They had a very significant elevation, an odds ratio of 2.1. But it was indian tobacco and they put other stuff in there

besides tobacco. It's not what you're thinking. Charcoal and some other kind of funny things.

And then also their cigarettes aren't really like American cigarettes. They're wrapped in other plant leaves, which aren't tobacco and -- who knows what they are. So we didn't include it on this table. But if we did, that would be yet another statistically significant --

PANEL MEMBER BLANC: When you referred to it in the text, then why is it you don't include it --

SUPERVISING TOXICOLOGIST MARTY: We had to put that in. We didn't say why didn't want to put it in the text. I realized that yesterday. But we should.

PANEL MEMBER BLANC: You mean it's not in the text either?

SUPERVISING TOXICOLOGIST MARTY: The study is described in the text. But we didn't explain why we didn't put it on the table.

PANEL MEMBER BLANC: So you should add the point in which you refer to it in the text.

SUPERVISING TOXICOLOGIST MARTY: We should do that.

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SUPERVISING TOXICOLOGIST MARTY: Okay. So we're --

PANEL MEMBER BLANC: There's no -- and then you haven't come across a formal meta-analysis of these data?

SUPERVISING TOXICOLOGIST MARTY: There may have been one that combined -- yes, there one that combined SGA with low birth weight. That was the Windham paper. And she felt she could do that because the low birth weight study she used had adjusted for gestational age, which is an important confounder for low birth weight. So she combined both of those into one, which was actually the previous slide we showed.

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SUPERVISING TOXICOLOGIST MARTY: That one. Exactly.

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SUPERVISING TOXICOLOGIST MARTY: Okay. So we considered that, and was suggestive of an association between ETS and small for gestational age or intrauterine growth retardation. And this actually is an interesting study on why tobacco smoke would do that.

Next slide please.

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SUPERVISING TOXICOLOGIST MARTY: ETS and risk of preterm delivery. Again here we have a number of studies which showed elevated risk. And the filled-in ones were statistically significant elevated risk. And, again, over

30 years old you seem to have a larger issue with association with ETA. And whether that's because you've been exposed for a longer period of time than the younger women, no one's really sure.

And, again, for Windham's study she's found that non-white women had a higher risk of preterm delivery with ETS exposure than white women.

And Marty Kharrazi finds an overall elevated risk of preterm delivery.

There's actually an additional study in which the Panel can think about. It's Yuan et al and -- 2001. They divvied up their women by hair and nicotine levels. And we had some issues with how they did their hair and nicotine analysis, which we can talk to the panel about at some point. But they also had an elevated odds ratio of 6, which was statistically significant. So that would be a fourth data point on there that was statistically significant. At this point we're calling this suggestive evidence rather than --

PANEL MEMBER BLANC: Can we -- I'd like to hear for a second from the leads on this document at this particular point. What is it that you would need for this to be more than suggestive? And how did the two leads read this particular section?

PANEL MEMBER BYUS: The preterm delivery or the

entire --

PANEL MEMBER BLANC: No, the preterm delivery, because it's --

PANEL MEMBER PLOPPER: Why they -- why do they make the choice between suggestive and --

PANEL MEMBER BYUS: Yeah. It's difficult. I have no problems with the low birth weight. I thought that data was extremely persuasive, the fact that you can have -- even if it's small, it's extremely to me significant of something happening if you can affect the birth weight. I mean you can do a lot of things -- at least in animal studies -- we've done a lot of animal studies where you can do a lot to animals but not affect birth weight at all. So the fact that the birth weight is being affected is very, very persuasive to me about the risk of environmental tobacco smoke.

In terms of this data, it's a little harder for me to follow it and the significance of it. And I was impressed by that nicotine and the hair, when you bend the data out that way and got that extreme risk factor. So I would be interested in hearing your explanation of that.

SUPERVISING TOXICOLOGIST MARTY: Yeah, we're taking another look at that study and trying to decide whether we need to put that up there as well.

CHAIRPERSON FROINES: But Paul's raising a

specific but also generic issue, which is quite simply how do you decide when something is sufficient. I think that's an accurate statement.

PANEL MEMBER BLANC: Yeah, because -- I look at the left side of this and I say, okay, I see why in 1997 they had five studies. None of them were statistically significant. The point estimate was less than 1 in one study. The point estimate was essentially 1 in another study. An the point estimate was elevated in three studies, none of them -- so, okay, suggestive because -- and suggestive is, you know, pretty mild. Now I see 1, 2, 3, 4 -- I see 1, 2, 3, 4 studies, two of which have stratified analyses. Each study is positive in at least one strata in the direction. Two of the studies have substrata that stratify parts of them that are statistically significant. One has a -- the whole study is statistically significant. Kharrazi is statistically significant. One of them is quite close to -- I don't know -- Horta, is that statistically significant also?

SUPERVISING TOXICOLOGIST MARTY: No, it was not.

PANEL MEMBER BLANC: But it's very close.

SUPERVISING TOXICOLOGIST MARTY: Close.

PANEL MEMBER BLANC: And now you're telling me there's a study you don't have on here because you weren't fully satisfied with the -- but it's from Jaakkola, right.

SUPERVISING TOXICOLOGIST MARTY: Yes, it's Jaakkola.

PANEL MEMBER BLANC: And so it's like the premier ETS research group in the world has this study, which is positive. And I looked at this and I said well -- you know, boy, that if -- you know, you could say very, very, very, very suggestive. But what else is it that you want? I mean is this a situation in which you guys are trying to do some kind of internal meta-analysis is what is required for you to go from -- to cross the Rubicon in to conclusive?

SUPERVISING TOXICOLOGIST MARTY: We'll wade into the Rubicon and see what we can do.

PANEL MEMBER BLANC: Get your feet wet?

CHAIRPERSON FROINES: You know, the thing is -- it's always been interesting to me that different regulatory groups or risk assessment groups talk about using the weight-of-evidence approach. But I never have understood what the weight is. Be a quantitative way to approach, if you did a -- which is what we normally do with meta-analysis. And so it seems to me that in this case it may be that you have to do at least some rough estimate of meta-analysis or develop criteria where some weight is sufficient. Otherwise the weight is rhetorical, I think.

PANEL MEMBER GLANTZ: Well, I think here you should just do the meta-analysis. It's not that hard if you've got all the data you need. And there are --

PANEL MEMBER BLANC: How do you do it when you have -- when an author has only provided you with two stratified things? You treat them as completely separate studies of meta-analysis?

PANEL MEMBER GLANTZ: Well, you can do it different ways. I mean some people will try to recombine them and other people will treat them as separate studies. They're separate groups of people. And the sample sizes of the two strata are going to be smaller than if you treated it as one study. So I think it would come out in the wash.

But, yeah, this was one when I was reading it. I was sort of surprised you were still saying "suggestive" for the reasons that Paul outlined. I mean the new -- this is a place where I think you'd have quite a lot of strong new evidence. So maybe you should weigh it into the Rubicon on this.

CHAIRPERSON FROINES: You may conclude that it is still suggestive. I don't think Paul's saying you have to come up with a conclusion. But I think that what he's really saying is tell us what the criteria for your decision is.

SUPERVISING TOXICOLOGIST MARTY: Well, there's, you know, a certain amount of judgment involved on whether you think there's enough studies that have been conducted and how those -- how the positive studies pan out in terms of are they better in terms of exposure estimation than the studies that were not statistically significant? So it really is a --

PANEL MEMBER GLANTZ: You know, but I think part of it is that you should -- you know, that's one of the things you get when you do the meta-analysis calculation, is if you have -- you can have a series of small non-significant studies, that when you pool them you would find a significant elevation. And I think just looking at the 1997 thing, I would be shocked if you went through that exercise and found a significant elevation. But I would think, again just eye-balling it, you may well if you look at all of the studies today. But I mean I agree with John. I mean I think you should also apply some judgment here. But it's a much stronger -- certainly a much stronger case than it was before.

PANEL MEMBER BLANC: You would -- I mean your life would have been easier, I suppose, and I maybe wouldn't even be hassling you as much if in 1997 they said that those data were inconclusive. And maybe they sat here and had a very long argument about that at the time.

And then you said, well, we're going from, you know, inconclusive to at least suggestive. But it's hard. So you may in fact be boxed into a corner a little bit by how they did it. But it does on the face of it seem -- and if you had some category that was between suggestive and conclusive, okay, you could park it there. But this --

CHAIRPERSON FROINES: B-1, B-2.

PANEL MEMBER GLANTZ: I think we're now thinking it --

PANEL MEMBER BLANC: Well, it's generic. I think this is going to come up --

PANEL MEMBER GLANTZ: No, I agree with you.

CHAIRPERSON FROINES: This is going to come up with -- this comes up all the time with other agencies and this agency. I mean it's -- I mean it's one of the reasons that people have tried to adopt Bayesian approaches to decision making, right? So the short -- you know, the standard in Greenland would say do a meta-analysis. But somebody else in Boston would say do a Bayesian approach to how you make decisions. And we're sort of not saying that. But that's obviously an option. So that it seems to me that the simpler thing to do would be to make some kind of estimate based on the meta-analysis.

SUPERVISING TOXICOLOGIST MARTY: Will do.

I just want to go through one of the better studies, a couple of slides. Although we probably don't need to do this. I could skip over to the comments if you would like.

PANEL MEMBER BLANC: Yeah, I would.

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CHAIRPERSON FROINES: It does mean that to the degree that to the degree that we don't go through a specific study, it is useful for the people who are reading that chapter to make sure they're aware of those specific studies.

SUPERVISING TOXICOLOGIST MARTY: Okay. We got a number of comments on Chapter 3, primarily related to our analysis of low birth weight. One of them is that there are numerous factors linked to low birth weight, and this presents a problem with confounding. And maternal smoking is the biggest confounder.

And our response is that the effect is seen in babies of non-smoking mothers exposed to ETS, not just smoking mothers. We relied a little more heavily on studies adjusting for many known confounders. And while adjustment generally lowered the effect estimate, although not always, they were still significant, even those that got lowered.

And we also note a dose dependence of low birth

wait with maternal cotinine measured mid-pregnancy of non-smoking mothers in Kharrazi. And then the consistency of finding across numerous studies really supports causality.

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SUPERVISING TOXICOLOGIST MARTY: We got a comment that while most studies did not reach statistical significance for either decrements in birth weight, low birth weight, as defined by 2500 grams or less, or small for gestational age.

