MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

MILLBERRY CONFERENCE CENTER

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SAN FRANCISCO, CALIFORNIA

THURSDAY, JANUARY 6, 2005

9:00 A.M.

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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper(via teleconference)

REPRESENTING THE AIR RESOURCES BOARD

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APPEARANCES CONTINUED

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. George Alexeeff, Deputy Director, Scientific Affairs

Dr. James Collins, Staff Toxicologist

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

Dr. Mark Miller, Air Toxicology and Epidemiology Section

Dr. Bruce S. Winder, OEHHA, Associate Toxicologist

ALSO PRESENT

Dr. Kenneth C. Johnson, Senior Epidemiologist, Public Health Agency of Canada

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PROCEEDINGS

CHAIRPERSON FROINES: We will officially open the Scientific Review Panel meeting on January 6th, 2005.

And first announcement is that Dr. Plopper from UC Davis is not able to be with us because of a prior commitment. But I believe he's on the telephone.

Is that correct?

PANEL MEMBER PLOPPER: That's correct.

CHAIRPERSON FROINES: Charlie, can you hear me?

PANEL MEMBER PLOPPER: I can hear you fine. Can you hear me?

CHAIRPERSON FROINES: I think the whole room can hear you fine.

PANEL MEMBER PLOPPER: Oh. Maybe that's not good, huh?

(Laughter.)

PANEL MEMBER GLANTZ: Sort of like God talking.

CHAIRPERSON FROINES: Right. You literally sound as though you're coming out of the ceiling.

PANEL MEMBER PLOPPER: Well, you know --

(Laughter.)

PANEL MEMBER PLOPPER: -- if that helps, that's good, I guess.

CHAIRPERSON FROINES: We'll listen very closely to everything you say today, for fear we'll have wide

ramifications.

So we are going to continue where we left off. And, that is, with OEHHA continuing their presentation.

Peter Matthews is passing around a new set of slides. Dr. Landolph has prepared some written comments. And we're going to ask him to discuss them at some point so we can have them on the record verbally.

So at this point, Melanie, why don't you begin.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Good morning. Thank you.

Before I actually start on my presentation -- sorry, this thing's loud -- I did want to introduce Dr. Ken Johnson from Health CANADA who was a consultant to OEHHA on the breast cancer issue.

So Ken is in the second row.

He came all the way from Ottawa, not just because it's minus 10 there and 55 here, but because he's helping us out in a big way.

Okay. So he will be here throughout the discussion, which might -- you know, we might be able to turn to him for a few issues.

PANEL MEMBER FRIEDMAN: You need to speak into the microphone.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Sorry. Actually it sounded really loud to me.

Is that better?

Okay. Good.

What we -- if you'll recall the November 30th meeting, we were part way through the discussion.

CHAIRPERSON FROINES: Can I interrupt you?

I just want to say for the record that all the members of the Panel are in attendance with the exception of Dr. Plopper, who's on a telephone, and Dr. Roger Atkinson, who did not join us.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. At the last meeting we were part way through our presentation on the associations between ETS and breast cancer. And we'll take up where we left off. The discussion was turning towards a comparison between the data on active smoking and breast cancer and passive smoking and breast cancer, as well as looking at use of referent categories that did not include ETS-exposed people and the difference that made in analyses. So I think we'll start from there.

And Mark Miller and I will tag team this presentation.

DR. MILLER: So this slide --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, Sorry.

For the Panel members who have the handouts, page

16 is basically where we're starting. So there's a blank on the top of your page 16. And then this slide is not there, but we're just going to use it for a brief introduction. And then the next slide will be starting there.

And, Dr. Plopper, there's a blank somewhere about the middle of the presentation. So if you look for the blank slide, you should be able to be --

PANEL MEMBER PLOPPER: The comments, right?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, will be right -- it's actually not comments. It's a few slides before that there's another blank.

PANEL MEMBER PLOPPER: Okay.

DR. MILLER: And for the audience, if you have Kathy's with six slides per page on your handouts, it's beginning on page 6. Except where we pulled this one slide as the introduction from previous -- a few slides earlier just to remind you that this was a slide that looked at pulling out studies that utilized referent unexposed category that excluded at least to some attempt lifetime passive smoke exposure.

CHAIRPERSON FROINES: Just one comment.

There was an extensive discussion at the last meeting raised principally by Dr. Blanc about issues of causality. And then he followed up with an E-mail to you

folks.

Are you going to address those issues today?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. We can do that right after we finish with the Chapter 7. I have a whole list of things that I wanted to tell the Panel that we're doing with their comments, including this idea of --

CHAIRPERSON FROINES: Paul has to leave at 11:20. So hopefully we can --

PANEL MEMBER BLANC: I might -- I'll be back. But I have to leave a little bit earlier than lunch break.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We'll get it in before then.

CHAIRPERSON FROINES: Just for everybody, we're going to take a break around 12 o'clock, because Paul is at a -- going to be unavailable. And so we want to take an earlier -- slightly earlier lunch break than we normally would so he can then -- will be available in the afternoon.

DR. MILLER: So when we're looking -- the left side of the figure is active smoking and the right side are passive studies. And these are all studies that included some historical measure for exposure in childhood and adulthood, residential and occupational, and other exposures. And basically the point of this is that when

you take those studies, there seems to be relatively similar risk between the active studies and the passive studies.

And --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Now we're on the slides that you folks have.

DR. MILLER: And then just a -- well, why do we look at those studies as being a better quality study?

And this is example. There are several that within the same study they've looked at, you know, measures of exposure and compared smokers to nonsmokers and come up with -- these are the odds ratios for 1 to 9 cigarettes her day, 10 to 19, greater than 20. And so if you have smokers versus nonsmokers without ETS exposure, these are the odds ratios, 2.2 to 4.6. And if you do as many of the previous studies had done and compare smokers with nonsmokers but not attempting to figure in exposure to environmental tobacco smoke, these are the odds ratios. And you see that, you know, overall they range from, you know, slightly elevated -- if you combine these kind of numbers, slightly elevated and generally not significant. And when you do the better studies, they're elevated and many of them are significant. This is all within Morabia, but Johnson and a study from Germany have also done the same thing within their own studies.

Next slide.

CHAIRPERSON FROINES: I just wanted to reiterate -- I'm sorry for all the logistical stuff at the beginning. I just wanted to reiterate that the Panel should feel open and able to ask questions at any time. Because by the time we get finished and everybody's trying to remember what their thoughts were, it never turns out to be as good as it is when we actually break up the Panel.

PANEL MEMBER LANDOLPH: Thank you then. Could I ask a question?

In your chart of active versus passive smoking, that nice graph you have, I was surprised. You're getting similar risk figures for the two. How -- did that surprise you?

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's this slide.

I think it surprised us a little bit only because the general feeling amongst epidemiologists is that there's no association between active smoking and breast cancer. But when you peel back the layers of the onion and start looking at studies that did a better job of excluding ETS-exposed individuals from their referent category, you start to see that there is an association between active smoking and breast cancer.

It's complicated because most people said, "Well aren't they getting lots more carcinogen?" But, there -- as we discussed at the last meeting, there are countervailing effects of anti-estrogenicity that actually mitigate the risk from the carcinogens in the cigarette smoke. So that's, you know, part of what's going on.

So in a way it's surprising and in a way it's not.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: The other piece of that is, if you look at, for instance, the Morabia study where you just gave -- we broke out the details as a dose response, clearly there is a dose response when you do the comparison to those who are not exposed to ETS, those from 2.2, 2.7, 4.6. And so only -- the only spot -- the plot point that's up there is only two. So is that the one that includes the ETS exposed in the referent group?

DR. MILLER: You know, these are -- we did -- these are -- those would be collapsed into a single --

PANEL MEMBER HAMMOND: But even if you collapsed, if it goes from 2.2, 2.7, 4.6 when collapse those up, I would think it would be higher than 2.2. And it doesn't look like it on the point on the graph. That point looks --

DR. MILLER: I don't know what the point is

actually.

Yeah, I know what the point is. But I don't know what the actual number is on there.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. You know, when you look at these studies, there are many, many, many estimates of risk.

PANEL MEMBER HAMMOND: Right, with that study.

DR. MILLER: And so when we put the tables together, we try to take something that represents an overall estimate rather than any of the substratifications. So we'd have to go back and look at that.

DR. MILLER: That would be for all current or former active smokers.

PANEL MEMBER HAMMOND: Actually I'm --

DR. MILLER: So it's a different set of --

PANEL MEMBER HAMMOND: Actually let me go back. The act -- I was reading the -- yeah -- yeah, I just would have -- yeah, okay. But I just would have thought from this study. But I guess this is back to Joe's point, is the question of the active smoking versus the passive smoking risk. But maybe within a particular study that, you know, that's a better comparison of those risks. But I think you're also correct, that mechanistically there are reasons to look at that.

DR. MILLER: Well, you know, typically -- first of all, I mean one of the things that we point out in the document is that, you know, typically residential exposure is not quantified by, you know, how many cigarettes per day exposure hits. It's, you know, was there a spouse or a family member that smoked. And Dr. Eisner from here did this study where he looked at people that responded -- he did biomarker study along with historical study for a week. And people that responded that they had -- they lived with a family member who smoked and they looked at that week's exposure and compared it to workers that worked in a smoking environment. And if I remember correctly, something like a third during that week of the residentially -- potentially exposed were exposed and two-thirds were not. But nearly -- essentially a hundred percent of the people who were workers who said that they were exposed in fact were exposed during that.

So the measures of residential exposure -- that's just one of many factors. But the measures of residential exposure are not very good in general in these studies.

CHAIRPERSON FROINES: Has -- Did I cut you off?

PANEL MEMBER BYUS: Go ahead.

CHAIRPERSON FROINES: This issue of the mechanism of protective effect, the anti-estogenic protective effect versus the active smoking dose response issue I think is

extremely important.

Has anybody attempted to look at that issue on a quantitative basis to differentiate people who were -- smoking was around during menarche or what have you? The hypothesis that's put forward in terms of the protective effects, the question is: Have people tried to sort out those issues to actually solidify the ideas?

DR. MILLER: Yeah. Well, they have.

You know, there's somewhat mixed results. At the last session we reviewed one such study banned, we looked at active smoking. We can just go back through that. So it's a study of active smoking. The odds ratios are relative to non-smokers. So that's not as good as if they included ETS exposure. But an explore -- these hypotheses of these interactions between active smoking and its anti-estrogenic effect and these windows of susceptibility time periods principally prior to first pregnancy, puberty time prior.

--o0o--

DR. MILLER: So what they did is, in one part of the analysis they looked -- they said, okay, well, that we would assume that the tumorogenic action of the carcinogens would be displayed most prominently with exposure prior to the first pregnancy, you know, assuming these peripubertal issues that we know from other kinds of

studies about -- principally in radiation, breast sensitivity. And during that time period the sensitivity of the breast tissue because of proliferation, et cetera, would outweigh the anti-estrogenic effect and what they found, you know.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I just wanted to add that this is a time where the breast epithelium is not yet fully differentiated. And in vitro experiments with both human and animal tissue you can get cell transformation with polycyclic aromatic hydrocarbons and other carcinogens at a much greater rate when these cells are not yet fully differentiated. The differentiation occurs from pregnancy and lactation.

PANEL MEMBER BYUS: I have a question. I have some major issues with this anti-estrogenic hypothesis, as maybe you do as well.

In this study did they actually measure reduction in estrogen? This is just a hypothesis based on the timing of the exposure that may be related to estrogen. Did they actually measure reduction in estrogen? Does smoking cause a reduction in estrogen levels and over what time? Does passive smoking cause a reduction in estrogen as opposed to active smoking? And is there a dose response relationship with a reduction in estrogen?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, this

study did not look at estrogen levels -- in circulating estrogen levels. But other studies have looked at smokers versus nonsmokers -- and of course the nonsmokers are going to include people exposed to ETS -- to look at, first of all, age at menopause is reduced in smokers compared to nonsmokers. And it's considered by endocrinologists to be related to anti-estrogenicity. Osteoporosis risk is increased in smokers versus nonsmokers, which again is an estrogen effect.

Response to hormonal therapy is mitigated by smoking, that this would be menopausal hormone replacement therapy.

PANEL MEMBER BYUS: That's quite interesting.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And in addition --

PANEL MEMBER BYUS: What was the last statement?

OEHHA SUPERVISING TOXICOLOGIST MARTY: That the response to estrogen replacement therapy is actually lower in smokers than in nonsmokers. So in other words you need a higher dose.

PANEL MEMBER BLANC: Blunted.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Blunted.

PANEL MEMBER BLANC: Blunted.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, thank you. Blunted.

When folks have looked at circulating levels of estrogens, what they found, that in smokers you actually have -- if you add up all the estrogens it's about the same as in nonsmokers, but you have a higher amount of the less active hydroxy-estradiols in smokers than the more active hydroxy-estradiols. And it's the opposite profile in nonsmokers. So in other words, even though this circulating estrogen's total is the same, the activity is not. It's lower in those who are smokers than it is in nonsmokers.

This study in particular did not look at that.

PANEL MEMBER BYUS: Okay.

DR. MILLER: So what they showed -- what they found was that if we looked at premenopausal breast cancer by the timing of the initiation of smoking -- these are all in ever-pregnant women -- those who initiated less than five years after menarche compared to over five years after menarche, these are the odds ratios. In other words, the earlier exposure was related to a higher and significant risk for breast cancer compared to those later. So they have more years during this proposed time period when the breast tissue would be more sensitive and outweigh the estrogenicity.

And then looking at another measure of the same thing would be to look at initiation before first

pregnancy as compared to after the first pregnancy. And you have an elevated and significant risk for those exposed prior to first pregnancy and no elevated risk for those who are -- or at least a nonsignificant lowering of risk for those who initiate after first pregnancy.

And then if you look at high -- long-term exposure in those who were never pregnant, whom you would assume would be the highest risk, you have an odds ratio of almost seven and a half in very significant kind of data.

--o0o--

DR. MILLER: So the opposite part -- end of the spectrum then was they said, okay, well, let's look at the hypothesis that the most protective effect, or the anti-estrogenicity effect of -- or this proposed anti-estrogenicity effect of active smoking would be most pronounced in postmenopausal women with onset of smoking after the first pregnancy and who were relatively obese. In other words they're not exposed during that high risk pre-pregnancy time period. And they have elevated -- they have estrogen levels that are elevated postmenopausally due to aromatization of adrenal androgens in fat cells.

PANEL MEMBER BLANC: I understand that you're going back and forth a little bit in your sequence of the slides here in response to questions that the people are

raising.

But I think it's important for you to ask yourselves what is the -- what is the focus of this part of this document, and to what extent are you obliged to do a mini-National Academy of Science level report on smoking -- active smoking and breast cancer or the mechanisms of estrogen and breast cancer.

This will come back I think to your discussion about what are your criteria for a causal association.

But I fear a little bit that the degree of attention that you feel forced to give these various theoretical underpinnings for why it might be that the data in relationship to active smoking and breast cancer are not necessarily all they might be is somewhat misplaced.

If you'd go back to your slide that was -- the blank slide that -- Dr. Hammond asked you in fact why does the Morabia number assume to be what it is. I think that what you might need in the document is not this kind of slide, but simply a slide with two sides of active smoking. One is active smoking estimates that don't exclude ETS in the referent group and then active smoking estimates that exclude ETS in the referent population, and simply show that in fact there is a relationship between active smoking and breast cancer once you exclude the

ETS -- mixing the exposed with the non-exposed. And then you can have one paragraph that says why active smoking is a complicated issue which is beyond the scope of this document. And, you know, give a sort of litany of some of the issues, one of which might include estrogenic effects, one of which might include not only generic estrogenic effects but also the timing of smoking initiation in relationship to biological issues.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think you're making a good point.

Just some history of it. We actually started out with a much shorter chapter. When we got the comments, a lot of the comments were, "Well, wait a second. Active smoking doesn't cause breast cancer," blah, blah, blah.

PANEL MEMBER BLANC: I understand.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So we ended up responding to comments adding a whole bunch more into the document, which I think almost -- I think your point is we're almost muddying the waters instead of just showing what the data are and going with it.

CHAIRPERSON FROINES: Well, I think Paul's raising a fundamental issue, that this Panel has to decide how it views it as well as you do. Because in your document, you say, "There are" -- this is with respect to active smoking -- "There are now studies providing

evidence for gene environment interactions and susceptible sub-populations with highly increased breast cancer risk associated with active smoking." That's a bit of a strange sentence because it's -- and you go on to say, "Thus it appears that active smoking is associated with elevated breast cancer risk in certain sub-populations."

So you say, "Thus it appears," and then you say, "is associated with in certain sub-populations." So you don't exactly make a ringing endorsement that active smoking causes breast cancer. It's, at best, written in a way that, you know, is vague to say it that way.

And so one of the questions --

PANEL MEMBER BYUS: One of many statements -- this rings continually through the chapter.

CHAIRPERSON FROINES: I just want to make -- I really don't want to hold you up. But I think the Panel -- I think Paul's point is very important. This is not a National Academy of Science study on active smoking and breast cancer. And so the question is is to what degree does the Panel feel the need for OEHHA to draw a conclusion that active smoking draws breast cancer in order to make the subsequent decision about ETS in breast cancer? And, that is, is one dependent upon the other? And that's a very fundamental issue that I think we need to come to some terms with as a decision matrix, in a

sense.

I want to give Paul a chance to respond if he wants to.

PANEL MEMBER BLANC: Well, I think that -- yeah, I think that if you had no evidence whatsoever that active smoking was associated with breast cancer, then that would argue against biological plausibility and you need to come up with some countervailing argument of biological plausibility, which is how you got into this whole estrogenic thing.

But since you do have data that suggest that active smoking is epidemiologically associated with breast cancer particularly once you remove the passive smokers from the referent group, then you're far less obliged to have quite a detailed argument for why it is that smoking doesn't cause breast cancer. I think what you can say is that you acknowledge that the relationship between active smoking and breast cancer is complicated and could be affected by some countervailing estrogen effects and could also be affected by the timing of smoking -- active smoking initiation.

The other thing that -- since we haven't gotten to it it may be premature to bring up. But if it does seem that the most consistent finding that you have for passive smoking is with premenopausal breast cancer, then

to the extent that there are epidemiologic studies which look at active smoking and premenopausal breast cancer, of course that would further be relevant to the argument of biological plausibility.

So I would answer John's question about to what extent does active smoking have to be associated with breast cancer: It's not an absolute, but since that would argue against biological plausibility without some other explanation, there would have to be that other explanation. On the other hand, if you have enough data that shows that in fact it is associated particularly if you do the analysis correctly -- and you don't need to show me that it's a exponential or even a linear or an interactive dose response. It could have some attributes of the dose response occur which are not, you know, wholly satisfying or linear and you could give -- that's where you could give the comments about countervailing estrogen effects and timing of exposure and, you know, some of those other issues.

But I think that's how I would answer that question.

PANEL MEMBER BYUS: I have another comment. I mean I would agree, and I think you're exactly correct. You want to make the point that if you take out ETS environmental exposure, then the epidemiology studies show

a correlation with active smoking. That's great. And that's really exactly what you should do.

Now, the dose response issue is a key issue, in my opinion. And it's a complicated issue. But it's the key to causality in carcinogenicity in virtually anything. You have to address does response. You can't ignore it. And, in fact, in the original ETS data that's what was persuasive, was the dose response data with lung cancer, et cetera. That's what really convinced people that there was causality. And in this case it continues to ring true.

The problem obviously is the passive versus active smoking and putting those doses on the same scale and coming up with some kind of linear dose response. And that is in fact the difficulty.

But I would not ignore the fact that you have the dose response data for active smoking. I mean you've showed that.

And now do all the studies show it -- I mean it's hard for me to get that.

But I would make the point that where you can do it, if you subtract the passive smoking out, you can show a dose response with active smoking. That's very persuasive argument.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We can do

that with more than one paper.

PANEL MEMBER BYUS: Right. And that's very persuasive. And that is I think within the context of a dose -- you must have a dose response within some dose range. That doesn't mean you need to have it over the entire range that has to be linear. You see what I'm saying? And You lose that in this document. You keep saying that dose response is somehow less important. And it's not. You must show it over some range. It must be proportional. Otherwise I'm not going to buy that there's any causality.

And I think you can for active. Now, by question's going to be is: Can you show it then at the really low doses for the passive --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, there's lots of evidence of dose response.

PANEL MEMBER BYUS: Right. And so you should just make that point.

Now, the problem then becomes is when you try and join those two dose responses together. And that's when you say there could be these other mechanisms.

CHAIRPERSON FROINES: Well, I think -- I don't mean to cut you off.

I don't know if anybody else wanted to comment.

PANEL MEMBER PLOPPER: I had a couple of comments

if I could make them.

PANEL MEMBER GLANTZ: God is talking.

CHAIRPERSON FROINES: Dr. Plopper has a comment.

PANEL MEMBER PLOPPER: One of the things that I was concerned about is that it doesn't discuss in here the impact of the estro-cycle on bioactivation and creation of carcinogens. And that we found as much as a two- or three-fold difference depending on whether estrogen is rising or falling. And if that's the case, that means that exposure in relation to that's going to be very critical in producing tumors, because carcinogen rate is going to be way, way higher.

Does that make sense?

But I don't -- you're talking about breast cycles. And what you're not talking about is what happens to the biological effects of this on enzyme systems that are critical.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think your point is well taken. It represents another layer of the onion in terms of trying to do any dose symmetry in smokers who are cycling.

PANEL MEMBER PLOPPER: Exactly. I mean the dose -- you're going to have to -- the dose factor has to be along with when during the cycle the exposures occur. We find as much as a three- or four-fold difference in the

markers of injury or change in proliferation rate depending on the status of the estro-cycle during exposure.

CHAIRPERSON FROINES: Can you hear him okay?

PANEL MEMBER PLOPPER: I don't know where you'd work that in. But I think it may -- it will complicate matters in terms of analysis. But it will probably ease matters in terms of interpretation, because it looked to me looking at what you put together that a lot of that may be related to when exposure was during the cycle.

CHAIRPERSON FROINES: Charlie, is it all right if Melanie and Mark follow up with you after this meeting to --

PANEL MEMBER PLOPPER: Oh, sure.

CHAIRPERSON FROINES: -- discuss that a bit further?

PANEL MEMBER PLOPPER: Yeah.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah. And, Melanie, I certainly wanted to congratulate you and your staff. I mean an enormous amount of effort obviously has gone into this chapter.

One of the positive suggestions I could make would be that you try and winch the size of this chapter down. And I've listed a lot of places where you can

condense it. Because I do agree with the other scientists, that I do think the major points are getting lost.

Now, if you start talking about, for instance, benzapyrene and quinone formation and adduct formation, this thing can fill a box. You're going to have to make some decisions about how to chop it down. Because the problem I have now is I think your main points are being lost in a plethora text. And I think you really need to sharpen it up and sharpen the focus and condense the text.

CHAIRPERSON FROINES: Stan.

PANEL MEMBER GLANTZ: I think that OEHHA is a little bit on the horns of a dilemma here because, as Melanie said, a huge volume of the comments on this dealt with this active smoking issue. And I think to not address them would be viewed as nonresponsive.

I have a suggestion as a way to kind of -- I also agree with the people who say that it's gotten kind of out of hand. And why not in the report -- in the main body of the report deal with the active smoking issue fairly briefly, and then include an appendix that goes on with some of the this other stuff, to get it out of the way of your main argument but to still present the relevant -- I think even there that could be cut -- but to present the relevant information. Because I'm -- I mean there are a

lot of people in the general scientific community who are very interested in this report. And I think that these are the primary objections that are being raised by a lot of people in the scientific community. And I think OEHHA has done a good, in fact obsessive, response to it. So I don't think it should be left out entirely.

There's a couple other things. I got an E-mail from a colleague who's a breast cancer epidemiologist. She's one of -- been one of the skeptics on this and who -- and there's apparently a paper about to come out in cancer causes and control addressing just these issues. And she said this is like the first thing that really convinced her. So when that comes out, I'll get that to you guys.

And the other thing is I think that this whole argument that, "Well, active smoking doesn't cause breast cancer, so how can passive cause it?" is a little bit of a red herring, because I actually went back and read a major review that was written of active smoking about 15 years ago, which is the origin of a lot of people saying this. And it actually -- it had a meta-analysis and found, as I recall, about a 1.3 statistically significant risk for active smoking, despite using -- you know, they didn't break out the passive smokers from the control group. And what it said is, well, this is just so small that it can't

be real. You know, they kind of ignored their own result.

So I think that some of the argument that's going on over this issue in the general scientific community is based on people who haven't really paid attention to a lot of these details. But I think for this report to have -- you know, to reach -- to have credibility with the widest audience, those things need to be dealt with. But I don't think they would necessarily have to be dealt with in detail in Chapter 7. You could do the kind of brief presentation that Paul and Craig were talking about of these issues with a more complete appendix. So that would be my suggestion.

CHAIRPERSON FROINES: My only concern about the comments is I do think that they need to end up with a statement that's a little sharper in tone.

PANEL MEMBER GLANTZ: No, I totally agree with that too. Because I do think -- I mean I think that we -- you can say there's evidence that secondhand -- or that active smoking also increases a risk of breast cancer. I think the issue which is bothering a lot of the epidemiologists in the field is, you know, if you look at lung cancer, the risks of active smoking are 20 times the risks of passive smoking and here they're not. And how do you reconcile -- I think trying to reconcile that has to at least be discussed. But it doesn't have to be in the

main body of the report, I don't think.

PANEL MEMBER BYUS: No, I would disagree. I think it must be in the main body of the report. It just doesn't need to be as extensive. And it has to be done better. It's not done well. It doesn't make the case well. You have to read it over and over and over again. And it's lost in there, with all of the potential mechanisms.

I might add, everyone thinks that breast cancer is related to estrogen. But I have a new -- it's from the Journal of Clinical Epidemiology -- paper. It's entitled "Breast Cancer." "Critical data analysis concludes that estrogens are not the cause. However, lifestyle changes can alter risk rapidly."

And if you look at this article, it makes some very, very good arguments that estrogen levels may not be directly related to breast cancer.

And so the problem is is that this is a very, very complex issue in carcinogenicity. It could be one of the most complex, if not the most complex. So to really get involved in it --

CHAIRPERSON FROINES: But I think that's exactly what Paul was saying.

PANEL MEMBER BYUS: That's exactly what Paul is saying. And so I'm saying that to get involved in it --

even saying it's now anti-estrogenic. This article actually is fairly convincing that estrogen may in fact not be the cause -- might be causal for a variety of reasons, based on hormone therapy research, based on incidence of cancer continually increases even after menopause when estrogen levels fall markedly. I mean there's a lot of interesting things here.

But to actually get into this kind of data is way beyond this.

CHAIRPERSON FROINES: But I think that -- I agree with Paul, that what we don't want to do is to turn this into a debate on the mechanistic underpinnings of breast cancer.

PANEL MEMBER BYUS: That's right.

CHAIRPERSON FROINES: What we want to do is to identify -- is to identify the epidemiologic studies that have -- that identify risk especially when one considers taking out passive smokers from the control groups. And so that I think that we want -- my sense is -- and I think this is up to this panel -- is to what degree do we even want an extensive discussion in an appendix? And I'm not so sure that for the purposes of this determination that this is where that debate should be elucidated.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I --

CHAIRPERSON FROINES: There's a lot of people who

want to talk with Melanie and your --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I just wanted to let you know that we actually have done some analysis of active smoking and breast cancer -- and I just put up a slide that we put together yesterday or the day before -- that we did a small meta-analysis of a number of studies and are -- you can see from this slide that there are a number of studies that are positive, and statistically significantly so. This is active smoking now. And these are studies that -- Mark, you should probably be saying this -- but I believe did a really fairly decent job of exposure assessment, including fairly clean referent groups.

Anyway, we have a -- you know, we have done more work on the active smoking piece. We actually would like to rewrite that whole section and conclude that it's causal based on more recent studies. There's been a couple of new studies just in the last two months that have looked at this issue.

So we could have a, you know, small section within the document and do what Stan said, add more of the discussion about it in an appendix or --

CHAIRPERSON FROINES: Well, I think that what you may want to do if you've got new studies and you have these studies is to emphasize that issue -- those issues

as well as the point that Paul and Mark have been talking about. And even -- and get away from the estrogen protective effect and not even necessarily get into any lengthy discussion about that, because that does get you into the paper that Craig's talking about and gets you into a very major mechanistic evaluation, which is not necessarily appropriate for this determination.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. One comment on that paper. It is -- without a doubt estrogen is involved in progression of breast cancer. That's why you have Tamoxifen therapy, that's way the aromatase inhibitors work and so on. So --

PANEL MEMBER BYUS: Well, Tamoxifen has other effects other than as an anti-estrogen?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, it does.

PANEL MEMBER BYUS: As you well know, it's so complex that -- you know, once you say one thing, you then have to get the box of data that's out there.

OEHHA SUPERVISING TOXICOLOGIST MARTY: But I think there's a huge number of studies showing that estrogen is involved in progression of the tumor. And the fact that you have lower circulating active estrogen in smokers indicates that the tumor progression is the part that's being inhibited, not necessarily initiation. There

would be no reason why initiation would be impacted.

CHAIRPERSON FROINES: This exchange --

OEHHA SUPERVISING TOXICOLOGIST MARTY: So I think that --

CHAIRPERSON FROINES: This exchange between the two of you is a good -- is strong evidence for what I just proposed.

PANEL MEMBER BYUS: Exactly.

(Laughter.)

CHAIRPERSON FROINES: And I think -- do you agree?

PANEL MEMBER BYUS: I agree.

PANEL MEMBER GLANTZ: If I could just read -- I'm like speed reading this because I -- this is interesting -- I mean I agree. We don't want to turn the report into a 4,000 long page report on breast cancer mechanisms. But I don't think there's an argument here, because what this paper says is that it's probable estrogen acts as a promoter rather than being directly causal. So I don't see -- what you're saying, Melanie, it seems to be completely consistent with what this paper is saying.

PANEL MEMBER BLANC: What I'd like to suggest just in terms of focusing the discussion and getting back on track is on page 18 you have two -- you have a

stratified meta-analysis. And I'd like you -- I'd like you to go to that now for -- even if it's slightly out of whatever sequence you were thinking of, because I think it would frame some of the other questions coming back around to -- to the biological plausibility and the direct smoking data and how much of that you need to look at. I need to hear from you how you interpret these two stratified analyses and what they seem to mean to you.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Maybe Mark should start with the overall and move --

CHAIRPERSON FROINES: I don't want to leave the active smoking issue --

PANEL MEMBER BLANC: But I think it's tied into -- I want to come --

CHAIRPERSON FROINES: Do you think you're going to get back there?

PANEL MEMBER BLANC: I want to come back to it after we do this because I think I will.

CHAIRPERSON FROINES: Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Mark's going to run through the meta-analyses which we added to. So it's more current than what is in the document. And you folks haven't seen all of this.

DR. MILLER: This has two additional studies, Gammon and Hanaoka, both of which came out in the past

year. And we have some slides talking about Hanaoka we should try to get to. But it is in fact the first prospective cohort study that used what we would consider to be some kind of complete measures and compared the data for ETS exposed to actually relatively ETS nonexposed.

And so this is -- these are just looking at an overall exposed versus nonexposed to ETS in nonsmokers. And the data -- so the summary is on the right after the dotted line. And for all studies, that's the odds ratio. And I can't tell you off the top of my head exactly what it was. But you can see -- it was significantly elevated. But if you took the studies that had more complete sources ascertained, that -- again, as we've seen throughout this, that the risk estimates are elevated further.

--o0o--

DR. MILLER: I think we ought to just move on to the premenopausal strata, which again is higher. As I remember it, the risk is about 1.9, something like that for -- 1.9.

CHAIRPERSON FROINES: This is 1.9?

DR. MILLER: Something like that, for the premenopausal.

CHAIRPERSON FROINES: I'm looking at it. It doesn't look like 1.9.

PANEL MEMBER GLANTZ: It's a log scale.

CHAIRPERSON FROINES: Okay.

DR. MILLER: And, again, you know, slightly higher point estimate with all sources.

And then we went on Dr. Blanc's suggestion. And actually it was part of a comment from NCI, and looked at the few studies where there was postmenopausal data and did the same sort of analysis. And you can see it's, you know, what we would interpret as essentially a null kind of result.

I think I'll have Melanie then comment on how we interpret this.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Thanks, Mark.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: In the original wording of the document, we want to say that environmental tobacco smoke is causally related to breast cancer and that the evidence is stronger for premenopausal than postmenopausal. We would actually like to stick to that wording for a number of reasons.

One of the statistical reasons is that since breast cancer rises dramatically -- the incidents rises dramatically postmenopausally, you actually have a much noisier baseline to try and find anything.

In premenopausal breast cancer it's relatively

less common, and so you can actually find external causes a little easier relative to your baseline rates.

The other issue is that it may be that what you're seeing is a shorter latency time in ETS exposed people. So there may be something different about the biology of the tumor. We don't really understand very well.

And there's some studies which indicate in smokers and in passive smokers very long exposures are associated with breast cancer. And those people are postmenopausal. So you do see an elevated risk for long duration and combined -- especially combined with high exposure.

So we don't want to say that there's not an effect on postmenopausal breast cancer. So we would rather stick to the wording we have, which is "causes breast cancer, that evidence is particularly strong for a premenopausal."

PANEL MEMBER BLANC: Could you go back to the master slide, the meta-analysis.

What is your interpretation of the secular trend in the studies and does that have any -- does that matter to you?

OEHHA SUPERVISING TOXICOLOGIST MARTY: The chronologic trend?

PANEL MEMBER BLANC: Yes.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Actually these are studies of mixed at design. Most of the ones that bounce around zero are actually the -- looks to me like some of the studies that didn't have very good exposure ascertainment. Some of them are the cohort studies, but not all. So I -- you know, I've looked at that and tried to figure out what it was.

DR. MILLER: The solid -- the triangles that marks -- the point estimates that are solid are those that included, you know, all sources of exposure compared to the other ones. So that's another way to look at that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So in other words residential plus occupational plus other social. Some of them included childhood exposure. And the open diamonds were less complete in their questioning of exposure. Some of them only -- for example, in the prospective cohort studies only asking a single time, "Do you live with a smoker?" This is not much --

PANEL MEMBER BLANC: Then let's go forward to the next slide and then the next one.

--o0o--

PANEL MEMBER BLANC: This is the studies that you have of estimates where you can parse out the postmenopausal incidents.

There apparently are some studies where you can't divide them at all, is that right?

DR. MILLER: Yeah, there are many studies that didn't pull out premenopausal -- there was just -- over our postmenopausal, unless you have the raw data to go back at it.

PANEL MEMBER BLANC: Right. So in these 1, 2, 3, 4, 5, 6, 7, 8 studies, the meta-analysis that you have does not support an elevated risk of postmenopausal cancer.

So as one element of supportive evidence for an association which you would rank as -- I'm sorry, I may be forgetting your terminology. You had suspect and -- what were your three terms that you had?

OEHHA SUPERVISING TOXICOLOGIST MARTY: For --

PANEL MEMBER BLANC: In the whole document.

DR. MILLER: Suggestive evidence, causal --

OEHHA SUPERVISING TOXICOLOGIST MARTY:

Suggestive -- inconclusive, suggestive and causal.

PANEL MEMBER BLANC: And that was it, there was just the two?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, the three -- inclusive.

PANEL MEMBER BLANC: Inclusive, suggestive and

causal.

All right. So if you only had this data, I guess you could say at best it was inconclusive in terms of postmenopausal. What you're arguing is that there is other data which could be marshaled to argue in favor of a relationship. But I would find it hard to understand how that evidence could raise the bar -- I could see how it might take it from inconclusive to suggestive. I think that would be an argument you'd have to make, but maybe you could convince me.

But based on these data, no matter what your ways of explaining the lack of a relationship, which may take you from inconclusive to suggestive, it doesn't -- it seems a very hard row to hoe to get to causal. And I'm not sure -- do you have some either administrative or scientific reason why you could not, should you determine it, have separate findings in relationship to premenopausal versus postmenopausal breast cancer and ETS and secondhand smoke exposure?

OEHHA SUPERVISING TOXICOLOGIST MARTY: There's no administrative or procedural things that would get in the way of that.

PANEL MEMBER HAMMOND: I actually have a question following on Paul's comments.

Do you have dose response data in the

postmenopausal passed the smoking that -- I know this is parsing it. But this gets to his point of: Are there other data that support your feeling that there's some suggestion? That would be one type of thing.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. There are some data --

CHAIRPERSON FROINES: Can I make one comment --

PANEL MEMBER HAMMOND: The question is: Are there dose response -- let me just get an answer to that first, please.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think yes, that we have -- if we looked at it again we could find -- you know, try to ferret out the dose response just for the postmenopausal.

CHAIRPERSON FROINES: I just want to make one comment before you start.

I just want to make a general comment, because I think that there's a lot of discussion that's occurring about dose response that reflect people living in the past understanding of dose response. The notion that with increasing dose response just keeps going up is, at best, simplistic and often times wrong. There are lots of reasons why things plateau and why you get changes in dose response. And we have to understand that and not just sort of hold on to this old notion of the dose makes the

poison.

So as we get into this, I think we should understand that, yes, we'd like to see a dose response particularly in some regions. But as we reach high doses, we are not necessarily going to see a dose response, and go on with it.