And our response is that of 22 risk estimates for low birth weight, five were statistically significant, and the majority were elevated. You can't just look at an individual study absence of significance and then individual study is not evidence of no effect. And we saw dose dependence of both low birth weight and small for gestational age related to maternal cotinine. So this is a fairly good estimate of exposure. And then pool estimates from meta-analyses indicate significant decreases in birth weight.

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SUPERVISING TOXICOLOGIST MARTY: We did get a comment about confounding influence of adverse childhood experiences, which the commenter shortened to ACES, and that this was not measured. And the commenter cited

spousal abuse, lack of social support, and economic prosperity as being risk factors for lowered fetal growth, preterminal delivery and birth weight.

And our responses to the measures of SES are meant to reflect, to some degree, societal stress. Most of the studies that were conducted well considered SES. And the effects were still significant after controlling for SES. This may not control for every confounder of course because there's no possible way of doing that. But we don't think that the studies -- the database are therefore -- you can't say there's effects of ETS.

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SUPERVISING TOXICOLOGIST MARTY: And then, finally, we got a comment on the attributable risk calculation for low birth weight. This commenter said that since smoking prevalence has dropped, then the low birth weight should have also dropped, attributable to ETS exposure. And they also said you should use the mean serum cotinine from the latest NHANES to estimate the number of people exposed to ETS in that attributable risk calculations.

And our response is that -- well, first of all we used survey data to look at the number of ETS exposed individuals. But even if you try to use the mean cotinine, that reflects both changes in numbers of the

people exposed as well as the amount of exposures. You're not differentiating unexposed from exposed.

And that's essentially it for this chapter.

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PANEL MEMBER BLANC: Would this chapter be an example of where you would discount in the opposite direction the direct smoking effect even for the well established, and would not use that to be evidence of a dose response, coming back to my earlier question, because of the issue, for example, of maternal carbon monoxide?

SUPERVISING TOXICOLOGIST MARTY: We did not discuss the effects of ETS very much in the context of active smoking, other than to note that active smoking is a confounder for all of these endpoints and that it was -- it's better to look at moms who didn't actively smoke during pregnancy where that was possible. And some studies actually we're able to do that.

We didn't talk about it in terms of dose response. It's interesting, because who knows which chemicals are the most responsible? You know, carbon monoxide clearly is a candidate. Nicotine is a candidate. But so are the PAH's for our intrauterine growth retardation and so on. So it's -- you know, within that context it's pretty hard to talk about active versus passive.

And, Mark, I don't think we talked too much about that in the chapter.

Okay. I think in the interests of getting through the heavier-duty chapters, 6 and 7, where we actually boosted a health outcome up to conclusive, that we should go to those chapters now. Is that okay with the Panel? And then we'll come back to 4,5, and 8 after 6 and 7.

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SUPERVISING TOXICOLOGIST MARTY: Chapter 6 and 7 will be largely presented by Mark Miller.

CHAIRPERSON FROINES: I think that discussion was very useful.

MR. MILLER: So chapter 6 is ETS and respiratory disease. And you can see it's a substantially beefier chapter than the last one.

And highlighted in yellow on the chart are the two findings that went from suggestive to conclusive. And those are asthma exacerbation in adults and asthma induction in adults. As well as there are conclusive findings on a number of areas that were unchanged from the previous draft or previous 1997 document, which include exacerbation of asthma in children, respiratory -- lower respiratory infection, otitis media, sensory irritation and annoyance, asthma induction in children, and

respiratory symptoms in children.

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MR. MILLER: Starting with asthma exacerbation among children, which in the previous document it was concluded that ETS was a causal factor.

In this document that we're in, an additional 14 recent cross-sectional and cohort studies that were reviewed, ETS exposure was assessed in these studies varyingly by a questionnaire and some by cotinine and they were associated with reduction in FEV1, increased report of adverse symptoms, slower recovery from severe attacks.

It was noted that the cross-sectional studies were limited by possible selection effects and that smoking -- for example, smoking reduction by parents of children with severe asthma might fall under this.

This would tend to bias toward the null any observed risk estimate.

The longitudinal studies, which are less prone to assert bias, were the most consistent studies with an effect of ETS on childhood asthma.

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MR. MILLER: Moving to adult asthma exacerbation, which previously was listed as suggestive and upgraded to a causal conclusive status.

A study by Dr. Blanc in 1999 looked at

respiratory work-associated disability and found that it was increased by ETS; both a disability by an odds ratio of 1.8, and symptomatic asthma, which was also increased, though not statistically significantly so.

Another study by Dr. Eisner found serum cotinine associated with pulmonary function decrements in asthmatics. For example, an FEV run in women, a decrease of 261 milliliters.

Dr. Kunzli found an ETS decreased pulmonary function in asthmatic women and that there was a linear dose response in a number of years and other factors.

Next slide.

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MR. MILLER: Several -- at least two prospective cohort studies were added.

A study by Sippel found asthma care events, in other words needing to go into the doctor emergency room, et cetera, were increased. Those exposed to ETS had 28 per 100 person-years compared to non-asthmatics with 10 per 100 person-years if they were not -- these are asthmatics not exposed to ETS. Hospital care was more than doubled.

Additional study by Dr. Eisner found -- and this is one that we discussed earlier, where he did the nicotine personal badges. And he found over a week's time

that there was an association with respiratory symptoms in asthmatic adults.

The top number should be 0 to 0.05 micrograms per meters cubed. And so -- which is considered the low category. So there was non-exposed. There was the low exposed category, which, for example, had a doubling of bronchodilator; and the higher exposed category which had an eight-fold statistically significant increase in bronchodilator use.

PANEL MEMBER BLANC: Well, the study that I'm most familiar with is obviously the one that I'm first author of. And I think it's misplaced here. It's relevant to the topic of ETS respiratory effects, but it's not a study which is either focused on or directly applicable to asthma exacerbation. So I don't think it belongs --

MR. MILLER: Because it included any variety of endpoints that would --

PANEL MEMBER BLANC: Well, the main endpoint is workplace -- is changing your job because of breathing difficulties on the job. And ETS was a risk factor for that. But it wasn't looking at: "In asthmatics do you get more exacerbations of asthma compared to people without ETS?" So it's two steps removed from being able to -- and there wasn't a stratified analysis presented

just among persons with asthma. And so I think that if you have this sort of grab-bag section of other effects, I would --

MR. MILLER: Yeah, respiratory illness, probably.

PANEL MEMBER BLANC: Or respiratory effects. So you might want to expand that so that you have a place to put studies.

And also I think it's worth noting that when we did an analysis of data from other countries in the same study, that analysis, although the primary thing we were looking at which was workplace exposures to gases, dust and fumes, were still associated with changing jobs. In the larger European study where placing ETS exposure wasn't related to changing jobs because it -- probably because it included countries other than Sweden where, if you left one job with ETS, you'd go to another job with ETS. So it wouldn't be a reason why you would change jobs. In Spain, for example.

So there's -- you know, even if I thought you could put this here, because -- which I don't. I think that you would need to put it side by side and put it in the context of the negative study that, you know, used a similar approach.

So I think it needs to come out of this table. If you want to use it, you could use it in a sort of

different category, because it weakens your argument.

MR. MILLER: Uh-huh. Well, I think these other studies that are presented here are directly looking at asthma.

PANEL MEMBER BLANC: Yeah.

MR. MILLER: You know, there were a number of studies that either fit into more than one kind of category that we had or didn't quite fit into any exact category. Yet we wanted to include them. But --

PANEL MEMBER BLANC: Now, I thought -- in the extra studies that I sent you, was there one that was relevant to this topic? Because it seemed to me that there's been more -- it seems to me that the Jaakkola's have something related to this, for example. But maybe that's just asthma -- adult asthma incidents. I know this is adult asthma exacerbation.

But this is one area in which -- since the most recent study that you have is 2002, I believe that there's more recent than that.

And that brings up another generic point that I think is worthy of discussion here. I mean what struck me about this chapter was that the -- systematically -- the data from 2003 and 2002 were not mined as systematically. Now, I know that this can't be a never-ending iterative process. So, you know, there was a certain point where

you were writing this -- and you can't be expected to include all things. I think that there are things that came out in 2004, for example, after the time -- you release this in December of 2003, so you can't be expected to have all 2004 studies. And if you had to never-endingly go back to the literature and keep updating, the process would never end.

On the other hand, I think there are examples of 2004 studies that you're going to bring in because they're so important and so relevant.

So as a panel member, it would help me to know what makes you use a study that's after December 31st, 2003, and similarly that convinces me that before some date in 2003 you feel confident that you adequately searched the literature.

SUPERVISING TOXICOLOGIST MARTY: Well, I can tell you that we -- while the document was out for public comment and while we were responding to the comments, we did go back and search PubNet and a few other databases looking for studies that had been published that we thought would add value to the chapter. And it's very possible that, you know, we may have missed a few.

So we will definitely during this process go back again and take another look at 2003 and 2004.

We did pick up some studies for other chapters

that were published in the meantime and put them in. So that's why you see a few 2004's in here and some late 2003's.

PANEL MEMBER GLANTZ: I think it would helpful, Paul, if you had some specifics things in mind to just tell -- you know, send them the references.

PANEL MEMBER GLANTZ: I did that already.

SUPERVISING TOXICOLOGIST MARTY: He's done that.

PANEL MEMBER GLANTZ: Oh, ok.

PANEL MEMBER GLANTZ: But this is one in which, you know, I just sort of had this existential sense that there's other things out there.

SUPERVISING TOXICOLOGIST MARTY: We'll look.

PANEL MEMBER BLANC: Well, I'm happy look again myself. That's why I asked if one of the four things I sent you was relevant to this. I don't --

SUPERVISING TOXICOLOGIST MARTY: As my induction, yes.

--o0o--

MR. MILLER: Moving on?

PANEL MEMBER BYUS: Yeah, actually just as an aside, I found this discussion of the animal studies on the postnatal development tobacco smoke -- they exposed them -- was it OBA-specific IGE levels and they did these studies. It was really very persuasive. I mean you could

include these things in various parts. There's a lot of crossover.

SUPERVISING TOXICOLOGIST MARTY: Yes.

MR. MILLER: So I always thought why it was here and not me --

SUPERVISING TOXICOLOGIST MARTY: Yeah, that was part of our problem: Where do we put this stuff?

PANEL MEMBER BYUS: I know.

SUPERVISING TOXICOLOGIST MARTY: In fact, maybe that one really is in the wrong place.

MR. MILLER: That really I think is in the wrong place, because it doesn't even -- it isn't human. But --

SUPERVISING TOXICOLOGIST MARTY: All right. I'll move it.