PANEL MEMBER HAMMOND: John, that's misinterpreting what I was saying.

CHAIRPERSON FROINES: Oh, I'm not saying what you're saying. I think that's a general issue that we need to keep in the back of our minds. So let's go.

PANEL MEMBER HAMMOND: I mean what -- actually what I was trying -- another point I was trying to make earlier but I didn't get a chance to make was I think it is important to look at dose response. I agree with Craig. However, I also think it's not always simple. And in that degree I agree totally with John. And I'm not saying you're in opposition.

But I think it's important that both those points be there. We have to look -- I think we have to look at dose response, but we don't have to expect that when the dose doubles, the response doubles. I think that that would be a mistake. And I think we also need to remember that we have examples already -- let me just finish -- we have examples already where we don't say --

PANEL MEMBER BYUS: It's like five orders of magnitude is the range you're looking at dose response when you compare active to passive smoking. And in that case no one's going to expect it to stay the same. See, that's my point.

PANEL MEMBER HAMMOND: But actually -- and my point is going to follow right from that. We have five orders -- I mean we have -- well, first of all, we don't really know the dose because we don't -- the chemical lists. And they're different ratios. And so the dose is actually extraordinarily different depending on which chemical you're talking about in mainstream and side-stream smoke, A.

B) We have examples of two health -- the two most well established health outcomes, lung cancer and heart disease, where we see very different dose response curves. And we should not forget that.

All right. And we should -- maybe we need to even -- maybe you even need to talk about that someplace early on.

PANEL MEMBER BYUS: They're there.

PANEL MEMBER HAMMOND: There still is a dose response. But many people have said the passive smoking doesn't make sense because it's too close to the risk for active smoking. But in fact when you look in detail at

the active smoking, what you see is a plateauing effect of the dose, that it calms down. So I think it's important to go back. Remember what we already know about the different dose response curves that we observe in active smoking and the differences we see between active and passive smoking in two well established outcomes as we do this.

I still say, we -- to the degree it's possible we should look at dose response if it's inform -- you know, to see if there's any information to be gained, knowing full well the difficulties of establishing dose and the limitations of dose response.

PANEL MEMBER GLANTZ: I have a question about this graph. And then I want to weigh in on this discussion.

But when you say -- when you're talking about the risk estimate of ETS and postmenopausal breast cancer, I don't quite understand what that means in the following sense: And, that is, are you saying the risk estimates for people who are exposed postmenopausally to developing breast cancer or are you saying this is the effect of cumulative lifetime exposure and the breast cancer appearing postmenopausally or is this exposure a long time ago because it was a cohort study and they only measured at the beginning but whether or not the tumor appeared

postmenopausally. So could you just explain what this slide is showing.

DR. MILLER: Yeah. I mean this is -- the date of diagnosis is postmenopausal. And, you know, the exposure in general is either, you know, a large part of lifetime. So it's premenopausal exposure and, you know, postmenopausal exposure. But date of diagnosis is postmenopausal.

PANEL MEMBER GLANTZ: Well, wee if that -- that's what I thought. But if that's the case, then I think -- and this gets back to trying to simplify the report some -- is I don't think that we should be drawing a separate conclusion for premenopausal and postmenopausal cancer. I think we should just say that passive smoking causes breast cancer. To me -- and I've talked to a couple of the people in our cancer center about this -- it may be that the tobacco-smoke-induced cancers appear more quickly.

And so menopause here is actually a marker for age and it isn't related to estrogen. It's related to the fact that the tobacco-induced tumors appear sooner for some reason. I mean that's actually what Laura Esserman, who's the head of our breast cancer group, thinks just based on clinical experience.

And so -- well, wait. Let me just finish.

And so I think what we -- to try to simplify this, we should say that the -- the way I would word it would be something like passive smoking increases the risk of breast cancer, and the tumors appear -- seem to appear at relatively young. You don't see the passive smoking-induced tumors later. That's how I would interpret this.

Although there is the other result, which Melanie mentioned, which -- it's in the report that there is in effect a duration of exposure too. And so I mean -- so that kind of -- I don't quite know how -- if you're finding that the longer exposed people are at increased risk, how come -- I mean the question at least it seems to me is how come that wasn't reflected in this graph that you have up here? Because these are going to be the longest exposed people too.

CHAIRPERSON FROINES: I just want -- I want to make one comment.

This Panel has to decide, make its conclusions based on the evidentiary record. It cannot make decisions based on speculation. If Melanie can demonstrate that an evidentiary record for postmenopausal breast cancer, then the Panel can consider that.

But at this point, I think that the evidence before us, not the speculation but the evidence before us,

is that we have to look at -- I agree with Paul, that we're either at inconclusive or suggestive. We're not any where near causality. And that we should give OEHHA a chance to develop the evidentiary basis. But it can't be what your person from your cancer center said and what somebody else -- and Melanie's statement about duration. It has to be in front of us to draw --

PANEL MEMBER GLANTZ: Oh, no, I totally agree with that. But I think -- I mean are we saying -- I mean this is getting beyond what I have a lot of expertise in. I mean the implicit statement of what you're saying is that breast cancer that manifests premenopausally and breast cancer that manifests postmenopausally are two different diseases.

Well, you see, if -- you're shaking your head no. And, see I think if that's the case, then the question is: Is passive smoking associated with the risk of increases in breast cancer, period? And I think the answer to that question is yes.

Then there's this subsidiary question of, you know, when is it manifest and how is it manifest?

CHAIRPERSON FROINES: I think there are different biological mechanisms associated with breast cancer at different ages. I think it's a complex biological issue.

PANEL MEMBER GLANTZ: Well, I understand that.

CHAIRPERSON FROINES: But, again, I'm referring to the evidence that we have to deal with. That's all that I'm --

PANEL MEMBER GLANTZ: I agree with you. But, you know, we just had this discussion earlier about trying to simplify the report. And I think that to try to break out the postmenopausal versus pre -- I mean I think you've got to make a decision, are you going to treat them as two separate diseases or not -- or two separate endpoints or not? If people want to treat them as two separate ends points --

PANEL MEMBER BLANC: Well, they -- I fundamentally disagree with you. Fundamentally. First of all, the report makes a great deal of time to talk about pediatric asthma versus adult asthma, both asthma onset and asthma aggravation. There are reasons why it does that. Is it because asthma is a fundamentally different biological process in piediatrics and in adults? Not really. But on very strong clinical grounds there's enough difference in the epidemiology and the co-factors that it makes sense to consider them separately and to have findings on them separately, which they do.

And I think similarly there is a great deal which is clinically different about premenopausal breast cancer than postmenopausal breast cancer. People in the field

consider it an important enough difference that they present data categorized at least in some of the studies this way enough to allow the OEHHA meta-analysis to be stratified. So I'm not going --

PANEL MEMBER GLANTZ: Okay. But, see, then if you're saying that we -- see, taking what you said and putting it into the terms of what I just said, you are saying that we ought to be considering premenopausally manifest breast cancer as a different endpoint than postmenopausally manifest breast cancer. I mean if that's what people think, I mean --

PANEL MEMBER BLANC: If the date suggests that they're behaving differently epidemiologically and if the data suggests that the body of evidence reaches a more arguable threshold for a different level of association in terms of causally versus suspect versus --

OEHHA SUPERVISING TOXICOLOGIST MARTY:

-- inconclusive.

PANEL MEMBER BLANC: -- inconclusive, then I think that it is to the benefit of the report and it is public health protective rather than diluting the findings or the condition overall, because --

PANEL MEMBER GLANTZ: Well, no, I don't have any -- I don't have any problem with doing what you're saying, Paul, if that's what you people want to do. I

think though that if you're going to make that distinction -- and I'll defer to people who know more about breast cancer than I do on that -- then it should just be made explicitly as your suggesting and saying that the report and the committee are considering these two different endpoints, and with one saying we have strong conclusive evidence and with the other we don't. I mean if that's -- but then I think you're making -- I think the kind of logical problem that I see Melanie raise is, if you're making one statement about breast cancer, how can it be causal part of the time and not causal part of the time? I think if you want to make two separate statements, then that is a much more -- then I think you could do that logically. I mean --

CHAIRPERSON FROINES: Well, it may be an issue, you know, that there are different biological mechanisms that influence -- and genetics, for that matter -- that influence susceptibility to carcinogens. And it may be that the risk to the carcinogens in passive smoking or active smoking are still -- they're still carcinogens. It's not a carcinogen -- the carcinogen is a carcinogen, whether you're premenopausal or postmenopausal. So we may be talking about a quantitative issue, not a qualitative one. And that would argue in favor of Melanie's point of view. The trouble is, the evidentiary basis for the

postmenopausal is limited. And that gets you into the position I think Paul's taking.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we need to develop the argument a little more. Because, you know, we have things throughout the document about greater than 30 years passive smoke exposure has the higher risks. And most of those women, if it was passive smoking from the husband, they're already postmenopausal and so forth.

Also, Ken had a comment or two on this issue.

DR. JOHNSON: Ken Johnson. I had a couple comments on this tension between the premenopausal and the postmenopausal.

I think the first thing is that there is strong -- definitely stronger evidence for premenopausal than postmenopausal. One of the tensions even with this postmenopausal slide is that, for example, Morabia, which has probably the strongest results and the best exposure assessment, isn't on it because he didn't separate premenopausal and postmenopausal because probably the lion's share of cases were postmenopausal.

So he should probably be in there. And it's one of the reasons I never developed myself this particular slide. I just looked at all breast cancer and then the premenopausal.

Secondly, the evidence definitely -- of the six

studies that have the environmental tobacco smoke measures that are of the highest quality, two of them are only studying premenopausal women. So you only end up with four studies that have good data -- quality exposure data that include postmenopausal. And that's part of the reason the premenopausal is stronger as well. So it is partly an evidence issue, what's available. And so what you can draw stronger conclusions from is obviously where there's more data or more evidence.

PANEL MEMBER HAMMOND: You should be able to circle --

DR. JOHNSON: Some of them. Most -- Johnson and Zhao and Hanaoka are the only ones in there that shouldn't be solid.

DR. MILLER: Yeah.

DR. JOHNSON: I'm sorry. Just to follow up. Someone else asked about the secular trend in the data. That has to do -- more to do with the quality of the exposure measures that it's dropping. All of the last three or four except for Hanaoka are all ones that do not have complete environmental tobacco smoke exposure measures.

CHAIRPERSON FROINES: Joe.

Oh, sorry.

OEHHA SUPERVISING TOXICOLOGIST MARTY: By the

way, Hanaoka is a new study just published that we've now added. So you folks have not seen that before.

DR. JOHNSON: It just came out in December.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It is a prospective cohort study with good exposure assessment, and it's positive for breast cancer ETS, premenopausal.

CHAIRPERSON FROINES: Premenopausal?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

DR. JOHNSON: And not postmenopausal.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And not postmenopausal.

CHAIRPERSON FROINES: And does it look at postmenopausal?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, it does.

CHAIRPERSON FROINES: And it's not positive?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah, I actually would expect these types of curves. You know, based on that cancer incidents for breast cancer versus age where you have that nice inflexion point, and the slope dramatically decreases.

So this almost says to me, yeah, you've got ETS in both situations, but maybe the promotional face part,

although some of it is in the premenopausal exposure.

So I don't have a problem with this. But I agree with Dr. Froines. I could recommend you just stick to the data as it is and just call it as it is.

PANEL MEMBER BYUS: Actually, Joe, the slope doesn't change that much. It changes at menopause. It decreases. But the incidents still goes up. And it decreases no where near proportional to the drop in estrogen, okay, in terms of breast cancer.

Really. I have the curve right here.

It is significant, but it's no where near what you would expect based upon the drop of estrogen.

Again, my -- back to this dose response issue, which is key to me. And I -- I mean I have no problems understanding why you can have a nice -- passive smoke can cause breast cancer at no greater level than active smoke. Okay, I have no problems with that. But what I'm getting at, I would like to see where the data is for environmental and passive smoke for dose response within -- because to me that substantiates the causal relationship more than anything, if you have it. Now, if you don't have it, that's okay, because I understand hoe difficult it is to get the environmental tobacco smoke dose response. But if you have it, if you can highlight those studies, okay. But show a dose response in the

passive smoking range in a positive correlation and you can justify why these studies are quality epidemiological studies. That to me is the most persuasive data.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have that data. It's in the report. And there's even a table.

PANEL MEMBER GLANTZ: Ken keeps wanting to say something.

PANEL MEMBER BYUS: Yes, but it needs to be -- to me that's what will -- brings the argument home most persuasively.

DR. JOHNSON: Could I -- I could read you one paragraph of the paper I have under consideration right now, explicitly addressing that. It's a short paragraph.

"The British and Swiss studies did not observe passive smoking dose response relationships." That's two of the good quality studies. "However, in both studies the risk associated with the higher exposure was over 2."

The Canadian study -- that's the one I did -- observed a dose response great -- and we also have the largest number of cases, so you can look at the dose response carefully. We saw -- for premenopausal we saw risks of 1.5 to 2.9 and 3 for increasing exposure.

PANEL MEMBER BYUS: Great.

DR. JOHNSON: Let me continue just for a minute, because if you think it's that -- I think it's important

as well.

And the postmenopausal was much more modest dose response.

The Hirayama study found 1.32 overall, but 1.86 for women who had lived with men who smoked at least 20 cigarettes a day. The cohort study in Korea saw an overall 1.2 for wives of ex-smoking husbands, but 1.3 for wives with current smoking husband and 1.7 for wives of current smoking husbands with at least 30 years of smoking.

Furthermore, in the most recent Gammon study they found for -- they didn't see a dose response, but they saw at 2.2 risk for women who had lived with men who smoked for at least 30 years.

And the Hanaoka study -- no, I can't remember on that one. But there's definitely in the passive smoking literature, it's there.

PANEL MEMBER BYUS: To me that is the most persuasive argument of causality. If you have the data, it really implicates causality rather than just simple quantal --

DR. JOHNSON: I think the other thing is all of these risk estimates are based on the entire group of people exposed, which is not what you normally do in epidemiology. You always break them up into the most

exposed, the least exposed. And this is just a yes, no. It's very similar to with lung cancer just going yes, no, spouse no, and getting 1.2. And the reality is we know that for people with higher exposure it's more like 2, you know, for the highest exposure --

PANEL MEMBER BYUS: I understand why you don't always have the data. But when you have it in the studies that are done and where it's seen, you should highlight that and not get into so much of the other speculation.

DR. JOHNSON: Well, that's hopefully why they're --

PANEL MEMBER BYUS: Because that is real data, John, and that's what is persuasive.

DR. JOHNSON: That's hopefully why they're about to accept my paper.

(Laughter.)

CHAIRPERSON FROINES: I want to discuss the procedure. At the current rate we're going, we'll be discussing breast cancer until 2006.

And I think we're at a place where we should go through, Melanie, the remaining slides that you have, because you're going to be talking about responses to comments. Then I should think you should take your notes and the transcript and go back and develop the picture that you want to develop for breast cancer, hearing the

very strong feelings that at least some of us have about pre versus post, and then bring that back on March 14th to bring that to closure.

In the meantime, once we get through the slides, then we can go on to the other cancers and the other health endpoints so we can begin to move the process along so -- because, otherwise, we're going to get weighed down. We're already weighed down. And to get us, to use Paul's term, back on track, why don't you go through the slides, there will probably be discussion. But then let's try and move on to the other endpoints to get as far as possible.

PANEL MEMBER GLANTZ: Could I just ask one question?

I agree with that. And I think the answer to this is going to be yes. But I mean: Are there any issues relating to breast cancer that you think are, you know, points of discussion or controversy that we haven't talked about? I mean --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't think so.

PANEL MEMBER GLANTZ: I don't either. Okay.

CHAIRPERSON FROINES: There may be a little bit --

PANEL MEMBER GLANTZ: But I mean in terms of --

CHAIRPERSON FROINES: We're going to get into

biomarkers.

PANEL MEMBER HAMMOND: Can -- yeah, I was going to ask about one thing too.

DR. JOHNSON: I would like to address that, because I think there is another issue I don't whether you discussed at the last meeting or not. But I think for the epidemiologists I've talked to, the other key issue is this tension between the cohort studies and the case control studies.

DR. MILLER: We have talked about that.

DR. JOHNSON: Oh, okay.

CHAIRPERSON FROINES: Well, I think -- please make a comment for the record on that.

DR. JOHNSON: Well, the tension of course is: Do you choose -- the case control studies show things quite -- the quality exposure measure case control studies show things quite different than the cohort study poor quality measure studies. And the issue is is -- so there either is risk or there isn't depending on whether you buy into the case control or the cohort studies. So the real issue is the cohort boys would argue, "Well, there's recall bias and the case control studies aren't good; the case control people, who are more interested in the quality of the exposure measure would argue, "You can't have really poor exposure measures where you may have 40

or 60 or 70 percent of the people in the control unexposed group actually being exposed but you haven't measured it."

And so the tension is -- none of the cohort studies have good -- have reported based on good exposure measures except for this most recent Hanaoka study that just came out last month.

DR. MILLER: And is positive.

DR. JOHNSON: And is positive.

PANEL MEMBER GLANTZ: Yeah, I think -- I just want to add one thing to that because it is an important point. And, that is, most of the cohort studies just have an exposure measure at the beginning. And, you know, they leave out, you know, any of the cumulative exposure over time, they don't account for the fact that some people quit smoking and the exposure may drop.

So I think, you know, the sort of dogma in epidemiology is that prospective studies always trump case control studies. But I think that's if you're talking about a discrete well known event that you're following up on, like whether you had an operation or something or whether you received some treatment at a discrete time. I think when you're talking about things like this where you're -- where you could be talking about cumulative effects over a long period of time, the sort of default view that a prospective study is always better, it just

isn't true. And I think that's a very important, you know, point that needs to be kept in mind when interpreting all these studies.

CHAIRPERSON FROINES: As you go through the next month or so working on this, I think it's useful to talk to some of the Panel members as you go, because at this point there are at least some persons who believe that the emphasis should be on premenopausal, you took the position of wanting to have it cover everything, so there are in front of us sharp disagreements. And we're going to evaluate what's in front of us in March and make a decision on that. So that we're going to need clarity on the basis -- the evidentiary basis for the ultimate decision. In other words speculation is not going to fly.

DR. MILLER: You know, I think what we have looked at as far as the postmenopausal issue has been very rudimentary to date. It's really in response to Dr. Blanc's comments at the last meeting. And I think we could, you know, do our best job to parse out that issue, and then you can make a decision. We'll present you with --

CHAIRPERSON FROINES: I don't think anybody's drawn a hard and fast conclusion at this point. I think -- but I just want to keep arguing that some of the discussion about underlying biological mechanisms -- for

example, I was troubled by the low birth weight multitude of reasons why it might be a factor -- why it might occur. And that's the kind of thing that we're going -- I think we'll want very clearly defined arguments that can then let the Panel -- they may disagree, but they'll have the basis in front of them.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We plan on developing that argument and getting it to the Panel prior to the meeting so you can actually see the revised chapter, at least the breast cancer section, so that you have some time to digest it.

CHAIRPERSON FROINES: Yeah, and people can give feedback to you as individuals. We can't obviously as a quorum give feedback -- I mean as a body.

So let's go ahead with your slides.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Mark, you want to go over --

DR. MILLER: Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We could go over or skip --

CHAIRPERSON FROINES: Can I just ask: Is Gary comfortable with where we have gotten to?

PANEL MEMBER FRIEDMAN: Yes. And --

CHAIRPERSON FROINES: Because he hasn't said anything.

PANEL MEMBER FRIEDMAN: Let's see, maybe that's the only thing I'm uncomfortable about is that I haven't said anything.

(Laughter.)

PANEL MEMBER FRIEDMAN: I think, you know, I would really support Joe's comments about making the report shorter. I told that to group there. And he actually gave them a rewrite of a page just to show how much difference it could make.

And, you know, with regard to all this discussion about active smoking, I really think that's the elephant in the room. You know, the common conception that active smoking is not related to breast cancer, I think you're dealing with that. And then the question is: Why is there not a greater difference between -- once you accept that active smoking is a risk factor, why is there not a greater difference between active and passive smoking? I think you've got to deal with that.

I agree with Stan. I don't know about an appendix, but I think it could be dealt with shorter -- in a shorter manner, more concisely as I think about the whole rest of the report. But it's just got to be dealt with. So that's how I feel about this.

And as far as the pre versus postmenopausal breast cancer, you know, I hear good arguments on both

sides, so I'd rather not comment on that till we see the new report.

CHAIRPERSON FROINES: Thanks, Gary.

Okay. Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I think we can skip Hanaoka because we've mentioned it several times just to point out that it was a good study.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. There is some discussion in the report about the differences chemically in side-stream versus mainstream smoke. There are studies showing that some carcinogens are more concentrated in side-stream smoke versus mainstream smoke.

One of them is mentioned here. Lodovici, et al., 2004, reported about ten times more carcinogenic PAH's in side-stream smoke relative to mainstream smoke. And that was in terms of they were looking at micrograms per -- I forgot what it was. It was either -- darn it, I forgot the units.

And also U.S.EPA have looked at this issue earlier, in '92, and found somewhere between 20 and 100 times more nitrosamines and 4-aminobiphenyls in side-stream smoke and more other types of carcinogens.

PANEL MEMBER HAMMOND: If we move on, this data

should be in Part A. And the Lodovici -- you need to have it supported there.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER HAMMOND: And Lodovici's not in there.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Thank you.

PANEL MEMBER HAMMOND: Just bring the pieces together.

CHAIRPERSON FROINES: Melanie knows I'm going to say this because I sent her an E-mail yesterday, so she's all prepared.

I think this is interesting what people have done because they have gas chromatographs and can measure differences. It has nothing to do with bio-availability and toxicokinetics dosimetry. The fact that vapors disperse even though you've got more in one, whereas inhalation and particles and things on particles and so on and so forth, it's -- active smokers are passive smokers as well, so they breathe passive smoke. I think making anything about differences between side-stream smoke and mainstream smoke is so simplistic that it's embarrassing to have people even raise it.

The fact that you have more 4-aminobiphenyl, which we've heard about for 15 years now, doesn't have

anything to do with internal dose. And we should separate our ability to measure things in the air and -- we should separate a concept of internal dose from what we can measure in the air and comparing the quantitative relationships. And I think that -- I think this is just foolishness. Unless somebody can show that the internal dose of 4-aminobiphenyl is lower -- is lower in a smoker than in somebody breathing side-stream smoke, I think it has no carcinogenic relevance whatsoever.

PANEL MEMBER HAMMOND: John, I beg to differ. And I'd refer you to one of my papers on just exactly that point.

Okay. For the --

PANEL MEMBER BYUS: So you didn't review that paper?

PANEL MEMBER HAMMOND: Right.

(Laughter.)

PANEL MEMBER HAMMOND: 4-aminobiphenyl is 30 times -- is 30 times higher in side-stream than in mainstream, nicotine's 2 times higher in side-stream than mainstream, which means there's a 15-fold greater enhancement of 4-aminobiphenyl.

The ratio biologically is nonsmokers have 1 percent as much cotinine as smokers on average. And 4-aminobiphenyl in the study that I published we had 14

percent as much, which is a 14-fold ratio.

So I think you're right that it's simplistic at one level. But it's not uninformative. It just has to be treated in a more sophisticated way.

So the point was -- the point is that here you have a carcinogen, and it doesn't have this 100-fold difference that you see for nicotine; it was in fact only a 7-fold difference.

CHAIRPERSON FROINES: My point is very simple. Unless one can demonstrate that the internal dose is --

PANEL MEMBER HAMMOND: I'm talking internal dose.

CHAIRPERSON FROINES: -- And the bio-availability of these compounds is greater in side-stream smoke than in active smoking, then I think that -- I think that what one measures has often little to do with how much gets into cells in lungs.

PANEL MEMBER HAMMOND: I think -- I agree -- I totally agree it's complicated. But I'm saying that in fact -- I'm talking about a biologic dose. I mean it's 4-aminobiphenyl hemoglobins adducts. It's not the DNA adducts, but it certainly is what got into the human body. And of course you can go on and on and on about -- and it's important to do it. But I think in terms of showing that in fact the different ratios in side-stream and mainstream smoke have some relevance, that definitely

demonstrates that that's true. You have to go further to go beyond that. But I do think it shows that there's -- it goes to plausibility. It doesn't, you know, prove any point, but it goes to plausibility outside of just the, you know, saying, oh, well, you know, smoking is obviously a hundred times greater dose than passive smoking. It's not. It depends on the chemical.

CHAIRPERSON FROINES: I think that there's a thousand carcinogens in tobacco smoke. And the fact that we can measure some differences doesn't deal with all of the particle-associated compounds and the persistence of particle-associated compounds in terms of carcinogenesis relative to vapors that have very much different uptake.

So I think this is fine to say. I just don't think people who smoke are exposed to carcinogens. And I think that without dealing with the toxicokinetics one can't make much of this.

PANEL MEMBER FRIEDMAN: Well, under the data -- on the toxicokinetics, if there's no data, this is probably the best that they have. So why not mention it?

CHAIRPERSON FROINES: It's okay to mention it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think that's the point. Part of it is that people have said, oh, smokers must -- you know, they have passive smoke exposure too and plus the active -- you know, the

mainstream smoke exposures, so their exposures must be orders and orders of magnitude higher. And I don't think you can make that statement without a lot more data.

Our point is that, yes, smokers also breathe passive smoke. Lodovici happens to think that their total carcinogen load is more from the side-stream smoke they're breathing rather than their mainstream smoke.

And, regardless, the epidemiology is telling us that passive and active smokers in terms of breast cancer have about the same risk. So I don't -- you know, we're trying to point out there's mammary carcinogens in ETS, which is this slide, just at least 20 rodent model mammary carcinogens in ETS. And so that the biologic plausibility is there you have exposure to mammary carcinogens.

PANEL MEMBER BYUS: I do agree with you, John. It's really the tone -- I agree with both of you. It's the tone in the document of why you're bringing the data up.

I mean you really need to say -- if you make the statement that John just made that it's really the internal concentrations that are really important after you take -- rather than the external. And we understand that and that there is market differences, yet the compounds themselves, if you analyze them, you do find this. But it really doesn't get back to any kind of

dose -- internal dose reality. If there was one molecule of, you know, PAH and it increased 10-fold in side-stream smoke versus normal, so you'd have 10 molecules. And what relevance would that really have unless you really were exposed to sufficient amount internally?

You don't really -- it's the tone in the document that's -- I wouldn't say you're being defensive, but you're not being objectively complete enough is perhaps what I really want to say. It's more like you're being more defensive and more responding rather than objectively complete in your statements. And it rings consistently through a lot of these paragraphs.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I think --

PANEL MEMBER BYUS: Is that fair?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, I agree with you. I think part of the problem is that we --

PANEL MEMBER BYUS: I know you understand it. It's just when you read it -- and I've read it over and it isn't always clear. You know what I'm saying? And so I -- and I know a fair amount about this stuff. Not probably as much as you do. But I'm just trying to -- it needs to be more objective and more complete in your statements and less defensive and responsive.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER GLANTZ: Well, you know, it may be that what OEHHA -- we were talking about this a little bit before the meeting. But I mean it may be that what OEHHA needs to do is like get an editor who hasn't been living with this document for however long it's been and who can come at it -- you know, look at the comments we made and -- you know, Gary's little experiment of cutting it in half -- and just go through -- get a fresh pair of eyes to just go through it and help OEHHA with the language and the presentation.

CHAIRPERSON FROINES: But I think that there's an incorrect assumption -- implication is being made. This slide implies that there may be a greater carcinogenic risk from passive smoking because of the differences in few compounds that have been measured. That's the implication that's being said. And what I'm saying is that's not correct in my view. I think there -- that unless one can -- and one would never -- in terms of airborne particulate matter, where we're doing a lot of research on disposition within cells and are thinking about how do chemicals and particles -- how do they -- how do we deal with them in terms of their disposition within cells, we would never make arguments like this.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't think we're making that argument. I don't think we're

saying that there's a higher risk because there's a higher exposure. All we're saying is there is exposure.

CHAIRPERSON FROINES: It's by Implication though. It's --

PANEL MEMBER HAMMOND: I think this argument's best made in Part A, I would suggest, rather than within the chapter. And then I think you should refer back to Part A. And I think the -- and I do totally agree with you, John, in terms of -- at the superficial level, if it looks like you're trying to say that the passive smoking exposure is higher, that's incorrect. And I think it is very important not to make that statement.

I think that the important statement that I was trying to make -- and I didn't say it well -- probably still won't -- but is that the ratio of active to passive smoking exposure is different for different chemicals. And for some of them it's not trivial. And because we have -- most of the biologic evidence we have for biologic markers is cotinine and it's a 1 to 100 ratio, people tend to think that's the entire picture of the exposure. And I think that's what needs a careful explanation, that for some chemicals we already know it's 1 to 7 ratio -- you know, ratio and for -- we don't know about some of these others and maybe we could -- you know, you could think about some of these things. But we have evidence of these

ratios being different by different things.

But I think that's all a discussion that belongs in Part A. And just a brief reference to it in these other areas to say that -- you know, that -- I think it's a stronger way for whole document, because it becomes a --

CHAIRPERSON FROINES: -- wants to say something that Melanie should go first.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think just to back everybody up, the reason it's in Part B is we're talking -- when we're talking about biological plausibility, that what we're saying is there are carcinogens in tobacco smoke, there are mammary carcinogens in ETS, that mammary epithelium is capable of metabolic activation of the carcinogens, that you can find DNA adducts of these carcinogens in the breast tissue. In other words, the carcinogens reach the breast tissue. And in fact on page 179, we talk about several studies, one of which looks at 4-aminobiphenyl DNA adducts in normal breast tissue, and there is a linear trend from never either active or passive, ever passive only, ever active only to both. So there's a linear trend in the 4-aminobiphenyl DNA adducts in breast tissue.

And our real point is at the bottom of the page, is these studies provide evidence that carcinogens in the tobacco smoke reach mammary tissue and form DNA adducts.

That's all we're trying to say.

CHAIRPERSON FROINES: I think that's absolutely perfect and I think you should do that. I think where I get into trouble with you is where you quantify it and start to suggest implic -- and therefore there becomes suggested implications for it.

And so I agree with Kathy or whoever said it. I'd put it in Part A. It's relevant information.

But the point that people are exposed to mammary carcinogens is a very important point to have in your document in terms of biological plausibility and I think it's fine. It's just -- I think I would just avoid getting into what are basically toxicokinetic issues that you're not prepared to deal with and so it just kind of sits there; and people who do toxicokinetics then find fault. And so --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. That's an easy effect. So we'll remove that --

PANEL MEMBER FRIEDMAN: Just respond to Stan.

I think an editor would be very good in terms of just cutting out unnecessary words. But this kind of issue, you know, and the defensiveness and so on, they can't deal with, so it's got to be you guys that deal with it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: Joe, did you --

OEHHA SUPERVISING TOXICOLOGIST MARTY: All right. So --

PANEL MEMBER LANDOLPH: Yeah. I thought the comments, you know, that were made are fine. I found the listing of some of these data useful, because in my mind I was always having problems with why ETS was as active as it is. And so I think if, you know, somewhere you worked in a very concise wording, that these may explain -- these data may be one of six steps explaining why ETS may be as active as it is in the breast, something like that.

I also agree, Gary, and Stan's comment. You know, in terms of editing, I think you could just simply reduce a lot of the wordiness and just say what you're saying much more concisely, and your points would stick up very dramatically and -- because I can go through just turning 13 pages of discussion, which is very good, but it lulls you into almost a sleep state when you're trying to find the real crucial bottom line to the document would help you.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So next time you have insomnia, read this document.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I have three summary slides, which I'll go through quickly,

and then we'll get to the comments on that chapter.

Recent population case-control studies and a recent cohort study controlling for important factors have identified significant elevated risks for breast cancer --

CHAIRPERSON FROINES: Melanie, are you not going -- this document that I have has the mammary carcinogens slide and the tobacco smoke.

PANEL MEMBER HAMMOND: She's had those up.

CHAIRPERSON FROINES: Did I miss --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I basically -- well, I shortened -- I contracted this by my statement about what's in the document.

CHAIRPERSON FROINES: Can I just make one very quick comment about this?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

CHAIRPERSON FROINES: You say on page 799, overall neither current nor active nor passive smoking was statistically associated, blah, blah, blah. Thus the adducts did not appear to be a useful biomarker for smoking in this study.

On the next page you say in inclusion, blah, blah, blah, this study suggests a role of PAH DNA adducts.

And so on two pages you've kind of said it's not useful, and then on the second page you say it is useful. And I would just clean that up. Let it go at that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: You can't say on one page it's useful, another page it's not useful. And we all saw it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. So --

CHAIRPERSON FROINES: Onwards.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So we believe that studies that did a reasonable job of exposure ascertainment and controlling for important factors identified significant elevated risk for breast cancer associated with exposure from both residential and occupational sources, particularly in premenopausal women.

Many, but not all, studies find positive associations between passive smoke and breast cancer. The risk appears to vary by menopausal status and timing of exposure. These factors were not always controlled for in the large cohort studies.

Studies with a better exposure assessment are consistently positive. And most of these -- in fact, all of these I think are statistically significant.

When you compare the exposed to a referent category that has nonsmokers/non-ETS exposed, there's

consistently showing stronger associations.

PANEL MEMBER FRIEDMAN: Would you please explain. Stronger than what?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Stronger than when your referent category did not take out the ETS exposed nonsmokers.

PANEL MEMBER FRIEDMAN: It sounds like now you're talking about active smoking.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's both -- actually it's both in active and passive you see the same thing.

CHAIRPERSON FROINES: Well, because we live in the world of word processing and things like this end up in documents, I think that you'd probably want to make sure it's clearly stated if it raises a question with Gary.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: And I would -- at the bottom what I'd say, to strongly support risk of, blah, blah, blah, from exposure to side-stream smoke. In other words, since this may show up in another place because of somebody's Microsoft Word, make sure that the summary kinds of things are very clearly defined.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. And then of course the toxicological data continue to strongly

support risk from exposure to side-stream and mainstream smoke by virtue of the carcinogens identified in those smokes.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: Summary, slide 2. In here we're talking about relationship to active smoking. Many, but not all, studies find positive association between active smoking and breast cancer. This may be complicated by the apparent countervailing protective effects of anti-estrogenicity. It may vary by menopausal status and also timing of exposure shown in a number of studies.

And, again, comparing to a nonsmoking, non-ETS referent group shows stronger association than if you have ETS exposed individuals in your referent group.

There is also evidence that risk from active smoking might be modified by the hormone receptor status of the tumor by metabolic enzyme gene profiles and by family history. We have several studies describing our document that looked at that.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Finally, there is evidence of windows of susceptibility to mammary carcinogens. And this is any mammary carcinogen, those in ETS, those in mainstream. In pre-pubertal and

pre-pregnancy years this does complicate a little bit the analysis of the associations because it makes the data more messy.

Overall, the weight of the evidence including biomarker, animal, epi studies and breast biology is consistent with a causal association between ETS and breast cancer, which appears to be stronger for premenopausal breast. Of course we're going to get back to that -- to the Panel with looking at pre versus post menopausal.

CHAIRPERSON FROINES: I still -- going back to the last meeting, I still have a little problem with the term "weight of evidence". And we all use it repeatedly. But we all assumed therefore that everybody understands it. And I think it would be useful to have a paragraph or two someplace where you say, "At OEHHA weight of evidence means" something, because -- and if it's in there and I've missed, it I apologize. But -- I think it actually is in there. I think it is --

OEHHA SUPERVISING TOXICOLOGIST MARTY: It is in Chapter 1. And Dr. Blanc sent us something from the Institute of Medicine. We have a couple slides. We were revising that wording to make it clearer that this is what we were -- this is what we're talking about when we're looking at that.

PANEL MEMBER BYUS: I have the same concern, and I guess back to the epi studies, which are not my area of expertise. But as I read it, I'm looking for the weight that the epidemiology study have evidence. And there's less focus on the quality studies, which is what one normally does is pick out the quality studies because of the more complete exposure assessment and whatever all the parameters are and highlight those studies, instead of necessarily averaging every one of them altogether.

And that's a lot of that in the document. I mean you read about this one and then the next one. This says this and this one says this. And there's not the feature on -- I mean I would say these studies for whatever reason are the best ones based upon epidemiological standards of studies and they show the strongest correlation. And that's not clear always throughout the document. And that gets -- it's not -- it is weight of evidence, but it's featuring on the best, most accurate studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We did do that in terms of trying to look at those studies that did the best job of exposure. So we did do that.

And we also have some critique of the quality of individual studies, which is part of what makes the darn document so wordy.

PANEL MEMBER BYUS: That's right. But you don't

actually -- I mean it's in there if you look, and I have to look over and over again. But it should be featured. These studies -- these three, whatever they are, from environmental tobacco smoke, these because of -- for active smoke because they subtracted out the baseline, are the best. These over here are the best. These show the dose responses, both studies. That's the clear picture. That's what we want to look at. Then you can leave all the rest of it in there if you want. But it's not clear always.

CHAIRPERSON FROINES: I do think it's useful for OEHHA to say to the reader -- as you go through or summary or something like that, the form you can work out. But I think it's useful for the reader to know what studies you thought were good and of solid quality.

And, therefore -- because otherwise, Craig's right, you're left with this long review. And when you want to find out what studies you thought were the most -- were the best or the most useful or in the highest quality, it's hard to find.