MR. MILLER: -- I would move it into the lung, because it gives a good, you know, overview of how you may sensitize the lung with environmental tobacco smoke allergens in a producing eosinophilia, altering lymphokines production. It's quite a -- at least from the description here, it's quite a nice bit of data.

So that was all. Just move it.

SUPERVISING TOXICOLOGIST MARTY: Okay.

MR. MILLER: Continuing with adult asthma exacerbation.

In a nested case-control study, Tarlo found

exacerbation of asthma with ETS exposure in the past year; 39 percent of the cases reported ETS exposure compared to 17 percent of controls, which was statistically significant.

--o0o--

MR. MILLER: In summary, current studies provide conclusive evidence that ETS exposure can cause asthma exacerbation in adults. And although there were fewer studies than in children, the data that we had appeared to consistently link ETS exposure with poorer status among asthmatic adults. And there was evidence in several studies of dose response, and that the data on top of that were quite consistent with the evidence in children, which had already been conclusively linked.

PANEL MEMBER BLANC: And there are, by the way, no controlled human exposure studies in those -- the last interval that look at persons with underlying hyperactivity who are exposed to secondhand smoke?

SUPERVISING TOXICOLOGIST MARTY: You mean challenging them in a chamber study?

PANEL MEMBER BLANC: Yes.

SUPERVISING TOXICOLOGIST MARTY: Not that we found.

PANEL MEMBER BYUS: Yeah, I was going to ask that too.

MR. MILLER: The airport stuff -- they had an airport smoking room --

SUPERVISING TOXICOLOGIST MARTY: That wasn't --

PANEL MEMBER GLANTZ: That was a cardiovascular --

SUPERVISING TOXICOLOGIST MARTY: That was a cardiovascular paper, and it wasn't controlled where they had a specific concentration of PM or whatever.

We'll look to see if they're out there.

--o0o--

MR. MILLER: Respiratory illness in children has had a recent meta-analysis which looked at the effects of either or neither parent smoking on lower respiratory infection in children under three years of page.

The meta-analysis result is this red figure at the top. But there were 26 studies included. And you can see the vast majority were positive and significantly so.

--o0o--

MR. MILLER: In summarizing lower respiratory infection in children, there were 11 new studies which strongly support the previous conclusion. And I think -- interestingly, there was a study that looked at annual doctor consultations and the costs in Asia, and that there was -- they were 14 percent higher with one smoker, 25 percent with two or more, and as well as various other

data.

I think we should move on here.

--o0o--

MR. MILLER: ETS and otis media --

PANEL MEMBER BLANC: Well, why does it say 6 in your table and you say 11 in the slide?

MR. MILLER: In that -- that last table? Was 26 studies in the --

PANEL MEMBER BLANC: Eleven new studies.

MR. MILLER: Yeah.

PANEL MEMBER BLANC: And your table says six additional studies.

MR. MILLER: I don't know which table we're talking about.

SUPERVISING TOXICOLOGIST MARTY: I think he means the table in the very beginning.

PANEL MEMBER BLANC: You're talking --

SUPERVISING TOXICOLOGIST MARTY: It does. It says six.

PANEL MEMBER BLANC: -- about respiratory illness, children.

MR. MILLER: I don't know. We'll have to look at that.

SUPERVISING TOXICOLOGIST MARTY: Yeah. You know, that could be one of the leftover things we never fixed.

As we kept adding stuff, we had to go back and find where we said there were X number of new these type of study. And we didn't -- clearly didn't catch them all.

MR. MILLER: We'll look.

PANEL MEMBER BLANC: And then I think that where you have the zero in that table for 1997 studies, and then a --

PANEL MEMBER HAMMOND: That was conclusive.

PANEL MEMBER BLANC: -- a footnote that says there were no studies looked at because they accepted the USEPA and Surgeon General's report. If you could at least put in parentheses how many studies the Surgeon General's report used, it would make it seem --

PANEL MEMBER HAMMOND: The USEPA was more recent.

PANEL MEMBER BLANC: Or whichever, make it seem less bizarre.

PANEL MEMBER HAMMOND: Conclusive results on no studies.

--o0o--

MR. MILLER: Otitis media previously was conclusive and there were seven additional studies reviewed, which are consistent, would then support the previous conclusion. There was an estimate of the number of office visits per year for otitis media in California, children under three, attributable to ETS. And that has

decreased significantly primarily as a result of decreased smoking.

--o0o--

MR. MILLER: ETS and asthma induction in children. There were 37 recent studies. And on top of that OEHHA has conducted a meta-analysis, which is actually an update of the meta-analysis that was done for the 1997 document. There were 85 studies that were evaluated, over 460,000 children in 29 countries.

The pooled odds ratio for new onset asthma was 1.32 with tight confidence intervals. And that was based on 29 well-controlled studies.

The relative risk of asthma onset among children exposed to postnatal-only ETS -- that was an important factor that had previously been difficult to pull out -- for the last five years was 1.22 and ten years was 1.42.

All preschool children appeared to be more at risk. Older children exposed to ETS also appeared to be at significant risk for new onset asthma. And the new data analysis strongly support the previous conclusion that ETS exposure is causally associated with new onset asthma in children.

PANEL MEMBER BLANC: And this is again another place where your first table doesn't bear any resemblance in numbers. So do double check what you're --

MR. MILLER: Well, that certainly is an area that we had continued to update right up to the last --

CHAIRPERSON FROINES: Paul, say that again. I didn't understand what you were saying.

PANEL MEMBER BLANC: Their table says there are 28 additional ease in this update. Actually you said 37 recent studies. But I think you took from the wrong column. But even so, there was nothing you had that was like a 28.

And, again, this is another -- we talked in a previous section about some way of giving due credit to meta-analysis that have been published, you know, systematically throughout the review. If you can -- you know, these table, I don't -- it gets a little complicated, but there must be some way of putting them in prominent --

MR. MILLER: Adding those in?

PANEL MEMBER BLANC: Yeah.

Another column of meta-analysis maybe, yeah.

MR MILLER: Adult onset asthma, start by looking at dose-response relationships. There were studies -- the number of studies that demonstrated dose response relationships between their studies, including looking at total duration of ETS exposure, number of smokers in the environment, duration of exposure to smokers, duration of

working with a smoker, measured nicotine levels, and index of intensity and duration of exposure. Obviously with many different metrics and hard to absolutely compare sometimes between these.

Next slide.

PANEL MEMBER BLANC: Okay. Now, wait a second. Not so fast.

Another example of a study that I thought was in the wrong place -- not that it's not relevant somehow in this chapter -- is the -- this Eisner nicotine level, isn't that the same study you were quoting previously, which was only done among persons with asthma? Is this some other study? Ice ice mark ice err

SUPERVISING TOXICOLOGIST MARTY: This is Mark Eisner, who did the study.

PANEL MEMBER BLANC: So that should not be in this section. It was --

MR. MILLER: Should be in the other section.

PANEL MEMBER BLANC: It was in the other section, which is where it should be. But it should not be cited here.

MR. MILLER: Okay. We'll talk to Dr. Eisner about that.

Next slide.

--o0o--

MR. MILLER: The consistency of study findings supports a causal association. Associations were found in different populations that range from clinical to population-based studies. And they were across many different countries. There were consistent findings in a variety of study designs including cross-sectional case control and cohort studies, and in different environments such as home and work exposures.

--o0o--

MR. MILLER: Biologic plausibility is supported by studies of adults finding a small but significant deleterious effect of ETS on pulmonary function, some examples of which are there.

ETS contains potent respiratory irritants that adversely affect bronchial smooth muscle tone and airway inflammation. So this isn't surprising.

Coherence is supported by associated and related health outcomes, such as chronic respiratory disease, respiratory symptoms such as wheezing, cough, et cetera.

SUPERVISING TOXICOLOGIST MARTY: I might add --

CHAIRPERSON FROINES: So could you go back to that.

MR. MILLER: Okay. I'm going to go slow.

CHAIRPERSON FROINES: No, go ahead and --

PANEL MEMBER BYUS: I just have a question about

asthma in general. I mean are -- so you're saying here adult new onset asthma. So are we assuming that if people were not exposed -- that these people would never get asthma if they were not exposed to ETS?

PANEL MEMBER BLANC: We'll, that's the --

CHAIRPERSON FROINES: I mean that's kind of the question here.

PANEL MEMBER BLANC: That is -- that's what differentiates this from studying asthma exacerbation --

PANEL MEMBER BYUS: And that's what you're saying. So in other words --

PANEL MEMBER BLANC: That's what the studies --

PANEL MEMBER BYUS: They would not be -- they would never be asthmatic if it wasn't for ETS?

PANEL MEMBER BLANC: Well, let me -- I can answer your question in a different way. You could calculate an attributable risk fraction for asthma based on these studies; because it's a relative risk for an odds ratio of asthma, and the presumption is without this factor you would not have asthma -- you would not have gotten asthma --

MR. MILLER: You mean they attempted --

PANEL MEMBER BLANC: -- from an epidemiologic point of view.

MR. MILLER: Yeah, the attempt is to take two

comparable groups of people, and the difference is the ETS exposure.

PANEL MEMBER BYUS: But in terms of etiology -- I'm asking just in terms of the etiology of what we know about asthma as a disease -- is that a likely conclusion?

PANEL MEMBER BLANC: Yes, because I think the one issue of biological plausibility that should be alluded to is the -- there are two issues related to cigarette smoke. One would be the growing body of evidence which indicates that chemical irritants can induce asthma. So I think that needs to be mentioned in your discussion of biological plausibility with, you know, one or two citations of reviews of irritant-induced asthma.

And, secondly, there's a growing body of evidence which also shows that cigarette smoke can act -- and other inhalants can act as adjuvants for sensitization. So it could be a mechanism towards sensitization. But what --

PANEL MEMBER BYUS: That's an explanation, right.

PANEL MEMBER BLANC: But that's not the main explanation. The more straightforward --

CHAIRPERSON FROINES: Who can act as an adjuvant for sensitization?

PANEL MEMBER BLANC: Irritants.

But irritants without invoking sensitization are associated with adult onset asthma.

But in that vein -- just before you asked your question, John -- is this a situation in which your apriori belief would be that an association between direct cigarette smoking and asthma onset in adulthood would be supportive of your argument?

SUPERVISING TOXICOLOGIST MARTY: I would -- yes, I would think so, yes.

PANEL MEMBER BLANC: So why is it missing from your argument here? Why isn't this in particular a situation in which you would want to address that literature? Now, that literature has certain problems, I grant you. Because people who develop respiratory disease in adulthood who are smokers tend to get labeled as having COPD and not labeled as having asthma. So there's a certain diagnostic bias.