And so not to make more work for you, but --

PANEL MEMBER FRIEDMAN: So they did that partially by looking at, you know, whether the passive smokings were removed from the reference group by looking at periods of time when the passive -- so they did that --

PANEL MEMBER BYUS: It's there, but it's not -- it doesn't ring out clearly. You have to put too much work into it to find it, is what I'm trying to tell you. At least a lot of work for me.

PANEL MEMBER HAMMOND: And that's kind of a summary of a lot of the evidence in the document. But I totally agree. It's all there. But I think the point should be there should be maybe a summary of this -- where you summarize the evidence, you say here are the three strongest studies, that are methodologically the strongest studies. Not by the outcome but by methodological.

PANEL MEMBER BYUS: Methodologically here are the strongest.

PANEL MEMBER HAMMOND: Here are the strongest studies. And this is the evidence we get from these strongest studies. Here's the strongest biomark, here's the strongest this, that. But you pull out all -- you know, what it is, if you had to bet your life, you were at a Congressional hearing, this is what you're going to bet it on, what would you pull up?

PANEL MEMBER BYUS: There you go.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And we will do this in a paragraph or two.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: And what might help you

is -- I don't think -- while I think you've done a herculean job discussing all the methodologies of each study, I don't think you have to do all that. Just toss them off real quickly, get to the bottom line and what's the odds ratio, and then put more effort into the most important studies. Because I think that's exactly why it's not jumping out. We're bogged down in all this minutia of each study, and so you get lulled by the time you come to the really important ones. It disguises them.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: I have a different -- I agree with everything that's been said, clearly. And I have a different agenda. I used to think that this was a scientific meeting. And then I got -- we got sued from the diesel people because it isn't a scientific meeting. We're actually in a courtroom in this room. And the fact of the matter is I think it's useful to say what you think is good, because later we may have to justify what you thought was good. And I think the more clarity, the better in the long run, because it just -- it shows this is what OEHHA thought were the best studies and what we based our decision on. And then we can argue that in the future if unfortunately those kind of things occur in the future.

PANEL MEMBER GLANTZ: Well, I agree with what

everybody is saying too. But I think you want to make -- I think for completeness, and also to avoid criticisms, all of the available literature does have to be addressed. I mean I it can be -- we've said -- everybody said it could be done more tersely, you know, with many fewer words. But I don't think you should interpret what -- and I don't think you're saying this. But I don't think this should be interpreted as like dropping out certain studies from mention. I think the encyclopedic nature of the report is something that I think needs to be there. It just needs to be there more compactly and clearly with a clear focus, as everybody's saying, on sort of the what are the really important bits of evidence, the best studies, et cetera.

CHAIRPERSON FROINES: Well, I think there's another reason, which is we are paid to read these -- this thousands of pages of documents. And, you know, we sock it away in our savings accounts --

PANEL MEMBER BYUS: We are not getting a hundred thousand dollars, as the Governor said, for --

CHAIRPERSON FROINES: Let me make my point here.

PANEL MEMBER BYUS: Are we?

PANEL MEMBER HAMMOND: No, we don't get paid to read the documents, just to be at the meetings.

(Laughter.)

PANEL MEMBER GLANTZ: We get paid to come talk about the documents.

PANEL MEMBER HAMMOND: Yeah, we don't get paid to read them.

PANEL MEMBER FRIEDMAN: And not very much at that --

CHAIRPERSON FROINES: For the record, we were all joking just then.

(Laughter.)

PANEL MEMBER GLANTZ: That's true. And the diesel experience showed that we need the jokes to be clearly identified.

(Laughter.)

CHAIRPERSON FROINES: I just want to make one more point though, which is: We read these with some thoroughness. But a lot of people who will end up reading this document won't read it with the same thoroughness that this Panel does or the OEHHA people who worked on it. So the more you tell the public what's important, the easier it is for them to understand what they're reading. And so the more road map is always helpful. But obviously we don't want you to do a lot more work, but just enough so that when Joe Smith, you know, reads the document and they say -- he says, "Oh, I know, these are the studies that they used," that makes -- it's good public education,

I think.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I think we can do that.

I'm just not --

PANEL MEMBER GLANTZ: In other words it's a standard reviewer comment. Add all of these issues, deal with all these issues, and cut it in half.

(Laughter.)

PANEL MEMBER FRIEDMAN: Make it shorter.

DR. JOHNSON: Make it clearer, simpler.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I'll go into the comments.

We got a comment from Barsky, on behalf of RJ Reynolds, that the weight of evidence provided by animal models of breast cancer is insufficient to show causal association with the ETS.

The comment was that: "Most are mouse models relying on the mouse mammary tumor virus, or use genetically engineered mice."

That "Carcinogen-induced mammary tumors including those induced by DMBA are not metastatic.

"Thus the overall relevance of murine models to ETS and human breast cancer is questionable."

And our response is that: "Some mouse strains show latent infection by MMTV, but many which are

sensitive to mammary carcinogens such as NTP's B6C3F1 mice do not have this infection."

And also "Chemical virus interactions are relevant to human disease.

The common DMBA experimental model actually uses the Sprague-Dawley rat and not mouse model.

And many chemically induced mammary tumors show invasion and metastasis including those induced by DMBA.

And there are parallel findings in rodent models and in exposed humans such as DNA adduct formation p53 oncogene activation. And these are in our document.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Mark's going to take up the rest.

DR. MILLER: From Dr. Thun and RJ Reynolds, comment came that the data showed no overall association between active smoking and breast cancer. And we've discussed this really. And that's the figure that we showed you earlier. The studies do vary somewhat. But recent studies and those that evaluate multiple sources of ETS exposure are fairly consistently positive, and we'll do more work on that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I would like to point out that Dr. Thun is not with RJ Reynolds. The two separate commenters.

PANEL MEMBER GLANTZ: Thun is with the Cancer Society.

CHAIRPERSON FROINES: I think it's -- you should at some point put a sentence in someplace that says DNA adducts are measures of exposure to carcinogens. They are not implications for cancers. Since obviously the first step in a long process is not -- DNA adduct formation is obviously not sufficient to generate cancer. And to the degree that it gets -- the biology and the chemistry get mixed together, it's --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

DR. MILLER: From several commenters, more or less the same comment that boils down to: "Data show no overall association between active smoking and breast cancer. Therefore it is implausible that ETS could find an association." We've actually discussed this in great length already, so I think we --

PANEL MEMBER FRIEDMAN: I think I would put the last one first.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

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DR. MILLER: Comments from Dr. Thun and from Dr. Croyle at the NCI about the collaborative group study. This was a meta-analysis of 53 epidemiologic studies that was quite large, and found that those who drank no --

let's see. There was no overall association between active smoking and breast cancer in this study. Authors noted that no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposures. So there was no consideration of that. These are essentially all of the studies that have been done, which include many older studies where there was large passive exposure in the referent population. If passive exposure resulted in risk approximating active smoking, you'd be likely unable to identify risk.

--o0o--

PANEL MEMBER GLANTZ: One little comment. That actually wasn't a meta-analysis. It was a pooled analysis.

DR. MILLER: Pooled analysis.

But those were directly from the commenters, you know, this wording.

And, additionally, Dr. Tune said that the association between alcohol and breast cancer may account for smoking association.

Several -- and all of these are -- well, most of these are the better studies, found little or no modification of risk when adjusting for alcohol.

Reynolds risk estimate for active smoking actually increased when examining only the nondrinkers in

her cohort. And we do abstract a -- we published in this an abstract, one of the few that we did.

But Zhang, in which they illustrated an additive effect of alcohol and smoking in breast cancer risk.

--o0o--

DR. MILLER: On misclassification of exposure, LeVois, who was writing for one of the tobacco companies, commented that "Every method used to assess smoker misclassification is prone to error, and is likely to underestimate the true rate, especially the true rate of former active smokers."

And our response is that several studies report -- looked at this and report that misclassification of exposure leads to an underestimation of the effect, including DeLorenze from California, Dr. Johnson's paper, and then Morabia, not an overestimation. And that --

PANEL MEMBER HAMMOND: But the comment wasn't underestimation. He didn't say that.

DR. MILLER: I think that maybe is supposed to say overestimation of the true rate. Yeah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So we screwed up.

CHAIRPERSON FROINES: So it's --

PANEL MEMBER HAMMOND: The comment was overestimate?

CHAIRPERSON FROINES: A typo in the comment?

DR. MILLER: I think that's a typo in the comment.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think so. Sorry.

MR. MILLER: "This may be primarily due to the ETS exposures in individuals in the non-exposed group biasing the results towards the null."

--o0o--

DR. MILLER: I think actually this is -- we took this one very seriously, from Dr. Thun, in which he said that never smokers/not exposed to ETS represent a small portion of nonsmokers." And in Dr. Johnson's study in the premenopausal group that was 10 percent. And his assertion is that this may introduce bias since it's a relatively small portion of that.

And our response to that was -- first of all, the alternative is to utilize a known exposed referent group, which seems counter-intuitive.

In most studies the cases and controls that were not ETS exposed actually ranged from 20 to 50 percent, not 10 percent, including the most recent Hanaoka, which is also a prospective cohort study.

And in the quoted data from Johnson's premenopausal data, the small proportion of non-exposed

was compensated by adjusting the control group to include ETS exposure for up to 10 years to stabilize the results, in which case 17 percent of the cases and 29 percent of the controls in that group were non-ETS exposed under that classification. And the odds ratio was still high and more statistically significant in that evaluation.

--o0o--

DR. JOHNSON: Just one comment.

In any of the studies where you see a dose response relationship, then shifting the number that are included in the, quote-unquote, nonexposed to make it larger, unless somehow different, it's just going to reduce your odds ratios. The risk profile is not going to change at all.

I'm sorry. One other thing. In many occupational studies, the irony of passive smoking is that you have almost everyone exposed. In many occupational studies the problem is to find enough people that are exposed. So you end up with only 5 or 10 percent of the sample that are exposed. And in those studies they never complain about it being a biased group because it's so small. So I just don't -- I don't think epidemiologically -- I just don't buy it that because the group that's unexposed is small, it's somehow strange and curious and biased.

DR. MILLER: And further from Dr. Thun, he comments that the ACS and Harvard Nurses cohorts too, American cohorts, found no elevated breast cancer risk for ETS exposure despite positive findings for lung cancer and cardiovascular disease. And asserts that the prospective data should be weighed more heavily.

And our response is that those are, as we've discussed, you know, incomplete measures of ETS -- that utilize incomplete measures of ETS exposure, that lung has a very linear dose response curve and so the comparison is difficult.

Data collected may be -- may more closely reflect exposures important for lung cancer and heart disease than breast cancer in these studies where there may be this complicated windows of susceptibility and all these other things we've discussed.

And on top of that we now have the first prospective cohort to utilize data on all sources of exposure and a non-ETS exposure referent, Hanaoka, which is a large study. And that prospective cohort does find a positive association.

--o0o--

DR. MILLER: On genetic susceptibility Dr. Thun comments that studies of genetic susceptibility are not supportive of an association.

And many studies that look at polymorphisms of metabolic enzymes showed elevated point estimates for at least some groups. And, you know, while he points to the lack of significance of those, it's -- uniformly these are small populations that were looked at.

A single enzyme may not give you the whole picture. And Firozi found that smokers with certain CYP and GSTM1 null polymorphisms combined have higher levels of adducts than either do individually.

And these studies are unable to account for these windows, these other sorts of interactions that would be important to look at.

--o0o--

PANEL MEMBER BYUS: I happen to agree with him. I found all those discussions fairly unconvincing. I mean there's some indications, but it's far from convincing.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah --

PANEL MEMBER BYUS: I mean it's good to have it in there for completeness, but it's not -- you know, it's -- I mean I agree with him.

OEHHA SUPERVISING TOXICOLOGIST MARTY: There's some really interesting findings, but it's hard to know what to do with them.

PANEL MEMBER BYUS: It's stuff, but it doesn't add much.

DR. MILLER: And I don't think -- well, we could shorten that. And I don't think that in our summary we tried to overplay that.

PANEL MEMBER HAMMOND: I mean it doesn't go into the treasure chest. If there's a treasure chest of this is the data that really help us come to a conclusion, we could think of that.

PANEL MEMBER BYUS: That's right. That's a good way of thinking of that, exactly.

DR. MILLER: And then regarding control of covariates. "Several studies" -- this again from Dr. Thun. "Several studies do not control for important covariates such as age at first birth and/or alcohol consumption." And he lists several studies.

And the studies on which we relied most accounted for at least a number of covariates. And the studies mentioned above all had incomplete exposure assessment except for Smith. So in fact those are ones that were in the lesser strength group of studies.

Risks were higher when examining studies with the more complete exposure assessment studies. And many studies found no significant change with adjustment for alcohol, as we mentioned earlier.

Smith included adjustments for multiple measures, including all alcohol consumption at 18 years of age, and

we feel belongs with the more complete studies.

--o0o--

DR. MILLER: And this is in fact the figure that goes along with that. I think we looked at that enough.

--o0o--

CHAIRPERSON FROINES: I think you could add -- I'm sorry. I'm still with genetic susceptibility.

(Laughter.)

CHAIRPERSON FROINES: Because I think that we take an emerging science and all of a sudden say that it's ready for all sorts of advanced purposes and it's not. And I think that you could say that since we don't really understand the biological and chemical mechanisms underlying breast cancer from environmental tobacco smoke, that the studies of genetic susceptibility can only be of interest rather than to, you know, cement a point of view. I just think the science is not there. We don't understand the science well enough or no other mechanisms to actually use these -- these studies are interesting, but they're still in the early development of genomics. And so to use them as an argument against something is really --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'll go back and look and see how we use it. You know, I don't recall that we use it other than to point out that there's

inter-individual variability.

DR. MILLER: And I think in our actual response at least to that comment we did -- you have that same discussion.

PANEL MEMBER LANDOLPH: Yeah, because they're actually negative studies. They may just be looking at the wrong markers.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: People select the wrong knockout mice all the time to do studies. And then they come up with negative results and have no way to interpret them. So I mean it's --

DR. MILLER: So this is, you know, regarding the weight of cohort studies, which came from three commenters, and really is the thought that Dr. Johnson had brought up earlier, in that one of the arguments is that more weight should be given to recently published findings from the cohort studies in view of their large size and ability to clearly establish exposure as occurring before recognition of the cancers.

Our response is that the earlier cohort studies, exposure assessment is problematic, very problematic. And Hanaoko is the first prospective cohort to utilize data on all sources of exposure and non-ETS exposed referent and is consistent with the bulk of the evidence from case

control studies.

When weighting studies you need to balance between minimizing recall bias, which is what we -- you know, the strength of the cohort studies, and minimizing exposure misclassification, which is less of a problem with the case control studies, at least in these set of those studies.

Reporting bias related to retrospective studies is mitigated as a potential link of smoking or to ETS to breast cancer in that it's not commonly -- this association is not commonly known to the public or in fact accepted by the medical community either.

PANEL MEMBER FRIEDMAN: When Paul was here he brought up the question of the trend over time of the study showing less and less of a risk -- elevated risk. I Didn't hear a response to that. And I think maybe you would like to and maybe it should be included in the report.

What is your response to that?

DR. MILLER: Well, the response is, you know, if you look at it from the quality of studies and exposure assessment, the trend that he's seeing is this group of studies that were of poor quality that were clumped --

PANEL MEMBER FRIEDMAN: But as I recall, the black diamonds, which were the good studies, also showed

that trend, although there were few of them.

DR. MILLER: I wouldn't say that --

DR. JOHNSON: Well, except for the Hanaoka study, which is the most recent one, which shows for premenopausal breast cancer, passive risk of 2.6 statistically significant, an active risk of 3.9 statistically significant, as good exposure managers and is a cohort study.

PANEL MEMBER FRIEDMAN: Was that one of the black diamonds?

DR. JOHNSON: Yeah, but it -- see, it was for pre and postmenopausal.

PANEL MEMBER GLANTZ: I think you've got a graph wrong if Hanaoka shows 2. --

DR. JOHNSON: No, no, that's overall. And I'm talking about premenopausal.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER HAMMOND: You know, but I think this all points out where if you lay out these are the most important studies because they're methodologically the most sound studies, then you can kind of get -- you get away from having to deal with all this, all these studies that don't seem to show anything. Well, you say, "Here are the reasons we choose these as methodologically most sound." And they actually then have clearer results, but

you're basing it then on the -- it's clear what you're basing it on.

PANEL MEMBER BYUS: Right. I think you should really use the word that you're using, methodologically the faster, methodologically the sound, not the best studies. Because the implication -- there's other implications there, and we don't want those implications. You're talking methodologically what are the best studies? And these are for these reasons.

And then they show -- methodologically the best ones show the most positive results. So that's your case.

DR. JOHNSON: I think the one point there though is, as an -- for the epidemiologic community, the one point about that, what you're saying is that there's a very strong Harvard-based belief in the cohort study. And so there's a tremendous emphasis, because it's a cohort study, it must be better. And that -- and I think that just has to be essential thing about methodologically --

PANEL MEMBER BYUS: That was one of my questions, what's the difference -- I mean are the cohort better than case control, et cetera? I don't --

PANEL MEMBER HAMMOND: You know, one of my questions --

PANEL MEMBER BYUS: You need to make your argument, whatever it is, and make it clear what you think

is methodologically the best given this scenario, given what you know about ETS, about past smoking and what you need to know about breast cancer. In this situation what is methodologically best? Not in general. We're not talking about that. We're talking about in this scenario.

DR. JOHNSON: Well, that's what we do argue.

PANEL MEMBER BYUS: Well, I know. But lay it out.

PANEL MEMBER HAMMOND: And also a cohort study -- I mean part of the things that make a cohort study superior often are the ability to do better exposure assessment. If you go back to why is it a better study, you know, it's not because it starts with a CO instead of CA or something, you know. So you say, "What are the underlying assumptions?" And if in fact in the cohort studies they actually have poorer exposures assessment, then that's undermined. So I think you go back to what's the reason.

And so, yes, cohort studies in many cases enable a better exposure assessment, a cleaner exposure assessment and therefore they're superior However, because in the past we didn't recognize the importance of environmental tobacco smoke, we haven't gotten that information very cleanly or very well. Then that's not an advantage for these cohort studies for these effects.

PANEL MEMBER GLANTZ: Yeah, and I mean -- I think as I said earlier, I think the big difference here is that when you -- when most people are thinking about cohort studies, it's where there was a discrete event that occurred at one time, like you gave -- you're comparing, you know, treating them with surgery versus medical therapy at a discrete point in time. Or where there's a discrete toxicologic exposure like a chemical spill or something like that. And not a thing where you're looking at this at an exposure over time.

PANEL MEMBER HAMMOND: Or even an exposure over time but is occupational, so it's more clearly related to this job, this company. Right?

PANEL MEMBER GLANTZ: Yeah. So I think that's to me the really important point. I mean the thing that generally that -- when you're talking about like a clinical trial or something makes a cohort study better is you know what the exposure was because you got it at the beginning. But it's not like there's some continuing exposure or changing exposure. If you operated on the person, you operated on them, and that's not going to change in the future. And I think that's the big issue here, is we're dealing with a distributed exposure that can be changing over time, people can be getting more, they can be getting less. You don't have their issues of

background and all that stuff, which is I think better captured for this kind of thing in the case control studies.

PANEL MEMBER HAMMOND: Well, in that similar vein though, an occupational cohort study is superior generally to a -- generally to a case control because you can define the exposures better. You know, again, if you -- because you limit the industry as to where the -- in which people have worked, and therefore the exposures, and you're going to do a better exposure assessment, in general, than in a case control where it's all comers. You'd have to take everyone who's got a diagnosis of pancreatic cancer or whatever.

DR. MILLER: In addition, besides the issue of recall bias from -- you know, you already have a diagnosis and you're trying to recall, that in fact is indisputable. But the prospective cohort is better. But the issue, you know, in which it's not better is that the time period that you may be of most interest, you know, is perhaps before the first pregnancy, in which case, you know, the prospective cohorts generally have enrolled their patients in the late 40's or 50's. And so they're looking back a long time. It's really no different than the case control from that particular perspective.

DR. JOHNSON: I think the other quick point on

that is there's no reason why the cohort studies couldn't have measured things as well. There's a logistical reason why they didn't, because in a cohort study you've got to ask a hundred thousand people the same question instead of just the thousand who actually are diseased and a thousand that aren't. So that they don't ask the same detail because it's too expensive and it's back in the early eighties, for example, for the Harvard study and it's before then for the other one. And so we just don't end up with the exposure --

PANEL MEMBER HAMMOND: Well, what I mean -- and then Harvard nurses study, right? I mean that was -- wasn't that fundamentally a nutrition-based study. All the energy went into nutrition. And then there was just this very tiny amount. And it might be useful to know what level of ETS exposures were in the various ways of the questionnaire. But, you know, it was a nutrition -- But it was fundamentally designed to be nutrition. I mean it's something that -- so that --

DR. JOHNSON: They only add courtesy. Occupationally they only asked, "In 1982 were you exposed to tobacco smoke or secondhand smoke or not full stop?"

PANEL MEMBER HAMMOND: Yeah. And It think that's an important point to make. It's probably one of the best for nutritional exposure, but not --

MR. MILLER: It's in there. And it's in more depth than the response to that comment too.

PANEL MEMBER HAMMOND: Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: This is a nice academic discussion, but I think we should move on.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. That was it for breast cancer.

I need to remind the Panel that at the last meeting we skipped over the first part of Chapter 7 just to jump to the breast cancer. There are a few other slides we had on lung cancer. I don't know if anyone's interested in it, looking at those slides. We've all read the report. I didn't hear any controversy over lung cancer and we didn't get a lot of comment on that from the public. And there was also a few other slides. So I don't know if you want to stop now, go back to that.

CHAIRPERSON FROINES: Well, we have half an hour before noon. Why don't -- what would you think would work best to get started on? I don't know -- does the Panel have questions on lung cancer? I think the active smoking element of this is probably not debatable in this group. But joking aside.

PANEL MEMBER FRIEDMAN: It raised an issue with me about, you know, the work -- this group has done a

tremendous job. I mean and it's been a tremendous amount of work. And it's not clear to me why they had to go through this with things like lung cancer when they had a beautiful report before which was published nationally. And I'm just wondering, not so much about the scientific issues in this, but about the utilization of resources and why they had to spend so much resources on this particular -- on passive smoking when perhaps this could have been used on other things. Was it a bureaucratic thing, the failure to address -- call it a toxic air contaminant that led to all this?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It was a -- yes, actually. It was bureaucratic in the sense that law requires us to look at all available data on a candidate toxic air contaminant, such that the attorneys felt we better update all of those -- all the portions of that earlier document, including the lung cancer.

PANEL MEMBER FRIEDMAN: But why wasn't this declared a toxic air contaminant on the basis of your first report?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, that -- you'd have to ask the ARB what happened back then. It was --

PANEL MEMBER FRIEDMAN: I would like to just surface that issue.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Jim.

PANEL MEMBER GLANTZ: Why don't we just table that.

CHAIRPERSON FROINES: The answer to the question is the ARB did not ask us to consider environmental tobacco smoke as a toxic air contaminant. It was -- they didn't put it on the table. And so whatever is the underlying reason for it is a policy decision made by the Chair --

PANEL MEMBER FRIEDMAN: -- of the ARB. But I mean why was the first report generated at all then?

CHAIRPERSON FROINES: Well, one could argue that Stan Glantz --

PANEL MEMBER GLANTZ: Why don't we just table this discussion.

(Laughter.)

CHAIRPERSON FROINES: Let's talk about it over lunch.

PANEL MEMBER GLANTZ: There's a short answer.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have five slides covering the other endpoints in that chapter. We could do that now for completeness.

CHAIRPERSON FROINES: Why don't you go through it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: Because I have one question about neuroblastoma. And somebody else might have other questions.

Joe.

PANEL MEMBER LANDOLPH: Oh, yeah. Just I thought that section was written pretty well. Just on page -- and I wrote this down for you -- 750, paragraph 5, to 751, paragraph 1 -- try and squash that down a little bit. That discussion is a little verbose. It's all written down for you.

OEHHA SUPERVISING TOXICOLOGIST MARTY: The lung cancer in the recent epidemiology literature consistently report elevated and often significant risks for lung cancer, particularly for women married to smokers. Several recent studies provided evidence of positive increasing trends with increased exposure. This supports the earlier conclusive designation in the 1997 report that ETS is causally related to lung cancer.

And misclassification of exposure in the unexposed populations occurred in some studies by not measuring lifetime exposure. This resulted in biasing some of the results to the null, which we've been talking about.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: This is a

meta-analysis from Taylor, et al., 2001. It just gives you an overview of what the data looked like. Cohort studies on the left. In the center panel are case control population-based studies. And case control studies not population-based on the right. And you can see that there's a general trend for those studies to have elevated risk estimates. And in a large number of studies they're significantly elevated. And the overall summary risk estimates are around 1.3.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: This is based on Johnson, 2000. It's ETS and lung cancer risk in never smokers. Population-based studies that include quantitative adult lifetime residential and occupational assessment of ETS exposure. And the point is here when you do a better job of exposure ascertainment, your summary estimates go up from about 1.3 in previous slide to 1.8.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: We had a small section on nasopharyngeal cancer. There were no previous studies in the '97 report. There were four new studies that got reviewed to case control which reported null associations and two which find positive associations, Yuan and Armstrong.

And Yuan was a population-based case control study in China, with a nonsmoking odds ratio of 1.29 for men, which was not statistically significant, 1.95 for women, which was statistically significant. And there's a positive dose response trend for a number of cigarettes smoked by the mother, the father or the spouse, and also the number of cigarettes smoked in the workplace around these women. So this is considered suggestive of possible association. And that was our conclusion in our report.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: And then finally lymphoma. In 1997 the results were inconsistent and based on a small number of studies and small numbers of cases in those studies. Although there were some that had slightly elevated risks, their recent data on ETS exposure and risk of lymphomas remains inadequate for adults.

However, recent data are suggestive of a relationship with childhood lymphoma. It's all combined or non-Hodgkins. In particular in one study, Ji, greater than 5 pack years of postnatal ETS exposure was associated with an elevated odds ratio of 5, which was statistically significant.

Risk for all childhood lymphomas combined was also significantly associated with paternal smoking in the

series of studies by Sorahan. And the odds ratio was 1.67.

And there were also some evidence in the series of studies for dose response trend with duration in years or pack years. And it also included exposure prior to conception. So it brings up the issue: Is this an issue of preconceptional heritable mutation resulting in elevated risk of lymphoma in the offspring or is this actually ETS exposure to the child that's resulting in the elevated risk of lymphoma?

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we have asterisked that in our front-end table indicating that we're not sure what sort of effect this is.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: And that's it. That's all the slides we have for the chapter.

PANEL MEMBER FRIEDMAN: Can I ask a question?

We talked when we met outside of this meeting about -- the confusion about head and neck cancer versus nasopharyngeal and so on. What have you done to resolve that?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We're in the process of revising that chapter and sticking nasopharyngeal as a sub-category of head and neck. I

think that was our plan. Right, Mark?

DR. MILLER: Yes.

CHAIRPERSON FROINES: Comments, questions?

Craig?

PANEL MEMBER BYUS: No.

PANEL MEMBER GLANTZ: I just have one quick -- I think we've given you a pretty good grilling here. But I think -- I mean my sense of -- I think you guys are doing a really good job with this. And I think there's work to be done, but I -- personally I'm impressed that how thorough you've been and the quality of the answers to the issues. There are things to be dealt with, but I mean you've done a really good job I think this morning.

PANEL MEMBER FRIEDMAN: I have a few other points, some of which I brought up with you when we met, and others I thought of since then.

One was that -- you know, you refer frequently to the Bradford Hill criteria. And one of the main ones is strength of the association. So I was hoping that you would add some discussion of that, because some of these are fairly weak associations.

Second, You had results for all cancers. I'm not sure if you're still going to include that. But you have to deal with the issue of the fact that if there's positive association with lung cancer and breast cancer

and there's no relationship with all cancer, why is that the case? I mean I personally think it's a dilution effect, but I think that has to be discussed. Because otherwise someone will say, "Well, if it doesn't relate to all cancer and it's positively related to at least some of these, then it must be protective against certain others." And so I think you just need to deal with that briefly.

And, finally, you have about the number of deaths due to environmental tobacco smoke in California being 12 percent of those in the United States because we constitute 12 percent of the population here. Yet smoking and probably exposure to environmental tobacco smoke is lower here. So I don't think you should just automatically use the 12 percent. I'm not sure what percentage you should use, but I think you need to deal with that a little more deeply than just saying 12 percent of the population, therefore 12 percent of the cases.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We actually say it's probably lower because of the difference in smoking rates. But we're at this point not sure how to deal with it in a quantitative sense.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: Nothing.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: I thought overall it's a

great chapter. It's comprehensive. It's well written. It's balanced. So I very positive about the chapter.

Rather than waste the committee's time I gave you -- let the record show I gave you about four pages of comments, mainly to shorten some of the long sentences. But those are on others -- those are on other chapters too. And areas where you could just make it more terse or concise so that the whole chapter is very hard hitting and has the appropriate impact commensurate with the quality of the data study here.

CHAIRPERSON FROINES: I just wanted to make one minor comment.

I wasn't so sure I agreed with you about the way you approached the neuroblastoma chapter, because there -- I would have argued that the data is in fact suggestive. But you don't draw that conclusion. It's certainly not inconclusive. There are -- as far as I can tell, you say the smaller Schuz study did not support this, that is, the Sorahan study. But in fact the Schuz study is not entirely negative by any stretch of the imagination.

So you have a case control study which was positive. You had -- I don't know what the four case control studies you referred to in here -- you say four case control studies including the three OSCC reports. Who the hell knows what OSCC is.

And then you go on to the Sorahan study which is positive. Then you go to the Schuz study which actually finds an odds ratio of 1.5. That's significant based on 39 cases. I can't -- I wouldn't exclude that and say that that's a negative study, which is what you basically say.

And admittedly with the other higher doses where you have three cases, that the numbers are too small to draw very much in the way of conclusions. But I certainly would not -- I think it's a little cavalier to assume that that's a negative study.

And so if you take the case control study that you start with in your previous report, the Sorahan study and the Schuz study, I would not end up with nothing at the bottom of that section, where you don't basically draw a conclusion. And I think neuroblastoma is sufficiently important that if it is a factor, that it's something that should be looked at. The childhood brain cancers is something that needs to be looked at with some focus of attention over time. And I wouldn't -- I don't entirely agree with you in terms of the fact that at the bottom of the page, at the bottom of that section there is no OEHHA conclusion. I would actually conclude that you're somewhere between -- you may not be suggestive, but you're not inconclusive either.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We're

having a hard time following where you are, because we actually have in our text that we're saying suggestive evidence. But it's possibly preconceptual paternal. So there is that -- there's that issue with all of the childhood tumors. And Schuz in our table is not an elevated risk. So I don't know if we're flipping through and looking at the wrong table --

CHAIRPERSON FROINES: I'm looking at page 7-240 and 7-241. And the Schuz study, smoking 1 to 10 cigarettes a day, the odds ratio is 1.5 and the confidence interval is significant.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. It's lymphoma. I'm sorry. I thought you were saying brain tumors. We're looking at 7 --

CHAIRPERSON FROINES: 7-240 is neuroblastoma in my draft. October 2004.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Let me look at your copy afterwards and we'll go through that again.

CHAIRPERSON FROINES: Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It could be a matter of depending on which printer you used to print out the chapter. The pagination is different, so I'm -- unfortunately. Anyway, we'll go ahead and take a look at that.

CHAIRPERSON FROINES: I would just argue with that issue, that you might consider drawing a conclusion even if it's very limited. But it's -- but given the fact that -- you know, I mean we have naphthalene in cigarette smoke. And we have -- I mean they are carcinogens that cause brain cancers. So that I'm just quarreling with no finding whatsoever.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm beginning to wonder if you're looking at the earlier draft. On page 7-1 for brain cancer in children, we are saying it's suggestive asterisk with the fact that it may reflect an association with paternal preconceptional exposure rather than ETS. You can't differentiate those two.

CHAIRPERSON FROINES: Well, why don't we let it go.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, okay.

CHAIRPERSON FROINES: Mine is -- I will say that I am looking at the draft with all your yellow marks on it. So it can't be too far back.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's not that far back, but it's different than this. I'm sorry.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER GLANTZ: Could I ask one question?

CHAIRPERSON FROINES: Please.

PANEL MEMBER GLANTZ: I assume we're going to break for lunch soon. But there are some people here at UCSF that I -- or have just become interested in the meeting to listen to all the in-depth discussions.

And could you -- do you know what the agenda for the afternoon -- what order we're going to treat different issues this afternoon, just so I can tell people?

CHAIRPERSON FROINES: Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, we have several things. I was -- paul wants to talk about the issue of causality, so we have a couple of suggested changes that we just wanted to run by the Panel for Chapter 1.

I could -- I have a brief list of things I just wanted to tell the Panel this is what we're doing based on the comments from the last meeting.

Then they have Chapters 4, 5, and 8 to go through. Eight is cardiovascular, four is postnatal development, and five is reproductive. Five is very short. Four isn't that long. Eight is the longest of those, but it's also the cleanest data, in my opinion.

PANEL MEMBER GLANTZ: Is there going to be any discussion of Part A and the exposure assessment stuff?

OEHHA SUPERVISING TOXICOLOGIST MARTY: ARB's here

prepared to do that. So --

CHAIRPERSON FROINES: Can I ask you a question about your reproductive?

Are you talking about reproductive separate from developmental?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: You're not talking about developmental?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We did prenatal developmental manifestations in the November 30th meeting. And we separated out the postnatal. And the post-natal's primary talking about SIDs and then some neuro-cognitive function studies.

CHAIRPERSON FROINES: So I think it sounds to me like -- well, go over it again so I don't keep trying --

PANEL MEMBER GLANTZ: Well, no, you don't have to.

Are people going to want to talk about Part A, do you know? I thought Kathy had some things. Or no?

PANEL MEMBER HAMMOND: Well, I've spent some time this -- we've had a couple of conference calls and we spent some time on that. So --

CHAIRPERSON FROINES: Jeanette, do you have slides?

ARB AIR QUALITY MEASURES BRANCH CHIEF BROOKS:

Yes, we do.

PANEL MEMBER HAMMOND: Yeah, I think they've done a lot of work.

CHAIRPERSON FROINES: So let's try and get -- what would you prefer, Stan?

PANEL MEMBER GLANTZ: I don't care. I'm just asking just so I can tell people what's going to happen.

CHAIRPERSON FROINES: I would keep Melanie going since she's on a roll. And then --

(Laughter.)

PANEL MEMBER GLANTZ: We have a room with a bed, so you can take a nap during lunch, Melanie.

CHAIRPERSON FROINES: Would you prefer ARB went ahead of you?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Actually I'd rather finish OEHHA's section. But ARB's champing at the bit also, because they did a lot of work between last meeting and this meeting. And I would hate for them not to be able to show that.

CHAIRPERSON FROINES: Okay. So then I think what we're going to do is break.

Can I make one comment to you? Going back to the developmental issue that I never thought about until I went back and reread your document.

I think that there's an interesting problem we

have. ETS relates to tobacco smoke. But this Panel was formed initially to deal with issues of air pollution, as you know, and pesticides. And one of the interesting questions is you have this laundry list of possible mechanisms about low birth weight. I don't find that very effective.

I thought it -- it looked like a laundry list. And it wasn't based on any hypotheses where evidentiary data were developed. And so as far as I'm concerned, you could either do a lot more or a lot less. And so it wouldn't hurt to take it out, because it's very speculative.

But I did want to raise one -- and if you want to leave it in, it's okay. It just reads like a lot of different -- you know, I can't remember all the chemicals that you listed that may be associated with the factor, but it's pretty speculative. If you want to leave it in, it's okay with me. I'm not quarreling. If you want to take it out, it's okay as well.

But I did want to raise one issue. And, that is, interestingly enough there is not a single reference to Beate Ritz in that document. And Beate Ritz has done a lot of work on low birth weight, as you know, and pre-term birth. And some of her work is associated with carbon monoxide exposure. And we all assume that it's not carbon

monoxide. We assume carbon monoxide's a surrogate for something else. And she's also done work on traffic density.

Well, as I was thinking about the fact that Beahta's work is missing, because you could use it to say there is a CO association which deserves further follow-up, I realize that we have this interesting problem that we have all these endpoints that we now associate with particulate exposure, and we're talking about ETS. And there's a very interesting intellectual question and certainly an area for future research, which is to link environmental tobacco smoke exposure and air pollution exposure.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Actually we have now added Beahta's work into that chapter because we were thinking about the same thing, how ETS is just like kind of concentrated air pollution basically. So -- I don't know if you made that suggestion to me. I think maybe you did at the last meeting or over the phone or in an E-mail or something. But we did do that.

CHAIRPERSON FROINES: You know, I'm getting older. I can't remember what I said anymore.

PANEL MEMBER BYUS: He didn't tell you, did he?

(Laughter.)

CHAIRPERSON FROINES: But it raises some -- you

know, it raises some very interesting issues about the relationship between environmental tobacco smoke and people driving two hours on a freeway with one and a half million particles per cc of ultrafines. And so there's really an interesting level -- area of research that we have yet to begin that links tobacco smoke and particulates in general and air pollution beyond that. So it's something to think about from a research standpoint.