But, for example, there is an article that just came out from the Jaakkola's in the last month that is on adult onset asthma in association with direct smoking. And it has a good discussion of, you know, the epidemiology of the subject. And I think that -- doesn't one of the Surgeon General's reports talk about direct smoking and asthma?

SUPERVISING TOXICOLOGIST MARTY: I think so, yes.

PANEL MEMBER BLANC: So I think that that should definitely be invoked here. Because if direct smoking

didn't cause asthma, it would be hard to imagine how ETS could cause asthma.

SUPERVISING TOXICOLOGIST MARTY: Exactly.

PANEL MEMBER BLANC: Whereas some of these other arguments I could buy about not linear or even anti-linear responses, but not here.

CHAIRPERSON FROINES: I just had one comment, which could open Pandora's Box with my friend Blanc. So I will be cautious about it. But I don't think -- I think that as a matter of mechanism, we're not really dealing with mechanism in general here. And so, whereas, I agree that there is certainly literature on respiratory irritants in relation to asthma, I don't think that is the only substances that are capable of producing asthma.

SUPERVISING TOXICOLOGIST MARTY: Absolutely.

CHAIRPERSON FROINES: And so making that statement seems to imply to me that there are other things that I think are important that Blanc may not.

(Laughter.)

CHAIRPERSON FROINES: And so I think that we need to say respiratory irritants and other agents or something so that I -- that I have my piece of the action in terms of this --

SUPERVISING TOXICOLOGIST MARTY: Actually I had asked the staff to put respiratory irritants in

immunotoxicants, thinking back to the diesel literature and looking at PAH's and how they can moderate the immune system.

CHAIRPERSON FROINES: Well, we'd like -- we of course like things like to generate reactive oxygen. And it's not only --

PANEL MEMBER BLANC: Don't you want to say something about mytroso -- polycyclic mitroso in --

CHAIRPERSON FROINES: No.

(Laughter.)

CHAIRPERSON FROINES: But I would say something --

PANEL MEMBER BLANC: Because if I don't get through one meeting without you talking about --

CHAIRPERSON FROINES: But I would say something about quinones.

PANEL MEMBER BYUS: But it seems almost as good, right?

CHAIRPERSON FROINES: I mean I wouldn't want to leave the room without having said the word "quinone" once during this discussion.

PANEL MEMBER GLANTZ: No jokes now.

CHAIRPERSON FROINES: Oh, that's right, no jokes. This was meant as a joke, not entirely.

(Laughter.)

CHAIRPERSON FROINES: Let's go ahead. The point's made.

--o0o--

MR. MILLER: Okay. Several studies directly support the impact of ETS exposure on incident adult asthma. And other studies have prospectively examined the relationship between ETS exposure and incident wheezing.

--o0o--

MR. MILLER: So for once we go over this?

SUPERVISING TOXICOLOGIST MARTY: I think we can skip it.

MR. MILLER: We'll pass it.

--o0o--

MR. MILLER: This is the prime study. Just to remark that to take a look at the information on Jaakkola's 2003 study. That is probably the gold standard as far as what's been published to date.

--o0o--

MR. MILLER: So looking at the variety of studies that were reviewed in the literature that we looked at in this document, there are -- as well as a few of the older studies. Here are from Cohort Case Control and Cross-sectional Studies the spectrum of associations. We see that most of the studies are positive, nearly all of them; and many of them significantly so.

Next.

--o0o--

MR. MILLER: So in summary, there were nine recent studies of variety of designs, eight of which showed significantly increased risk for adult onset asthma in one or both genders, ranging from odds ratios of 1.14 to 4.8.

ETS exposure in childhood increased the risk of adult asthma in several studies that looked at that.

PANEL MEMBER BLANC: Yeah, that was an area of this document that was -- I started to get a little lost in. And it made me wonder if -- you know, you were using adolescents as children when it served your purposes and using adolescents as adults when it served your purposes. And I didn't -- I found that troublesome in the document -- in this chapter. I can't cite you chapter and verse. Actually I'm citing you chapter but not verse where this has happened. And then there was this business about so and so was exposed in childhood and then they -- it's seemed like a somewhat different issue.

MR. MILLER: Well, at least one study had the onset of the whole -- where it was in secondary school, followed them I think to page 22. And so it crosses all boundaries.

PANEL MEMBER BLANC: So is there -- I mean I

1 don't know whether you want a separate discussion about
2 adolescence and second-hand smoke and respiratory effects,
3 whether that's -- whether there just aren't enough data to
4 allow you to do that, or in the miscellaneous category.
5 But, anyway, that was one study that I just seemed to
6 muddy the waters more than clarify for me.
7 MR. MILLER: I mean I looked at that as -- I mean
8 where you want to cross the boundary -- you know, in the
9 childhood stuff, I think we basically looked at 12 as --
10 you know, kind of this early childhood. Then there's a
11 break in the early childhood and then the later early
12 childhood. And --
13 PANEL MEMBER BLANC: But in asthma it's a
14 particularly important period with a lot of different
15 things going on because it's when the ratio of male to
16 female asthma switches, it's when smoking is initiated,
17 it's therefore when ETS exposure among peers is initiated,
18 you know. Children who are -- adolescents who come into
19 adolescents as smokers -- I mean as asthmatics actually
20 tend to start smoking as much as non-asthmatics. But
21 adolescents who get asthma in adolescents tend not to. I
22 mean there's a lot of weird, you know, temporal
23 complicating factors.
24 A general, I would say, that if your argument
25 isn't substantive, we can -- by taking out that study, I

would put it somewhere else in this chapter.

--o0o--

MR. MILLER: Looking at lung growth and development. There were additional seven studies. And it really was consistent with the previous information.

--o0o--

MR. MILLER: There was some difference in FEV 1 between children of smokers and non-smokers looked at in this study, with decreases in nearly all the -- this is a meta-analysis from Cook in nearly all the studies that they've looked at.

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MR. MILLER: Move to responses to comments. The American Lung Association and Lorillard both had a comment that more or less read that the review of the data in the draft report lead us to believe that the link to asthma induction in adults requires further scientific study to merit conclusive findings.

And our response was that the evidence satisfies the Hill criteria that exposure response by measures of daily exposure and a number of other ways of looking at that was shown.

PANEL MEMBER BLANC: I think the last name is Bradford-Hill. Bradford is not his first name. It's Austin Bradford-Hill, something like that, just so you

know.

MR. MILLER: The Bradford-Hill criteria.

PANEL MEMBER BLANC: Thank you.

MR. MILLER: Temporal relationship was showing that asthma follows ETS exposure. There was consistency between studies found in a variety of different settings and study types. There was biologic plausibility. And that the recent population-based-incident asthma study by Jaakkola distinguished between incident and between previous and new onset asthma in adults, as well as being a very strong study in other measures.

--o0o--

MR. MILLER: The additional comment from the American Lung Association --

PANEL MEMBER HAMMOND: Excuse me. I'm sorry.

What's the difference between incident and new onset?

MR. MILLER: That changed the wording there.

PANEL MEMBER HAMMOND: You said something different. I just -- yeah, okay.

All right. Fine.

MR. MILLER: The point was that in the past there's been with a number of the studies an issue about, you know, are you really looking at new onset in adult as opposed to somebody who had it as a child and didn't have

it for a period of time and now it's diagnosed again. And Jaakkola's able to do that because of their -- they have this national data of both, you know, as far as medications that are paid for and as well as they were able to survey all clinic visits and that sort of thing.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Scandinavia effect.

(Laughter.)

MR. MILLER: I have some additional from the American Lung Association. And they said it's not as clear as to whether post-natal ETS exposure triggers an attack in a child who is pre-disposed to asthma or induces the first attack of an existing condition. More or less that same thing we were talking about in adults, but a little more difficult to understand what the question is.

Well, at least in several studies that were evaluated I think there were four that fit into this being able to look at that question, that were looked at in the meta-analysis that we had done. But here's an example of one of those, where Mannino classified the children by their cotinine levels and then specifically was able to pull out those that were positive PNS, in other words that was prenatal smoking by the mother, on the top line. And then the next line is negative PNS, so there was no prenatal smoking. So that their exposure was postnatal.

And you can see that there was significant elevation in current asthma in children who were not exposed to prenatal smoke, but were exposed to postnatal smoke.

PANEL MEMBER BLANC: Prenatal maternal smoke?

MR. MILLER: Prenatal maternal smoking.

Yeah, that was the primary issue, prenatal maternal smoking.

In addition, we felt that it was probably a semantic issue as to whether asthma after postnatal ETS on top of some in-utero exposure can be said to be induced asthma or an uncovering of a preexisting tendency that even though postnatal exposure leads to increased risk among those already primed by prenatal exposure, we would still consider that the onset of asthma induced by environmental tobacco smoke.

--o0o--

MR. MILLER: An additional comment from Lorillard. Analyses must account for obesity, infection, atopy, and other potential risk factors, as well as potential reporting, misclassification and biases.

Our response is that there's no evidence that unmodeled confounding explains the ETS-asthma association. And in the studies reported, after adjustment for multiple confounders, the evidence still points to a role of ETS in asthma causation.

Bias is always a concern. But we did not feel that that was adequate to suffice to explain the results we see.

--o0o--

MR. MILLER: There were -- Lorillard again -- nine new studies, are inadequate to conclude causality. Causality can't be determined by cross-sectional studies. The finding of causality was based on numerous studies of different designs, not just cross-sectional studies.

Additionally, self-diagnosis of asthma is unreliable. There's no biochemical determination of exposure.

The use of self-report and questionnaires is a standard technique which has been well validated in numerous studies. But, in addition, the recent study by Jaakkola used the clinical diagnosis and pulmonary function testings and showed association between ETS and asthma.

Recall bias can't be eliminated from retrospective studies. The results from the retrospective studies agree with those from prospective studies.

--o0o--

SUPERVISING TOXICOLOGIST MARTY: That's it for Chapter 6. And we are at 1:22.

PANEL MEMBER BLANC: All right. So now I have

some substantive comments.

I think that this chapter needs to be reorganized. I think for some reason you've locked yourself into whatever order it was that the last document had perhaps. But it would be far more logical to proceed through the childhood endpoints you're looking at and then go to the adult endpoints, rather than jump back and forth, childhood asthma, adult asthma, childhood, de novo asthma, adult, de novo asthma, childhood -- whatever.