PANEL MEMBER GLANTZ: Well, I don't want to delay lunch. But the -- in fact the American Heart Association a few months ago put out a major scientific policy paper saying air pollution was associated with heart disease. And that I was one of the people who suggested they look at that years ago using exactly the same argument you did, that in many ways ETS is simply highly concentrated air pollution.

And, indeed, many of the mechanisms that the Heart Association identified for air pollution in general being associated with heart disease were particulate levels, and searched some of the compounds which are in ETS which are also common in air pollution. So I think -- I mean that's a very -- you know, I think there's lot in this document actually that requires sort of going back and thinking more about some of the other issues relating to ambient air pollution. Because there's actually been

several studies, some of which we did and other people have done, looking at the effects of cigarette smoke from nicotine-free cigarettes, and most of the -- at least the cardiovascular effects are identical.

And I remember when we were doing diesel, Kathy Hammond showed up at that meeting and I said like "This is a meeting about diesel. What are you doing here?" And it was all diesel exhaust, and ETS have a lot in common in terms of their -- you know, viewed as pollutants. So I agree with you.

CHAIRPERSON FROINES: Well, Kathy would tell us -- I mean nicotine -- I mean smoke has a lot more nitrosamines and other kinds of nitrogenous compounds than diesel does. So it is different, but there are clearly similarities.

PANEL MEMBER BYUS: Came from plant products.

CHAIRPERSON FROINES: -- as well.

PANEL MEMBER BYUS: Originally, right?

CHAIRPERSON FROINES: So --

PANEL MEMBER HAMMOND: More so --

PANEL MEMBER GLANTZ: Anyway, I don't want to delay lunch. But I think the point you make, I'm just agreeing with you and saying that other people have actually started moving in that direction, you know, and saying that, you know, we should be -- you know, I think a

lot of the work on ETS got going because people started thinking about it precisely because it was air pollution. And now that we have all of this detailed information, I think it does make sense to go back and think about what does this mean in terms of ambient pollution from other sources. Because I think a lot of this information will carry over in fact.

CHAIRPERSON FROINES: Well, you know, the paper today is all about sea C-reactive protein and inflammatory responses for cardiovascular disease. And clearly tobacco smoke produces inflammatory responses and particles produce inflammatory responses. So that there's some very interesting interactive work.

PANEL MEMBER GLANTZ: Yeah, and it's probably the particulate matter in the tobacco smoke which is causing the inflammatory responses actually.

CHAIRPERSON FROINES: Well, let's break for lunch.

What do we think, 45 minutes is sufficient?

PANEL MEMBER HAMMOND: How long are the lines?

PANEL MEMBER GLANTZ: It's not a long line. There's a food --

CHAIRPERSON FROINES: So we'll be back at 12:45.

(Thereupon a lunch break was taken.)

CHAIRPERSON FROINES: Shall we begin?

Let me try that one again.

Shall we begin?

PANEL MEMBER GLANTZ: Sure.

CHAIRPERSON FROINES: Melanie?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. If it's okay with the Panel we thought we would start this afternoon with the cardiovascular health effects, which is of the last three chapters the most substantive in terms of information. I'm trying to leave room for ARB. They need about an hour.

CHAIRPERSON FROINES: They need an hour.

OEHHA SUPERVISING TOXICOLOGIST MARTY: An hour.

CHAIRPERSON FROINES: Now, an hour is always based on nobody saying anything.

So we need an hour --

ARB AIR QUALITY MEASURES BRANCH CHIEF BROOKS:

About a half hour -- an extra half hour. That's just to get --

PANEL MEMBER GLANTZ: Maybe what we should do is do 8 and then let the ARB talk. And then come back and pick up the other couple. Because I have the impression from just talking to Kathy, I think that she's going to have some things to say.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. That's fine.

PANEL MEMBER GLANTZ: That will let Melanie recuperate.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Bruce Winder is going to be giving the presentation on Chapter 8, cardiovascular health effects of ETS.

(Thereupon an overhead presentation was Presented as follows.)

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. This table has been revised, but it isn't reflected in this particular one.

The 1997 document reviewed 18 studies. This document, I've indicated here 11 studies. In fact that's 8 original studies and 3 meta-analyses.

The conclusions for both the original document and the update are the same, that CHD, coronary heart disease, is in fact conclusively associated with ETS exposure.

Now, part of that is that it's related to these various other endpoints that we're looking at. For example, altered vascular properties, there are 9 studies. And we feel the data indicate that this is now conclusively associated.

In terms of exercise tolerance, there were no new studies in this topic, so our conclusions from the original document remain unchanged.

And then for stroke, that wasn't addressed in '97. It was in two additional studies. But the results there are, at best, suggestive.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now, the cardiovascular effects, as I've indicated here, derive from multiple insults. We're talking about things like myocardial infarction, endothelial dysfunctions, thickening of the carotid wall, loss of arterial elasticity, and promotion of plaque formation.

Now, these are all interrelated. And many of them are the sort of phenomena that cause, for example, the MI listed at the top.

Also related are some of the changes that we see in the blood, for example, decreased HDL cholesterol, decreased anti-oxidant capacity, increased oxidized lipids, increased platelet activation, increased fibrinogen levels, and decreased oxygen carrying capacity. These sorts of endpoints have been documented in several of the studies.

And the net result seems to be an increase in cardiovascular disease of approximately 20 to 50 percent.

Based on the two studies that we were talking about with respect to stroke, there might be an increase in the neighborhood of 70 to 90 percent.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Now, the meta-analyses to which I'm in reference are these three, by He, et al.; Law, et al.; and Wells. You'll note looking at the odds ratios reported here that there's a fair amount of similarity among these. And probably that derives from their analysis of some of the same studies.

In any event, it looks like the odds for -- odds ratio for myocardial infarction, they're about 1.23. And this is statistically significant.

In the study by Wells, he broke out just adult exposures in all work place exposures. And again the ratios -- the odds ratios are in the neighborhood of 1.2, 1.23, something of this nature.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Now, more recent studies tend to support the same sort of finding. This study by Whincup is a prospective study. And the advantage of this study is that this is looking at cotinine levels at least established in baseline. Whereas the previous studies we're looking primarily at a self-report of ETS exposure.

Now, in this study we find that he's using cotinine levels of less than .97 grams per mill, is basically nonexposed. And we find here as you look across

this analysis of either all men in the study or just no former smokers that in fact there's a trend associated with this increasing level of serum cotinine.

He then also looked at the risk associated with follow-up in 5-year increments after baseline. And he finds that during the first 5 years after the start of the study there was a fairly high risk, 3.7. And over time this risk seems to decrease.

Now, it's not clear -- a couple of phenomena are probably at work here. One is that over time, as we've talked about with some of the other studies, some people are no longer exposed. In this particular environment -- this was done in Great Britain -- the incidence of smoking was going down. So the actual ETS exposure is likely also decreasing. And that may in fact be partly responsible for what we're seeing here.

PANEL MEMBER GLANTZ: I'd like to just say one thing about this study, because -- which relates back to the earlier discussion about cohort versus case control studies.

I think this is a very, very well done study. But there's an important detail. And it -- what they did was they -- this was a cohort of -- I think it was men, wasn't it?

ARB ASSOCIATE TOXICOLOGIST WINDER: Yes, it was.

PANEL MEMBER GLANTZ: That they followed for like 20 years. And they drew blood at the beginning of the study. And so the cotinine levels that the analysis is based on was the cotinine at study entry 20 years ago. And they only had that single exposure measurement from 20 years ago.

And I think the fact that they had cotinine makes this probably the best study of heart disease that's been done because by using cotinine instead of a questionnaire-type study, what they've done is they've captured -- they've got an integrated measure of all the exposure that's objective. They've got -- well, it doesn't matter if they were exposed at home, at work, at a bar or whatever.

And the second thing is that the odds ratios -- or the relative risk rather that they computed were all referred to the lowest quartile of cotinine exposures. And, again, that means that that's taking into account not only their, say, spousal exposure, but any background exposure. And the fact that they -- the risk they found associated with passive smoking, if you look at the 0 to 4 year follow-up group, is much higher than anybody's found from the questionnaire studies. And I think that's because the results are not contaminated by background exposure and the kind of misclassification errors that

were being discussed this morning.

The other point that I think is important is that you see that the risks fall with time since entry into the study. And some of that may be less smoking around and that. But it also may be the fact that the relevance of that one exposure measure at the beginning of the study is fading with time. And so the fact that the estimated risk falls with time I think makes this a good example of why, when you are talking about passive smoking, simply doing a cohort study where the whole thing is based on one exposure measurement and entry and you're looking at very long-term follow-up could lead you to be underestimating the risks. And so I think -- I think this is just the absolute best study anybody's done on heart disease.

But I think that this detailed analysis of the relevance of that first measure and also the estimate of background effects from -- which is discussed explicitly in the discussion section of the paper. And you should really look at that carefully. I think this bears very strongly on the whole discussion we had this morning about the cohort versus case control studies for breast cancer.

And in fact I remember, if you look at the paper, it's the last page at the top of the left-hand column is where they addressed these issues. So I would really commend you to carefully look at that and put it into the

discussion of cohort versus case control studies of ETS.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We did do that in response to comments. I'm not sure we've transferred that yet over to the actual text.

PANEL MEMBER GLANTZ: Yeah. I think it's very important.

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ARB ASSOCIATE TOXICOLOGIST WINDER: Now, also germane to our discussion this morning regarding dose response effects, this is a study by Rosenlund, et al. And the important thing about this particular study of myocardial infarction derives from several points here.

For example, these find that at 20 cigarettes per day versus -- excuse me -- less than 20 cigarettes -- greater than 20 cigarettes a day in terms of ETS exposure, there's a definite increase in dose response effect. Whether that's measured in that fashion or measured by number of our years of exposure, again, we see this trend of increasing dose response.

This next set of data is looking at individuals who have since stopped their exposure to ETS, and shows that the risk of myocardial infarction decreases over time. That is to say, in less than one year we've got still an elevated risk. But over time, in this case greater than 16 years, this thing becomes under -- below

background.

The study on the far right is one tends to be included in this particular slide, it's a study by Ciruzzi, et al., showing elevated risk for both men and women, higher for men than women.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Now, to go on to some of the effects that may -- or endpoints that may have bearing on the myocardial infarction. This is a study by Otauka, looking at coronary flow velocity reserve. This is a measure of the coronary vasculature's ability to respond to changing demands on blood flow.

So in the study what they do is measure the blood flow before and after administration of ATP to stimulate hyperemia, the idea being that the better this ratio, the better the capacity of the heart to respond to changes.

Now, what we see at baseline, nonsmokers and smokers are significantly different. That is to say, the nonsmokers have a much better coronary flow velocity reserve, that is, to say a better capacity to respond to dynamic changes. Whereas after just 30 minutes of a single exposure to ETS, while the smokers did not change significantly, the CFVR in the nonsmokers became indistinguishable from the smokers. So this study is significant in that it shows a very distinct and rapid

response to a single exposure of ETS.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Along these same sort of lines there are D studies. This is looking at flow-mediated dilatation. This is in brachial arteries in the arms in both these studies.

The study on the left, Raitakari, is looking at individuals who have either never been exposed to passive smoke or currently exposed to passive smoke and those who are formally exposed. Part of the point behind this study was to find out whether or not the adverse effects associated with ETS exposure decrease over time. And in fact that's what he has observed.

The important thing though is to show that the never smokers have a much better response of the vasculature as opposed to former and current ETS exposed people. The idea here is that in both these experiments, both this Raitakari and Woo, they've exposed individuals also to nitroglycerine to verify that this effect we're looking at here is reflecting damaged endothelium. So the idea is suggesting that ETS exposure has damaged the endothelium so there's no longer this kind of response that allows the body to respond to dynamic changes. This kind of change is often associated with a prelude to atherosclerosis.

Similarly the study by Woo, this is looking at --

CHAIRPERSON FROINES: Could you use the microphone a little bit closer.

ARB ASSOCIATE TOXICOLOGIST WINDER: Sure. There we go.

The study by Woo is looking at casino workers again compared to individuals who are not exposed to ETS.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: These are workers that are exposed for eight hours a day or more for 2 to 20 years. And what they report is there's a significant difference between people so exposed and those not exposed to ETS in terms of the same flow-mediated dilatation.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Further changes that would occur in the blood as a consequence of ETS exposure were investigated in this study by Valkonen & Kuusi.

Here they're showing that just six hours following a 30-minute exposure to ETS, Vitamin C content of the blood drops by about 25 percent. Similarly the reducing capacity measured in sulfhydryl capacity drops by about 21 percent. The oxidizability of --

CHAIRPERSON FROINES: How do they measure the

drop in --

ARB ASSOCIATE TOXICOLOGIST WINDER: This is looking at traps, total sulfiderols.

PANEL MEMBER BLANC: Can I ask, what in your mind is the difference between these series of studies that you're now presenting related to various in vivo and in vitro vascular effects and the data that you began presenting related to cardiovascular disease outcomes?

ARB ASSOCIATE TOXICOLOGIST WINDER: Well, this is showing what some of the changes are that may be causing those cardiovascular disease outcomes, changes that are associated within the blood, changes associated with avascular, this kind of thing.

PANEL MEMBER BLANC: Would it be safe to say that you view these data as being supportive of a causal association for the epidemiologic observation or are you rather trying to argue that these are health endpoints which you wish to separately evaluate?

ARB ASSOCIATE TOXICOLOGIST WINDER: I would look at these as mechanisms that are involved in the etiology of the endpoint of where this cardiovascular disease --

PANEL MEMBER BLANC: Because it is actually hard to tell that from your tabular presentation. Everything is all in one huge table.

It is also not so easy to tell from the tables

what in fact the cardiovascular disease endpoint was that was measured in the various studies. And since one of the things that would be supportive of your already conclusive association would be that the expected family or constellation of cardiovascular disease endpoints are all occurring if they're looked at that one would anticipate would be the manifestations of coronary artery disease or accelerated coronary artery disease. It would be helpful, therefore, to the extent that you have epidemiologic studies that looked at all cardiovascular death or looked at acute MI or looked at atherosclerotic congestive heart failure separately to make clear which studies had which endpoints. I would find helpful. I don't think it's going to alter your ultimate conclusion, but it is a little bit of a sort of a --

PANEL MEMBER GLANTZ: Well, I actually think these should be viewed as another health endpoint. Because the thing which is really most of the -- or in fact all the things that they're showing here and the great bulk of the work which has been done on vascular and endothelial function has been since the 1997 report.

And there are two things about this that I think are important. One is that it helps explain the elevation in risk that you see in the epi studies and the fact that the relative risks for active smoking or -- pardon me --

for passive smoking are much larger than you would expect if there was a linear dose response relationship to the passive smoking levels. And, in fact, the Whincup paper we talked about earlier showed risk profiles for passive smokers that were essentially identical to light smokers.

But I also think that one of the important new endpoints here is these vascular changes occur within minutes. And that's in terms of looking at the questions of acute toxicity, something that's important. And if -- and these kinds of changes in platelet activation, vascular reactivity and that could precipitate an acute event.

PANEL MEMBER BLANC: It is not in fact an acute --

PANEL MEMBER GLANTZ: Pardon me?

PANEL MEMBER BLANC: But is isn't an acute event.

PANEL MEMBER GLANTZ: No, it could -- these things could -- or have been -- you know, if you look at what people think the dynamics are of the precipitation of an acute myocardial infarction, these changes are among the things that actually cause the infarct to happen at the time that it happens.

PANEL MEMBER BLANC: Certainly I would never argue that these studies aren't relevant to the report or that they're not relevant to the causal association. But

I think that -- but if the attempt is made to treat these as health endpoints in and of themselves in the usual manner, it would I think sort of box OEHHA in in a way that would be -- that would weaken rather than strengthen its argument.

PANEL MEMBER GLANTZ: Oh, I don't agree with that at all. I think that it's a different class of effects. And I think that the -- the development of chronic coronary atherosclerosis. And I don't think this stuff -- passive smoking and heart failure's been looked at all that I -- at least I can't think of anything.

But, you know, the atherosclerotic process is sort of the end result of a lot of these acute effects. I mean the increased platelet activation or compromising endothelial function, those things over time contribute to the development and the oxidant effects of the smoke and things like that. All contribute to the development of an atherosclerotic plaque. But in terms of the acute precipitating event that occurs with the -- that generates a heart attack and makes a heart attack worse, these things are also acute. And so I really do think they are two different endpoints that need to be looked at.

And so while I think all of this stuff is supportive of showing you the mechanisms for the epidemiology, I mean these kinds of things in terms of

endothelial function, nitric oxide metabolism, platelets, I mean that's like a very hot area in clinical cardiology right now. And doing interventions directed at reversing some of these effects is a large part of what people do to treat acute coronary disease. So I think they should be kept separate. They support each other, but they're really two different things

CHAIRPERSON FROINES: I think this discussion is an important one because it speaks to a general problem, which is, as he said, the endpoints that's on the slides right now relate to, in a sense, the first stage of health effects, which is the pathophysiologic changes that have mechanistic significance. Then there's another stage where one tries to understand those mechanistic changes in terms of -- in terms of health outcomes. And that process of going from the mechanistically based studies to the health event itself is actually something that we sometimes fall into almost a religious belief that what this -- when this occurs, that leads to this. But we don't understand very well the process that leads us to that point.

And so it's --

PANEL MEMBER GLANTZ: Well, I think --

CHAIRPERSON FROINES: What he's showing is basically a mechanistic statement that oxidative stress is

involving cardiovascular effects that probably relates to some belief of inflammatory processes, and so on and so forth. But then you -- but then one has to make a leap from that inflammatory process and oxidative stress effects to a heart attack.

PANEL MEMBER GLANTZ: Yeah, but you see, I think --

CHAIRPERSON FROINES: Let me just finish. Let me finish. I listened patiently when you were talking.

And I think that there is a gap that isn't entirely possible to lay out. So it's very difficult.

It seems to me that this is interesting data from a mechanistic standpoint, but it is not consistent with an explanation for a heart attack.

PANEL MEMBER GLANTZ: Well, I think that -- I don't agree with you. I think this is the -- I think these gaps that you're talking about very often exist. But I think in particular in terms of the relationship between acute effects on lipids -- pardon me -- on platelets and on endothelial function, production of nitric oxide, that stuff is actually pretty well understood now in the last few years. And also the role that all of this plays in triggering an acute coronary event, I mean this is stuff -- all of this stuff is pretty new. But I mean when you go -- I mean people in textbooks

now have nice little pictures showing how depressed nitric oxide production, which is also tied up in all of this, is related to plaque rupture and increased platelet activation is related to plaque rupture, increased risk of thrombosis with a rupture. How increased oxidative loads acutely affect platelet activation, endothelial function, availability of nitric oxide. I mean we've done some of the work showing just acute clobbering of an enzyme called nitric oxide synthase, which is very important in all of this.