First of all, it makes this lung development thing sort of come out in the middle of nowhere, where it doesn't belong. So I would start with lung development since that's sort of pre-childhood. Then I'd do all your childhood stuff and then I'd do all your adult stuff. And I think you'd find that it would be more logical and easier to follow for the reader. And it may make the choices of where you put certain of these papers somewhat easier.

I also think that the category that you call respiratory symptoms should be respiratory symptoms and other effects, to allow yourself a place where you could put lung function decrements that aren't defined by a diagnostic category or other things.

And I'd leave it till you think about this adolescent question.

MR. MILLER: We should specifically try to look at which studies have parts of it which address adolescents?

PANEL MEMBER BLANC: Yeah. So I -- and then of course recheck your -- check your numbers. And then on certain of these things I would -- be hyper-vigilant about the literature where it seems like I would have expected more than before.

I guess another question is -- you know, if you'd just look at -- for many of these things of course the conclusive to conclusive is the -- or it's staying suggestive-suggestive. And it's only a couple things where you really have a step up in your level of causality.

And this, again, is a generic comment. Do you throughout the document use the same approach for those category shifts? Are you consistent? Is there a little mantra that you do every time you're jumping from suggestive to conclusive where that's where you do the Bradford-Hill drill and in other places you don't do the Bradford-Hill drill? Is that what you're --

SUPERVISING TOXICOLOGIST MARTY: We did do that in this case. Where it went to conclusive we did the Bradford-Hill --

PANEL MEMBER BLANC: And you do that throughout

the document?

SUPERVISING TOXICOLOGIST MARTY: -- discussion within the document.

There's only two places where it jumped from suggestive to conclusive.

PANEL MEMBER BLANC: Well, no. Here there's two separate categories. There's asthma exacerbation in adult --

SUPERVISING TOXICOLOGIST MARTY: -- and induction.

PANEL MEMBER BLANC: -- and asthma.

So you go through the Bradford-Hill twice -- two separate times at the conclusion of each subsection?

MR. MILLER: We just did it with induction.

SUPERVISING TOXICOLOGIST MARTY: We just did it with the induction because we thought that was more hairy.

PANEL MEMBER BLANC: Okay. So that's exactly my point. You're inconsistent.

I actually would suggest that for every place where you go from suggestive to conclusive and you've made that leap, that you go through systematically why you did it using a modified Bradford-Hill approach to the extent that it's -- rather than simply responding to these comments in a letter, which is not -- you know, which -- or printed comments, which are not actually in the body of

the report. And that goes back to our question about why did -- when you had nine studies all in the same direction for the, you know, other effect was that still only just more suggestive?

I'm not saying that when you do the reverse you have to go through that. When you don't make the leap you have to suddenly say why it is you don't. But when you do, I think you should consistently.

MR. MILLER: I think the only incidence would -- the only the point at which we didn't do that is asthma exacerbation in adults.

SUPERVISING TOXICOLOGIST MARTY: Well, the two places we did it were breast cancer and asthma induction in adults. Those were the two places we did that.

PANEL MEMBER BLANC: Well, for example, if in the end you decide that you're going to make the leap on --

SUPERVISING TOXICOLOGIST MARTY: -- preterm delivery --

PANEL MEMBER BLANC: -- preterm, and then the other stuff I think I sent you, the lengthy...

CHAIRPERSON FROINES: I think that some of what Paul is saying also could be added -- some shortened version could be added to the chapter summary and conclusions, so you'd know exactly where you can find the information.

I should tell you, by the way, that your table of contents is not accurate. According to this, the chapter summary and conclusions is 6-94. It's actually on 6-109.

SUPERVISING TOXICOLOGIST MARTY: How could that be? We did that one in Word.

MR. MILLER: A computer glitch. That was generated by the --

SUPERVISING TOXICOLOGIST MARTY: It should have been created -- it was generated by Word.

PANEL MEMBER GLANTZ: This is why I still use Word Perfect. It doesn't have these problems.

CHAIRPERSON FROINES: I have 6-109.

So it's on 6-109, 6-110, 6-111 in my version.

PANEL MEMBER BLANC: Do you have SRP version or the --

CHAIRPERSON FROINES: Yes, I do.

PANEL MEMBER BLANC: -- or the early-bird version?

CHAIRPERSON FROINES: It's October 2004.

Anyway --

SUPERVISING TOXICOLOGIST MARTY: It might be a glitch with going to PDF also.

CHAIRPERSON FROINES: Let's not take any more time on this.

SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: We can come back to this. But I still find that the chapter summary and conclusions would deserve further look, and let's just put it that way for now, in terms of its accuracy.

I'm very interested in having a document that a large group of readers can actually find conclusions very clearly stated. It's such a massive document.

PANEL MEMBER BLANC: Well, one question -- maybe this is more a question for John. If you go to page 6-110 and 111 as a prototypical chapter summary and conclusions, it's a very long chapter. One of the things that they have done is in some places put references in again parenthetically in your time summary. And, for example, that's not a place where I would necessarily be looking for you to recite the reference citations that you've cited, you know, five pages ago in the specifically things. Although maybe that's my own editorial quirk.

I mean I would rather have you do the summary and say, "As shown in Section 3, through 15 studies" blah, blah, blah, "as shown in Section," you know, X, blah blah blah. But I don't -- why do you have to reiterate all of these references in each of your -- because then you're citing some references but not the others, so these are the references you really, really like.

(Laughter.)

PANEL MEMBER BLANC: You know, what's the implication? It makes it -- well, anyway.

SUPERVISING TOXICOLOGIST MARTY: We can take them out. That's fine.

PANEL MEMBER BLANC: You certainly don't have references in your executive summary, do you, of the whole thing?

CHAIRPERSON FROINES: Well, Paul knows that I also think that -- and he and I actually disagree on this a little bit -- that citing studies that were your weight of evidence seems to me to be a reasonable conclusory approach. And he disagrees with that. So we have a slight difference of opinion.

I don't know what -- I do think that this could be broken out more so the conclusions are very clearly defined according to endpoints. And I think that Paul argued earlier with Charlie and me that we don't really need to have that list of the studies that were positive, because then it raises the question of "what did you leave out" was his concern.

So I think the two of them, judging from Charlie's nodding his head, that we probably don't need them. But we do need, therefore, a very careful statement about what the conclusions were in terms of...

PANEL MEMBER BLANC: I would certainly emphasize

in your conclusions of each chapter at the outset of the conclusions, as this chapter has shown, we have raised the status of two health outcomes that were previously considered suggestive to the level of conclusive. These are "exacerbation of adult asthma" and "new onset adult asthma".

For each of the other -- for none of the other -- for all the other endpoints, you know, the findings were -- or new studies were overall supportive of the original conclusions. And in two cases, findings which were suggestive are strengthened, although not -- you know, we have not determined that they're conclusive.

I mean, that -- you know, march the reader through what you think matters in the chapter.

MR. MILLER: Yeah, you'd like somebody to be able to go to the conclusion and use that as -- there's kind a summary of what was in there.

PANEL MEMBER BLANC: So that when you did an executive summary, what you'd really do is just pull these out and, you know, make them coherent.

CHAIRPERSON FROINES: The other thing is, I think in -- and I think this is true with breast cancer, is that it's almost as though your conclusions you rely on -- and it's in here -- you basically come to the end and you're ready for your conclusions, and in citing your conclusions

you rely on the meta-analysis as the statement of reasons. And I actually don't think that the meta-analysis is the basis of your conclusion. I think the meta-analysis is one of the elements that lead to your conclusions. And I think this goes back earlier to the earlier question about counting meta-analysis vis-a-vis individual studies.

And so this -- you keep going through meta-analysis in your conclusions as though they were the defining feature. And I'm not sure you really mean that. If you mean, then say it. But I'm not sure that's what you really mean. Or I'm not sure that's -- because people who hate meta-analyses, of which there are large numbers, are not necessarily going to be convinced by that level of argument.

I mean are you saying that positive meta-analysis is the base of your conclusion? No, you're not really saying that, are you?

SUPERVISING TOXICOLOGIST MARTY: It strengthens it.

CHAIRPERSON FROINES: It strengthens it. So that it seems to me you need a slightly different context. Because this reads as though it's a causal statement -- I mean it's a defining statement.

PANEL MEMBER BLANC: In fact, how -- Stan, maybe this is a question for you. How does a positive

meta-analysis fit into the causal argument in the Bradford-Hill view? Is it evidence of strength of association or is it evidence of consistency of the association?

PANEL MEMBER GLANTZ: I think both. I mean the stronger the association that you have -- or the larger the magnitude of the association that you -- or the larger the magnitude of the effect that you see, the easier it is to see. And I mean the meta-analysis is just -- I mean is just a way of saying if you take the studies together and sort of average them, what do you come up with on average weighting them by study size essentially?

So I think finding a significant elevation in a meta-analysis when you have a whole bunch of small studies is just the way of looking at the epi information all at once and coming up with a summary statistic. And, you know -- so if you find a significant elevation in a meta-analysis, that I think strengthens your case. But then I think, as they did in the breast cancer in particular and then cardiovascular disease also, to then look not just at the epi-studies, but at the toxicology and at the experimental work and the mechanistic studies and things like that. I mean that is what I view as a weight of evidence.

You know, do all the -- I mean when I look and

say cardiovascular disease, the thing which is to me most compelling is that if you -- you can look at a whole lot of different kinds of evidence and they all point to the same conclusion. And, you know, there's no one level of evidence which is perfect. I mean if you talk about an epi-study, it's always messy. There's always something wrong with all epi-studies. But the advantage of an epi-study is it's in the real world, you know.

But then the other extreme, if you go to a molecular biology or cellular biology studies that show toxic effects of the smoke or something in the smoke, then that is very supportive, but it's also a tremendously artificial environment.

And so, you know, I think what you want to do is step back and look at all of these different kinds of evidence and just see how consistent is the picture that they paint.

CHAIRPERSON FROINES: Let me just make one argument about that.

I think that this artificial environment that you just said I really would quarrel with, because I think that comes from a bunch of people who make lists of chemicals that are found in tobacco smoke, and I would agree with you there, if you say butadiene, formaldehyde, Benzene. And people who don't know anything about

chemistry often list chemicals and make a case as though that was sufficient.

However, the issue as far as I'm concerned is: Does the chemistry of those compounds support a mechanistic view of the health outcomes? And that actually I take as being a serious -- a real contribution.

PANEL MEMBER GLANTZ: Oh, no, I --

CHAIRPERSON FROINES: Just listing toxic chemicals is fine and well and good. But it's not sufficient because it doesn't go to the chemistry of -- and the basically chemical mechanism of these effects.

PANEL MEMBER GLANTZ: Oh, no, I -- that wasn't what I was trying to say. I think when you -- and I agree with what you said. But I think that when you do -- you know, for example, some of the work we've done where you'll take an experimental animal and expose them to secondhand smoke in a very highly controlled way, you know, you can be more confident about the effect -- you induced an effect in an experiment, but it's not a normal kind -- it's not like a human being walking around, living day to day.

And so to the extent that you constrained the environment in an experimental situation, which strengthens your experimental conclusions, it I think by its very nature takes you more distant from reality in

terms of what people walking around are actually -- you know, like if you're doing an experiment exposing rats to secondhand smoke, they're not out on the street breathing diesel exhaust, you know.

CHAIRPERSON FROINES: Kathy would --

PANEL MEMBER GLANTZ: Kathy would be measuring --

CHAIRPERSON FROINES: I want to give her a chance before I get back and --

PANEL MEMBER HAMMOND: Yeah. And I agree with both of your points there.

But going back to Paul's question about the meta-analysis. I think disagree with Stan on that. I think a meta-analysis is not going to give you a stronger effect or a higher, you know, relative risk. You know, usually it's going to be something in the middle. But rather what it gives you is it eliminates the likelihood that chance was the underlying reason for the result -- the positive result you saw. And so --

PANEL MEMBER GLANTZ: Well, no, what I -- I'm not just going -- because you're not disagreeing with -- I wasn't clear.

PANEL MEMBER BLANC: Heaven forbid.

PANEL MEMBER GLANTZ: What I was -- I was talking about two different things.

Okay. One of them is in the meta-analyses you

can increase the precision of your estimate --

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER GLANTZ: -- which is what Kathy is saying.

The other thing I was saying is that if in doing -- if in doing the meta-analysis, the higher the overall estimate of the risk that the meta-analysis yields, the more confident you could be --

PANEL MEMBER HAMMOND: But that's true of the meta-analysis of any single study.

PANEL MEMBER GLANTZ: That's true.

PANEL MEMBER HAMMOND: But I mean in terms of I think the contribution the meta-analysis brings -- the unique contribution in the Bradford-Hill is to narrow the confidence interval.

PANEL MEMBER GLANTZ: Yes, I agree with that.

CHAIRPERSON FROINES: I think Paul actually had a hidden position when he asked that question. Because I think he was --

(Laughter.)

CHAIRPERSON FROINES: -- really saying that he thinks it strengthens the consistency argument, but not necessarily strengthens the association.

PANEL MEMBER BLANC: It actually was not a -- it was not a rhetorical question, because as I think about

it, I'm not really -- I'm still not really clear. And maybe one of the problems with meta-analysis or the contradiction of meta-analysis is that we put a lot of weight in them, that we find them very reassuring. We don't -- they don't drive everything, but we're very -- we're very reassured when a meta-analysis yields results that are consistent.

But a meta-analysis is not so easy to pigeonhole in the Bradford-Hill way of divvying up the world, because in some senses it's an issue related to consistency and in some ways it's related a bit to strength of association. But it doesn't --

PANEL MEMBER HAMMOND: I don't think --

PANEL MEMBER BLANC: But it's not so neatly -- it's not so neatly categorized, well, maybe that's how --

PANEL MEMBER HAMMOND: No, I think it does --

CHAIRPERSON FROINES: I think there are differences of opinion about the strength of association.

PANEL MEMBER HAMMOND: No, I don't think it changes the strength of association. But I think what it does do is it reduces the probability that what you observe is due to chance. And it does that by --

PANEL MEMBER BLANC: But that's not a Bradford-Hill criterion.

PANEL MEMBER HAMMOND: Yes, it is. Yes, it is.

You want to --

CHAIRPERSON FROINES: Yes, it is. It's consistency or --

PANEL MEMBER HAMMOND: No, it's different, but I mean it's --

PANEL MEMBER GLANTZ: Yeah, that's true. I mean in your -- worded the way you're wording it, it increases your ability to estimate the level of consistency.

CHAIRPERSON FROINES: I mean one of the things that we saw with diesel is we -- there are two or three papers that took every epi-study and found fault with each one; and at the end of it concluded, see, there's nothing there. And so we know epidemiologists are very good at slicing up an individual study.

But I think the going to the other extreme, where you look at the meta-analysis and say it strengthens your association, I'm not so sure one can do that either. But I do think that it does indicate that the results may not be results of chance or it adds to our success of consistency. That's why everybody shows all these figures with everything above the line, because you can see this nice picture. And sometimes I think we have to be careful about those kinds of pictures too. But in a sense the meta-analysis does do that, don't you think?

PANEL MEMBER BLANC: And the other issue -- other

Bradford-Hill issue that we haven't talked about at all today, and it's very absent from most of your arguments, is the issue of specificity. And to me, that's a demand -- how can you make that demand of something like secondhand smoke that has, you know, 3,000 components to it? Why should it have a specific effect, or why should a health effect that it is associated with be specific only to it when you would expect that other exposures would do that?

PANEL MEMBER HAMMOND: That kind of goes back to the microbial view of epidemiology, you know. And Sir Richard Dole was actually talking about that on a campus recently. Originally that was exactly the reason people rejected the epidemiologic links between smoking and lung cancer, is that as soon as they started having other health effects related to smoking, then -- or other things caused lung cancer, you know, so it couldn't be that smoking was the cause. So it was -- and we know -- I think that's something that we know better than now, especially for complex mixtures. There are multiple effects and there can be multiple causes.

PANEL MEMBER BLANC: Well, yeah, that was one thing that Bradford-Hill developed, and he developed his criteria in relationship to smoking and lung cancer. It might be worth actually going back to the Surgeon

General's report and seeing how they spun that in that context.

PANEL MEMBER GLANTZ: Oh, I don't know --

PANEL MEMBER BLANC: I would say, because if you're going to -- you have invoked Bradford-Hill, you may be invoking it more. If you're going to invoke it, you better know what you're invoking. That's all I'm saying.

PANEL MEMBER GLANTZ: Well, why don't we go on to Chapter 7.

CHAIRPERSON FROINES: Well, I think this --

PANEL MEMBER BLANC: I'm talking about the respiratory, from my point of view.

CHAIRPERSON FROINES: Well, I think this is useful, because in fact I think we're covering a lot of ground I mean I thought we might end up covering come January. So it's useful. And I think the broad outlines are useful.

We're going to stop, I think what, Melanie? 2:15?

SUPERVISING TOXICOLOGIST MARTY: 2:15 to 2:30 would be good.

CHAIRPERSON FROINES: Yeah, because four of us are on the same plane to Washington DC.

PANEL MEMBER GLANTZ: Now, is that a quorum?

That was a joke. That was a joke.

(Laughter.)

CHAIRPERSON FROINES: There are no jokes.

(Laughter.)

CHAIRPERSON FROINES: Go ahead, Melanie.

SUPERVISING TOXICOLOGIST MARTY: Okay. I think, in view that we have a half an hour, we should not attempt Chapter 7. It's a very large --

PANEL MEMBER BLANC: That's the cancer chapter?

SUPERVISING TOXICOLOGIST MARTY: That's the cancer chapter.

PANEL MEMBER BLANC: I think you have to do the breast cancer, skip right to -- in that chapter. You have to do breast cancer. That's --

SUPERVISING TOXICOLOGIST MARTY: Do I have to do breast cancer today?

PANEL MEMBER GLANTZ: Yes.

PANEL MEMBER BLANC: You have to do --

PANEL MEMBER BYUS: Yes, do it today. It's the most controversial. We need the most time to think about it.

SUPERVISING TOXICOLOGIST MARTY: Okay. Fine.

PANEL MEMBER HAMMOND: Get started --

PANEL MEMBER BYUS: Get start on it.

CHAIRPERSON FROINES: Yeah, because I think that this will prepare -- everybody will realize they're going

to have go back and look very carefully at this issue since it's so important.

That means for the panel, everybody is committed to reading more and more and more over the Christmas break.

CHAIRPERSON FROINES: Are you okay?

MR. MILLER: Yeah.

CHAIRPERSON FROINES: We have half an hour to go.

SUPERVISING TOXICOLOGIST MARTY: Okay. Mark Miller is going to talk about the breast cancer section.

--o0o--

MR. MILLER: This is an overview of some of the endpoints actually. It doesn't fit on a single slide with the cancer chapter.

But the major changes --

CHAIRPERSON FROINES: Mark -- Peter, do you have handouts?

MR. MATTHEWS: Yes.

MR. MILLER: Major changes since 1997. The lung cancer argument was strengthened.

PANEL MEMBER GLANTZ: Just skip to breast cancer.

MR. MILLER: Okay. Breast cancer.

PANEL MEMBER GLANTZ: We speed through the rest of those slides.

That was a joke.

MR. MILLER: So the studies of ETS and breast cancer include case control studies, and most of which are positive; and many are statistically significant so. Case control studies with the best exposure assessment have the highest risk estimates; many statistically significant.

There's several cohort studies. A few have elevated but not significant findings. And some have null results.

And the meta-analysis -- meta-analyses, both ours and others, indicate elevated risk from ETS exposure.

--o0o--

MR. MILLER: And I thought we'd show two of the studies we thought were among the strongest. One is the relationship of breast cancer with passive and active smoking, by Morabia. It's a population-based case-control study with 244 cases and over a thousand controls.

And it was the first study to really do a good job of the lifetime history of active and passive exposure.

They went year by year from age 10 until the interview. They created three separate calendars of exposure for homework and leisure time. And in order to -- passive smokers were defined as at least one hour a day for at least 12 consecutive months.

The overall adjusted odds ratio for passive

exposure was 3.2, and that was significant.

So there was comparing passive smokers to a never smoker/no environmental tobacco smoke exposure.

--o0o--

MR. MILLER: Similarly, the paper by Ken Johnson from Health Canada looked at -- it was a registry identified incident cases of breast cancer. There were 805 premenopausal breast cancers and 1512 post-menopausal.

There was a questionnaire with telephone follow-up for each residence of at least a year. They were questioned how many regular smokers were at that residence for each job of a year or longer. They were asked, "How many people regularly smoked in the subject's immediate work area?"

--o0o--

MR. MILLER: And not only did they have positive significant findings in the premenopausal breast cancer area; they had a strong trend -- with P for trend -- .0007. This is for a total of residential and occupational years exposed by years.

PANEL MEMBER BYUS: What does the "P for trend" mean exactly? I mean what does that mean? It's in the --

MR. MILLER: I've had a statistician --

SUPERVISING TOXICOLOGIST MARTY: There's a trend test that's done on dose response -- in this case, dose

response data. And it tells you whether there really is an upward trend in that -- an upward dose response curve, essentially, in this case. So it's --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Essentially is the slope of the -- different from one.

SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: Does he mention the healthy worker survivor effect in this paper?

SUPERVISING TOXICOLOGIST MARTY: I don't think he relates the -- I don't think he does discuss the healthy worker effect. But this occupational plus residential exposure.

--o0o--

MR. MILLER: Looking at the cohort studies, there were two that had elevated risk, Hirayama and Jee. And an additional four that were not elevated. Neither of the two that were elevated were statistically so. Although they both -- the two that looked at premenopausal risk had elevations, neither of which was statistically either.

PANEL MEMBER BLANC: You say cohort. You mean longitudinal? You tend to use the word "cohort" as if you meant longitudinal.

MR. MILLER: Prospective cohort study. Yeah, it was --

PANEL MEMBER BLANC: But both the cross-sectional ones were cohort studies too. They were cross-sectional cohort studies, weren't they?

MR. MILLER: Yeah.

PANEL MEMBER BLANC: So I would suggest it would be cleaner, when you mean longitudinal, just say longitudinal; when you mean cross-sectional, say cross-sectional.

MR. MILLER: Okay.

--o0o--

MR. MILLER: I'd like to address head-on the results of cohort versus case control studies.

Some of the non-U.S. studies showed elevated non-significant risks. We just mentioned that.

To date, none of the cohort studies have measures of exposures that include childhood, residential adult, and occupational information of exposure.

SUPERVISING TOXICOLOGIST MARTY: Mark, let me interject here.

The reason we're discussing this is because a lot of people have said, "Well, those cohort studies weren't positive. And prospective cohort studies are the gold standard of epidemiology." So, therefore, in their minds they don't believe the case control.

PANEL MEMBER HAMMOND: Hence, Paul's point, so

important --

SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER HAMMOND: -- that these aren't cohort studies. They aren't gold standards.

SUPERVISING TOXICOLOGIST MARTY: Right.

MR. MILLER: You know -- well, we'll get to it.

As an example though, we'd like to point to Fontham, which was a case-control study and is readily recognized as the best lung cancer study because it had the best exposure history and it included all the relevant exposures and cotinine measurements. And it was a large study with a variety -- you know, a large varied population.

The bottom line is that we feel that the cohort study is only as good as exposure assessment.

PANEL MEMBER BLANC: Could we go back -- go back to the cohorts again.

How long was the follow-up in these cohort studies?

MR. MILLER: Oh, they varied.

SUPERVISING TOXICOLOGIST MARTY: They varied.

MR. MILLER: From a few years to 16 years, something like that.

PANEL MEMBER BLANC: And they were prospective cohort studies, all of them?

MR. MILLER: Prospective cohort --

SUPERVISING TOXICOLOGIST MARTY: Those were.

PANEL MEMBER BLANC: Cohort studies.

And the only measure of ETS exposure was the ETS exposure at the initiation of the cohort?

MR. MILLER: Well, they vary. But often that's the case, is a single -- I mean, for example, Wartenburg had -- well, the primary information was from the husband's questionnaire, so there was some information there. And then from the woman's questionnaire, it was "What is your exposure" -- "Does your husband smoke now, in 1983?" So that it didn't include historical information and didn't reassess it over the 16 years or so that --

PANEL MEMBER BLANC: Uh-huh.

MR. MILLER: So they vary from study to study. But they often are a single time point, they often are, you know, only spousal information.

PANEL MEMBER BLANC: Are these studies able to show an association between direct smoking and breast cancer?

MR. MILLER: Reynolds is one to point to, which is a recent study in California. It was --

SUPERVISING TOXICOLOGIST MARTY: I think there was only one.

Well, no, that's not the only one. Wartenburg, the active smoking part of that was called Calle C-a-l-l-e, which was published many years prior to Wartenburg. And they found an association with active smoking.

Egan finds an association -- you have to -- if you look at women who started smoking 16 years or younger, there was a statistically significant positive association in Egan.

Reynolds had an overall association, even though the only measure of exposure was residential exposure from Reynolds.

PANEL MEMBER BLANC: The reason I asked the question is because if their risk estimates of direct smoking associated with the breast cancer were substantially diluted compared to other people's risk estimates of direct smoking and cancer, that might support your argument that the -- and assuming that it had the sort of the same tendencies of not having good interval information and so forth, it would perhaps support your argument that there was too much exposure misclassification to give that it diluted it towards the null.

Am I making sense?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: The big concern with the proposal that the ETS is associated with breast cancer has been the fact that the association with active smoking is being regarded dubious at best precisely because these studies -- apart from Reynolds, which is a much more recent study, the previous studies generally have had a very diluted and dubious association with active smoking.

SUPERVISING TOXICOLOGIST MARTY: We're going to get into that. We should just keep going on this presentation.

PANEL MEMBER GLANTZ: I think it would be good to let them go through this, and then come back to the questions.

MR. MILLER: There's a Whole convergence of different information.

PANEL MEMBER BLANC: Okay. Go to your next one.

--o0o--

MR. MILLER: So to start with -- and then we'll move backwards -- we did this meta-analysis with Ken Johnson from Health Canada and looked at 17 studies, of which five assessed childhood, adult residential, occupational and social exposures.

--o0o--

MR. MILLER: Overall the 17 studies were a heterogeneous group. But if you looked at the studies

that collected the important sources of exposure, there was a homogeneous group. And our results were consistent with previous meta-analyses by Wells, Morabia, Khuder and Simon.

--o0o--

MR. MILLER: So here's -- just to look at those studies, the ones with the black triangles are statistically significant results.

The summary estimate for all studies was -- 1.31 was statistically significant. And if you isolated the studies with the more complete exposure assessment, that increases to 1.89.

Next slide.

--o0o--

MR. MILLER: Similarly -- this is looking at the studies that isolated premenopausal breast cancer. And as you see, all of the results were positive, and many of the studies were significantly so. And also again a slight increase in the risk estimates when you look at just the studies that had more complete exposure assessment.

--o0o--

MR. MILLER: So --

CHAIRPERSON FROINES: Sorry. Go back to that -- Just one second.

MR. MILLER: This is premenopausal risk.

CHAIRPERSON FROINES: Hirayama is where?

MR. MILLER: Hirayama's at the beginning here, '84.

CHAIRPERSON FROINES: And Wartenburg -- am I misreading it? -- it also doesn't show a significant result.

SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: Right.

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER BLANC: And you're saying that Egan, for example, doesn't differentiate between pre postmenopausal breast cancer?

MR. MILLER: Right. It was all premenopausal for Egan.

And Shrubsole -- you know, I mean we chose this, which was an overall number. However, if their estimate for work exposure was actually 1.6, then was statistically significant.

--o0o--

MR. MILLER: Historically, essentially what was said in the 1997 document was, well, we have these several studies that look at passive smoking. And all of them look suggestive or positive. But when we look at the cohort studies, we're not so sure. Actually when they look at the active study -- active smoking studies, it's

more of a mixed bag. And so that we don't know how to interpret this.

So the effect, seeing active smokers were comparable or weaker to those seen in passive smoking, they were also concerned that there were no dose response trends that were evident in the data and that there was uncertainty about the suggestion that there were certain susceptible subgroupings of women.

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MR. MILLER: So there are various hypotheses that may help to explain some of those findings, and we've started talking about those already. But there's a causal -- or presumed to be a causal preventive effect from current active smoking, and that's anti-estrogenicity. It may obscure an overall association between smoking and breast cancer.

While there's some variation in studies that have looked at the actual estrogen levels, there is an increase in the less active estradiol and relative to the more active 16-hydroxy estradiol.

There's also in numerous studies estrogen effect that's noted: Decrease in age at menopause, which is an anti-estrogen effect; increase in breast density; attenuated effects of hormone replacement; and increased risk of osteoporosis.

So the risk was similar for active and passive exposure. This is another hypotheses. And that highlights a need for unexposed controls.

Next.

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MR. MILLER: That sensitive subpopulations or time periods exist. For example, polymorphisms in metabolism. There's windows of susceptibility, either peri--pubertal or before the first pregnancy. And that there's a need to examine long durations of exposures, 30 to 40 years. And particularly in the earlier studies it was difficult to find women that would fit into that category.

Next slide.

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MR. MILLER: In examining windows of susceptibility, one important part of the argument is the breast biology. There's several periods of breast epithelial development. Lobules go through cell division and differentiation. They're quite immature up until peripuberty when they develop lobules. Then those further differentiate during pregnancy and lactation.

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MR. MILLER: In vitro studies there's some support for this. The lobules of varied differentiation

were isolated from reduction mammoplasty and cultured. And the least differentiated cells from the nulliparous women were most susceptible to transformation by Benzoate Pyrene and nitrosamines than the more differentiated cells from women that have had pregnancies. This is similar to findings in rodent cells.

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MR. MILLER: As well, there's a series of studies that was reviewed by Russo and Russo, where PAH induced mammary tumors in the rat model revealed the period of greatest mammary differentiation was the most susceptible period and that reduced sensitivity of mammary epithelium was seen after pregnancy and lactation, which could be mimicked by injection with chorionic gonadotrophin.

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MR. MILLER: As well in human studies from radiation exposure, we know that there's significant increase in breast cancer. For example, in women -- in girls that were treated with radiations of the chest for Hodgkins lymphoma, in fact that's 75 times the background incidence. But if you look at the ones that were treated between 10 and 16 years of age and compare those to the ones that were treated under 10 years of age, there's over a six-fold increase in those treated during adolescence. And that's consistent with other studies, both bomb

survivors and radiation from x-rays for girls that have had scoliosis and rods placed in their back.

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MR. MILLER: So looking at these factors, in kind of an interesting and complex study, Band did a study of active smoking; looked at the odds ratios relative to non-smokers; and explored these hypotheses of interaction between active smoking's anti-estrogenic effects, which are protective, and windows of susceptibility to the carcinogenic effects.

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MR. MILLER: And one part of the hypothesis would be the tumorigenic action of the carcinogens would be displayed most prominently with exposure prior to first pregnancy and during peripubertal times. The idea is that the breast sensitivity at that point would outweigh any anti-estrogenicity. So in order to look at that, they looked at premenopausal breast cancer by the timing of the initiation of smoking so that those that initiated earlier in life, less than five years after menarche, had a significantly more elevated risk, OR 1.7, compared to those that started more than five years after, or also looking at it similarly in relation to the first pregnancy.

If you initiated smoking before your first

pregnancy, you had increased risk. Whereas if you initiated after your first pregnancy, you did not.

And the extreme example is that a nulliparous woman and with a high exposure, she would have an odds ratio over seven-fold.

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MR. MILLER: So the other side of the argument is that anti-estrogenicity as a protective effect would be most pronounced in postmenopausal women, with onset of smoking after the first pregnancy and relatively heavy. That relates to the estrogen levels being higher in those postmenopausal women due to aromatization of adrenal androgens and that they would have avoided the exposure in the earlier sensitive period.

And, indeed, what seen in those women, that those who initiated smoking after the first pregnancy and gained weight had an odds ratio of .49, which was statistically significant; and those who initiated after the first pregnancy did not have a significant.

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MR. MILLER: So in regards to the risk being similar for active and passive exposure, here's several recent studies that would be considered as good exposure assessment studies that do have active and passive odds ratios that are similar.

PANEL MEMBER GLANTZ: So were those -- if you go back. The ones that are active smoking studies, were those ones where they were using as the control group, non-exposed nonsmokers?

MR. MILLER: Yeah, I think --

PANEL MEMBER GLANTZ: Or was that all nonsmokers?

MR. MILLER: Non-exposed nonsmokers. I think Lash was actually a variation on that, but more or less.

PANEL MEMBER GLANTZ: Okay.

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MR. MILLER: So there's a similar dose response for active and passive smoking, maybe related to differing chemical composition of mainstream and ETS. There are more carcinogens in the latter.

Dose response is difficult to characterize. And that's maybe because it's a non-linear for breast cancer. It's complicated by anti-estrogenic activity of active smoking, genetic polymorphisms and windows of susceptibility, as we've been talking about.

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MR. MILLER: This is from Morabia, looking at active smoking, and highlights that -- you know, this is adjusted smokers versus nonsmokers with no ETS, with elevated odds ratios. For example, 10 to 19 cigarettes per day, 2.7.

And then if you look at that -- instead of comparing it to smokers to nonsmokers without ETS, you just compare smokers to nonsmokers, which includes ETS exposed. You can see that each of the odds ratios drops significantly. And in fact, you know, for the lower exposure groups it goes from an elevated pretty much significant value to a non-significant value.

Similar results within individual studies are found in Johnson, Lash and Aschengrau, and Kropp and Chang. So this has been validated in a number of different studies.

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MR. MILLER: On top of that, looking at even -- considering that, looking at the active smoking studies and breast cancer, there's still considerable evidence that active smoking does appear to be related to breast cancer.

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MR. MILLER: Do you want to do this?

SUPERVISING TOXICOLOGIST MARTY: Yeah. Mark's having throat difficulty.

Just wrap this up.

CHAIRPERSON FROINES: Why don't we -- we're at a place that's a good place to stop I think, unless you want to --

PANEL MEMBER GLANTZ: If we could, I think it would be nice to just hear the whole thing and the --

CHAIRPERSON FROINES: We can't, Stan. We have four people making a plane to Washington. We can't --

PANEL MEMBER GLANTZ: Oh. I thought you said we could go till 2:30. No?

CHAIRPERSON FROINES: No.

SUPERVISING TOXICOLOGIST MARTY: I could move through a few more slides really quickly and finish.

PANEL MEMBER GLANTZ: Okay.

SUPERVISING TOXICOLOGIST MARTY: Would that be okay?

CHAIRPERSON FROINES: Well, my only concern is you're getting into an area that I have rather strong feelings about the science. And so when we get into mammary carcinogens and PAH and tobacco smoke and those things, if you want to skip those and come back to them next time, because there's going to be discussion I think associated with that.

I hate to sort of say -- I mean then I would skip to someplace where -- why don't you skip to "Comments" if you're going to --

PANEL MEMBER HAMMOND: We'll have discussions on them in January. I just thought this was just to --

CHAIRPERSON FROINES: Then why can't -- I would

like to be leave for the airport right this minute. And Stan wants us to go in 15 minutes so we can get --

PANEL MEMBER BLANC: Who are the two leads on this? Stan -- on cancer, the two of you?

What I would suggest is -- we have the copy of the slides handed out -- that we adjourn essentially now. People can look at the slides.

But I would also appreciate at some point between now and the January meeting in advance of the January meeting to have some brief comments from the leads on this chapter, not on the whole chapter, but on the breast cancer piece of it, because I perceive that this is going to be one of the more contentious and perhaps -- could perhaps lead to avoidable delays in the document. If there's some parts of it that we can thrash out or lay out the issues more clearly in advance of the January meeting.

PANEL MEMBER GLANTZ: Well, do you think -- I mean is there any chance even if John left that we could just continue talking?

PANEL MEMBER BLANC: No. He said four people on the plane.

CHAIRPERSON FROINES: I'm the Chair, and I'm not leaving --

PANEL MEMBER GLANTZ: Well, do you want to just say just on the record what your concerns are just so we

know what they are?

CHAIRPERSON FROINES: No, I don't think -- Stan, I think that what you're doing is you're trying to hurry a process that doesn't -- that won't get better by hurrying it.

PANEL MEMBER GLANTZ: Well, I'm not trying to hurry it. I'm just trying to understand.

CHAIRPERSON FROINES: Well, I don't think we should get into -- I don't think we should get into substance because that's going to get us into a lengthy discussion.

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: And I think that -- I don't think -- let me be very clear.

This process is not going to be hurried. No matter how much you want this to go through, it's not going to be hurried, because I want the record to indicate a very thorough careful analysis of all the data. And we have to do that. And so it's sort of like saying, "Can't we just hear what your concerns are and spend ten more minutes?" It's exactly the opposite of what I think we should be doing.

PANEL MEMBER GLANTZ: No -- and I'm not -- I mean I'm not disagreeing with you. I think we want to be careful. But I would have liked to have just heard the

rest of the presentation, because it gives us something to think about.

But if you don't want to do that, we can stop.

CHAIRPERSON FROINES: No. Let me just make clear.

We are going to hear the presentation. We're just going to hear it at the next meeting.

PANEL MEMBER BYUS: I have a brief request along the line of what you're saying. Why don't we try and prepare some written questions and written comments that can help you guide the next meeting in terms of constructing an agenda for it in terms of focusing on some issues. That's what I think you were getting at.

CHAIRPERSON FROINES: Well, I think that's fine. I think the important thing is to follow the process that we've established; namely, that if Paul has questions, he communicates that to the leads, and the leads communicate it to the OEHHA, so we keep an orderly kind of structure.

PANEL MEMBER GLANTZ: Well, I think that's fine.

CHAIRPERSON FROINES: And so that means people who have questions communicate with Joe and Stan. Who else was doing cancer?

PANEL MEMBER GLANTZ: Well, my only concern here -- I'm fine with that. But what I would like to see -- because, frankly -- I mean I've looked through the

drafts of the documents and raised the issues that I raised, which have been addressed. So I think I would personally -- if John or other people have issues that they think ought to be addressed, I would rather do what John just said, and we can transmit that to the staff to try to get them addressed before the next meeting. Because I don't think -- I don't think I have much to say, frankly, that would be of much value. I'm much more interested in hearing what the other people here have to say. So I would suggest we do that.

And can I just ask one other question?

And that leaving aside this discussion, there have been a whole bunch of suggestions made about parts of the report that have been discussed up to this point, and there have been a bunch of sort of generic suggestions made about the introductions and the tables and things like that. Would it be sensible or a good use of time to ask OEHHA to do a red-line and strike-out revision of the document based on the discussion so far before the next meeting, or is that a waste of time?

CHAIRPERSON FROINES: Melanie.

(Laughter.)

SUPERVISING TOXICOLOGIST MARTY: Well, we could do the easy stuff. But I'm not sure how useful that would be since most people have already written comments in the

margin of the copy they have.

It might be -- I think a better idea is to make sure that the transcript gets back to the panel members so they know what's already been asked of us. I think that might be helpful.

PANEL MEMBER GLANTZ: Well, do you see any of the things that were raised as substantive, or you see them as primarily editorial in nature?

SUPERVISING TOXICOLOGIST MARTY: Is this is a trick question?

PANEL MEMBER GLANTZ: No.

(Laughter.)

SUPERVISING TOXICOLOGIST MARTY: No, there were substantive issues raised. I mean one of the things is the preterm delivery. Are we going to call that causal or not? I mean that's a --

PANEL MEMBER GLANTZ: Okay. Well, I would hope then for the next meeting that of the stuff -- that you guys look through the transcript, and of the issues that were raised that you think are substantive, that when you come back next time that you have sort of what your response to the panel is on those points. You know, you don't necessarily have to revise the document. But so that there can be -- you know, so you guys can come back and say, "Okay, you guys brought these issues up. Here's

what we're recommending saying:" So that there'll be some closure to those questions.

And, again, I would just ask if -- I would personally -- I mean personally if people have issues with this stuff -- and I agree with you that the breast cancer stuff is very important and we don't want to rush it. But it would be helpful I think if those issues could be brought to OEHHA's attention so they can come to the meeting next time prepared to address them rather than hearing them called.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: You want us to give written comments to you to give to OEHHA? Or what do you want to do?

CHAIRPERSON FROINES: I thought it would be easier if any comments went to the leads, who then had responsibility for making sure there was communication rather than a sort of individual process that is kind of just more disorganized.

PANEL MEMBER GLANTZ: Okay. I mean I think that's fine.

PANEL MEMBER LANDOLPH: Send us stuff to take --

CHAIRPERSON FROINES: What I would do is copy Melanie on what you send to Stan. And so in case there's a glitch, that both people have them.

But -- I, for example, have some questions about the Part A document. And I didn't raise them because of the timing situation. I think Kathy does too.

So there are lots -- there are still unresolved issues. And I think just -- not to sound overbearing at all, because I don't mean to be -- but I think this process is going to go -- it's going to take awhile, and we're going to have to do it very systematically. And so -- that doesn't mean we have to go, you know, glacially --

PANEL MEMBER BLANC: I'm going to make a motion that we adjourn.

PANEL MEMBER LANDOLPH: Second.

PANEL MEMBER BYUS: Third.

(Laughter.)

CHAIRPERSON FROINES: All in favor?

(Hands raised.)

(Thereupon the California Air Resources Board, Scientific Review Panel meeting adjourned at 2:20 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 6th day of December, 2004.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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