So I actually think -- I think the general statement you made is true. But I think for this specific thing, there's been a huge amount of progress made in a basic understanding of all this in cardiovascular function. And so I think that there aren't very many holes left. I mean the holes now are getting down to like, you know, very detailed sort of where the molecules break kind of things, not that these connections exist or that -- their importance of their role acutely. I mean there are drugs on the market designed to counteract this right now.

CHAIRPERSON FROINES: Well, I know -- I'll let Paul respond in a second. But let's just take the NO Synthase. I mean we produce inhibition of NO Synthase all the time with our quinones in the laboratory through both

electrophilic and an oxidated stress processes.

And we get changes in blood pressure, we get changes in heart rate. But we don't get heart attacks. And I would maintain that the work that we do looking at the inhibition of -- both reversible and irreversible inhibition of an enzyme that leads to the production of NO doesn't necessarily take you to the CHD.

And so I would still argue that there is uncertainty between the two. In one case it represents a biochemistry mechanism and the other case it represents a health outcome. And there is -- I agree with you that there is linkages now, but one has to be careful about that.

PANEL MEMBER GLANTZ: But, you know -- but in those animal experiments you probably weren't dealing with atherosclerotic animals where you had a plaque already. And, you know, it's true. I mean people have inhibition of nitric oxide synthase all the time. All these effects are going on all the time. And there's really -- there's really two different ways that this stuff plays in terms of the relationship between secondhand smoke and heart disease.

One kind is the sort of long-term accumulation of risk by the sort of little bit of damage that you do each time to the vascular endothelium and other things. And

over time which facilitates macrophages getting into the wall and all this other kind of stuff. And over time you -- that contributes to the development of an atherosclerotic plaque. That's a very slow mechanistic type thing. But there's also loads of new data showing that once you have the plaque, that these kind of changes are very important in terms of precipitating an acute coronary event.

If you have an artery which is nice and clean and you do this, nothing will happen acutely. But if you've got an artery which has already got a plaque, these kind of things can contribute to a thrombosis or a plaque rupture or reduce the ability of the arteries to vasodilate to compensate for the blockage. And that stuff is all well worked out in laboratory studies, in human studies. It's just textbook cardiology now.

So I think -- that's why I think these things should actually be viewed both as mechanistic support for the epidemiology, but also as an important health endpoint. And that's why the CDC is now saying to people with heart disease they shouldn't go into smokey bars, because --

CHAIRPERSON FROINES: That then means -- all I'm going to say, and then I'll stop, is if you want -- to address Paul's issue, if you want to use this, then you

have to make the connection. You're arguing that the connection has been made. And I'm only simply saying that if you want to make that leap, then you need to make sure that the connection is described.

PANEL MEMBER GLANTZ: Well, I thought it was in the report. And the other thing is the way -- if you go back a slide or two to where you had your conclusive versus inconclusive, I mean I think the way they've worded it there where they're talking about altered vascular properties, I think that's a nice clear --

PANEL MEMBER BLANC: Altered vascular properties is not a clinical entity. And everywhere else in this document we are talking about clinical health outcomes which are recognized clinical entities.

Now, if you would like a document to have two clinical outcomes, one of which is chronic coronary artery disease and the other one of which is exacerbation of preexisting coronary artery disease with acute MI, all the power to you. And if they have the data, they should do it. But what you are forcing by using this kind of terminology in this structure is saying that you're going to call something conclusive which you have not one piece of epidemiologic data.

PANEL MEMBER GLANTZ: Well, I don't think -- there's other things you can do besides epidemiology. You

can go to a laboratory with people or with animals and induce these things. I mean maybe it should be called something -- I'll go talk to my cardiology buddies. Maybe calling it something like -- different than alter vascular properties would be -- but, you know, these things are just -- this is like probably half the grand rounds in cardiology now and in treatment. Deal with treatment of this --

PANEL MEMBER BLANC: Stan, I don't know if you're listening to me. I'm not arguing that this is not relevant. I'm not arguing that it's not causally relevant. I'm not arguing that it's not relevant to the issue of does secondhand smoke either cause or aggravate cause to -- or aggregated preexisting coronary artery disease. I think those are real issues. I think the data are very convincing.

I'm really talking about trying to be consistent in a very large document so that we don't go down some slippery slope where we're using different criteria for one chapter than we're using in another chapter. And that comes back again to the discussion I still hope that we will have about what is it that you are actually calling conclusive or suggestive, you know. In fact, would you call something conclusive that has no epidemiologic data whatsoever? Maybe you would. Maybe I'm off base, because

you've decided that for certain endpoints which cannot be studied epidemiologically you would not require any epidemiologic data and only in vitro data or a small experimental short-term exposures would matter. I don't know.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I think that -- in this case these are studies in humans. They're experimental studies in humans and they're -- these effects are clearly there. I don't see why you would -- you know, all the other endpoints that we've been talking about have been based on epidemiologic studies, with some support from animal data or toxicology data. This is basically a toxicology study in a human. And I -- maybe people don't like the terminology because it's sort of epidemiology terminology, but I think it's safe to say these --

CHAIRPERSON FROINES: But Paul and I are both saying the same thing. We're talking about connecting the dots. And the dots here are not connected.

PANEL MEMBER BLANC: I think I also would like to hear from some of the other panel members. I mean Stan and I disagree on this. But I have no idea what the other people are thinking. I mean I'll shut up if I'm so completely off base, you know.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Another way that you might look at it too is that -- which has already been discussed -- these altered vascular properties are the result of an acute exposure. This is like an acute toxic effect in humans. I think you can make the --

PANEL MEMBER BYUS: Different cancer mechanism that we're talking about.

PANEL MEMBER HAMMOND: It's not only acute, but it's reversible.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, right.

PANEL MEMBER HAMMOND: Which I think is important, because that make it -- if it's acute and reversible, that makes it a harder thing to study epidemiologically.

PANEL MEMBER BLANC: But you're arguing that --

PANEL MEMBER HAMMOND: And I'm not sure that that's necessary, frankly. But -- Oh, I'm sorry. Did you want to comment?

PANEL MEMBER BLANC: Well, I was just going to say one thing. You're arguing, for example, that the study of this temporary smoking ban that was reversed with the increase in myocardial infarctions is an epidemiologic study which supports this --

PANEL MEMBER HAMMOND: I didn't say that.

PANEL MEMBER BLANC: Stan.

PANEL MEMBER GLANTZ: Well, I think that does support it. But I think had we ever even done that study, it doesn't -- I mean these are effects, as Melanie said -- I think -- the way I think about -- and I think it's also what Craig said -- this is acute toxicology done in humans. It's different than looking at a long-term epidemiological result in a large population. But these are effects that are well recognized in, you know, zillions and zillions of patients.

And, you know, this -- if you're worried about logic, this would almost be like when we were looking at acute non-cancer effects. But these are very real and they're very important, I think. And they're important a) to understand the epidemiology in terms of the biology of why we see the relatively big increases in risk you see in the epidemiology studies. But I think -- I feel very strongly that the -- whatever you want to call it. And I can go find some clinical syndrome name if you want. This is a tremendously important acute effect. It's very, very, very well documented. And almost all of the evidence for that connection's been published since 1997.

And we have a huge review paper that's just about accepted dealing with this. So this is literature I know

really well. And it's very important. And it's not just biological plausibility. This is an important cardiovascular outcome that is mostly reversible. Nobody's really studied it totally. It's not completely reversible, because the cumulative effect of this is the development of atherosclerosis. And these effects that people detect in terms of vascular reactivity in that occur way before you see any kind of hemodynamic changes, like heart rate or blood pressure, anything like that. In most of these studies you don't see effects in gross hemodynamic variables at the levels that produce these changes in vascular function and platelet function. And they're all mediated through common pathways probably.

So this is very well understood.

CHAIRPERSON FROINES: I still would maintain that the blood --

PANEL MEMBER GLANTZ: Maybe it isn't --

CHAIRPERSON FROINES: -- anti-oxidant profile where you're measuring Vitamin C, which is an electron donor, the binding of sulfhydryl groups, the oxidation of LDL, and so on and so forth, those are mechanistic studies. Those deal with pathophysiologic changes.

PANEL MEMBER GLANTZ: Right, those --

CHAIRPERSON FROINES: They are not health outcomes.

PANEL MEMBER GLANTZ: No --

CHAIRPERSON FROINES: And so this goes to oxidative stress. It doesn't go to what you're talking about.

PANEL MEMBER GLANTZ: But what those things do -- and I don't want to --

CHAIRPERSON FROINES: Then it should be in a section that addresses the mechanistic underpinnings to justify that passive smoke causes cardiovascular disease.

PANEL MEMBER GLANTZ: No, I haven't looked at this section of the report in a while. But it is these kind of oxidative stresses which lead to the changes in platelet activation and -- I mean to me the biological endpoints are the changes in vascular reactivity and platelet function. The oxidative loads, the changes in oxidative donors and anti-oxidants and all of that, I agree with you. Those are not outcomes. Those are the mechanisms which explain the changes in vascular function.

But the changes in vascular function to me are themselves an important health outcome if you're thinking in terms of acute effects, just as we were thinking -- you know, in the other documents we've done looking at acute effects.

The changes in lipid metabolism acutely are -- I agree with you there. Those are explaining the

mechanisms. The way they get manifest in terms of the way the heart's working, the vasculature's working is in reduced vascular reactivity and increased platelet aggregation. That to me is the health outcome. This other stuff is explaining it. And maybe this is another place. They just need to edit the report appropriately.

ARB ASSOCIATE TOXICOLOGIST WINDER: Would it make sense to try and put these sorts of observations into a separate section?

OEHHA SUPERVISING TOXICOLOGIST MARTY: They're in a separate section.

PANEL MEMBER HAMMOND: I think what I'm hearing is -- and I'm looking at this table, Table 8.1 in the summary of -- no -- yeah, summary of studies, and there are different outcomes. I think maybe like primary outcomes, which are heart disease. And then these other -- and I'm not sure. I mean I really would defer to people who know the medicine better whether these are medical outcomes or whether they're mechanistic. I mean to me they're extreme -- but the important thing is I think these are very important findings that help us to understand the primary outcomes.

But I think the primary outcomes are coronary heart disease, you know, and some of the -- and also I think again this is where you can get lost in the detail.

Pull something out that highlights the main things that it's all about, that people care about, and then you can have another table or section of the table that perhaps focuses on either what you might call secondary outcomes or less important outcomes or mechanistic outcomes. Or I'm not sure what the terms should be. But I do think it's useful to make some distinctions here.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have it in the text under "Other Pathophysiologic Evidence," and then they're described. But in the tables we did not separate it. And so that one fix would be to separate that out totally, have the heart disease studies in one table and then this other evidence in another table just to help the reader.

Another thought might be in your summary table to indicate that altered vascular properties is not a clinical outcome, but it is perhaps a subclinical health endpoint.

CHAIRPERSON FROINES: It's a mechanistic endpoint. Some of the studies -- I mean there are differences. And the one I picked on was the oxidative stress one. But there are other -- NO Synthase is obviously -- you know what I'm saying.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Um-hmm.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah, I think I understand the arguments.

I would recommend pulling that altered vascular properties out, just put in a section called "Mechanistic Considerations/Precursor Lesions or something like that. And I think that might make it more clear.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So change the table from Altered Vascular Properties to --

PANEL MEMBER LANDOLPH: No, leave the table like it is. Just pull the altered vascular properties out.

PANEL MEMBER GLANTZ: Well, see, I --

PANEL MEMBER HAMMOND: Maybe a new table would --

PANEL MEMBER GLANTZ: Well, see, now I -- I mean we could think of a different thing to call it. But I think that is an important outcome. I don't think it's just mechanisms.

You know, the --

PANEL MEMBER LANDOLPH: Do you think it's a precursor lesion? Do you think there's a precursor --

PANEL MEMBER GLANTZ: I think at one level the altered vascular properties are precursors to development of atherosclerotic disease. But at the same time they are also acute events that precipitate heart attacks. And so I think that it's playing two different roles.

But I can tell you -- I mean the reason they tell

people to take aspirin is to prevent this kind of stuff. And the reason they say to someone, "When you've had a hard attack, take an aspirin" is to try to reverse these kinds of changes. So they're very, very important clinical events, in addition to -- in addition to helping to explain that epidemiology.

Now, as I say, I haven't looked at this part of the report lately. They definitely should be treated separately from the epidemiological studies, you know. And if they're not, they should be.

OEHHA SUPERVISING TOXICOLOGIST MARTY: They're in different sections.

PANEL MEMBER GLANTZ: Yeah. But I think the altered vascular properties, or if we come up with a better thing to call it, is an important endpoint in and of itself also. Not the oxidative stress. That isn't. That's clearly mechanistic toward altered vascular properties.

CHAIRPERSON FROINES: Well, I can accept that.

PANEL MEMBER GLANTZ: Okay. I was quiet this morning.

(Laughter.)

PANEL MEMBER FRIEDMAN: And the clinical things we're talking about are heart attacks and strokes. And this seems to be something farther along the line to

producing heart attacks and strokes. But it's not a disease. I mean you don't go to the doctor because you have some problem with your endothelium unless it leads to some --

PANEL MEMBER GLANTZ: Oh, yeah. No, they treat --

PANEL MEMBER FRIEDMAN: I know that's one of the things that is treated, but it's to prevent the clinical events of heart attacks and strokes. So I view it as a mechanistic type of thing but farther along the line than oxidative stress.

PANEL MEMBER HAMMOND: Let me be very naive. This is -- I'm probably totally off the wall. Is blood pressure -- is high blood pressure a disease?

PANEL MEMBER BLANC: Yes.

PANEL MEMBER HAMMOND: But you don't actually die of high blood pressure, right? High blood pressure leads to something else like strokes, is that right?

PANEL MEMBER FRIEDMAN: We're getting into semantics now.

PANEL MEMBER HAMMOND: Well, but I think it's the same semantics, isn't it?

PANEL MEMBER BLANC: No.

PANEL MEMBER HAMMOND: No? Okay.

(Laughter.)

PANEL MEMBER GLANTZ: Well, I don't agree. I think it is very much the same. No, I think it is very much -- I think that the high blood pressure is a good example. I mean that is something -- people who have, you know, abnormalities in platelet function and depressed vasodilatory capability, I mean there are people who are working on drugs to try to restore that. And --

PANEL MEMBER FRIEDMAN: I know, but you wouldn't -- hypertension is asymptomatic. And if it didn't lead to strokes and heart attacks and renal failure, you wouldn't worry about treating it.

PANEL MEMBER GLANTZ: I understand that. But also if you were looking at -- if you're talking about what are health outcomes, I mean we have done reports where one of the health outcomes that we looked at was increased risk of hypertension. I don't remember what it was in, but that was one of the things I remember, where we were looking at that you had a small increase in the distribution of blood pressures. And I think this is -- this to me, this change in vascular function is a health outcome. It's not a death. But it is -- you know, when you're setting things like reference exposure levels and that, you know, people are looking at when is there some substantial biological effect. And this is a very substantial biological effect that we need to talk about

in this report.

It's different than having a heart attack.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Well, you know, what might help out a lot -- I'm thinking of the carcinogenesis diagrams we always draw initiation, promotion, step 1, step 2, and progression. Maybe you ought to consider putting a line diagram in here with the various events and how they're connected, to give it an intellectual framework to it.

PANEL MEMBER GLANTZ: No. I mean I can work with them on that. I mean that's in textbooks on cardiology.

CHAIRPERSON FROINES: Well, I think that -- let me just give you an example. I mean it seems to me that -- just one example is that passive smoke causes -- constituents of passive smoke cause inhibition of NO Synthase, which results in changes in endothelial function for a number of reasons which we could describe. And the changes in endothelial function end up producing -- end up producing higher blood pressure. And then higher blood pressure ends up producing strokes. So to the degree that you can draw -- you can create a map that shows the process, that's very useful.

And so the point though is, that endothelial function, do you call that a health outcome? I would

argue it's not. It's part of the process, like inflammation, that leads to the health outcome.

And so the question is: How do you address it in this document?

PANEL MEMBER BLANC: Well, let me bring up an example and see if we can start to get at this at the level of how you've actually written the document.

First of all, in the separate sections that follow it does not follow the divisions that you've delineated. So there actually isn't any way in the sections that follow to know which is you're saying is part of the altered vascular properties and which isn't. And the order doesn't follow the table in terms of the listings. So you have stroke -- stroke is the last thing you talk about, but stroke is discussed before a lot of the vascular things.

Let's take Howard, et al., 1998, that study, which is in your table. It's on page 8-6. It's a longitudinal study of current past and passive smokers with change in intima-media thickness of their coronary arteries.

Which shows that in fact having secondhand smoke exposure is a risk factor for having more thickened --

ARB ASSOCIATE TOXICOLOGIST WINDER: -- increase in the intima-media thickness.

PANEL MEMBER BLANC: Which is another way of saying it's a risk factor for atherosclerosis, which is a disease.

Now, where have you put that? Is that in your altered vascular properties?

ARB ASSOCIATE TOXICOLOGIST WINDER: I think that fell into supportive evidence.

PANEL MEMBER BLANC: For what?

ARB ASSOCIATE TOXICOLOGIST WINDER: For the atherosclerosis.

We're looking for it here.

PANEL MEMBER BLANC: I mean it's really not possible to tell from the text or the table what you're considering --

PANEL MEMBER GLANTZ: Well, I think -- I mean I can work with them on this. I mean I would say in terms of that specific study that it actually supports -- it relates in terms of both things. I think it is -- it is along the pathway of how you get heart disease. It's also part of the constellation of changes that are associated with these altered vascular properties.

Although the kind of things I was thinking of more are the acute changes, the acute reductions in vascular reactivity, the acute increases in platelet activation, which sort of combine to increase the

likelihood of a plaque rupture or a thrombus, you know. I mean that's -- anyway.

PANEL MEMBER BLANC: But then the Helena study, which is given considerable text -- more than a page of text -- which is a study of an abrupt change in acute MI, in temporal relationship to a ban in -- a reduction in secondhand smoke exposure, correct?

PANEL MEMBER GLANTZ: Yes.

PANEL MEMBER BLANC: So that is not a study that is looking at the chronic effects of secondhand smoke on myocardial infarction risk; it's a study which is only looking at the acute effects?

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER BLANC: So why wouldn't that be a study which is relevant to your outcome of acute exacerbation of atherosclerosis or acute vascular --

PANEL MEMBER GLANTZ: Well, I mean, again I don't want to -- I think that study -- the Helena study sort of again relates to the epidemiology, because it -- I mean unlike most of the epidemiological studies, the Helena study, that was -- for those of you who haven't memorized all this, Helena is a city with one hospital. They banned smoking. Myocardial infarction admissions to the hospital dropped. The law got suspended and they went back up again.

And that sort of natural experiment I think does two things: It supports the epidemiological findings of the long-term studies. And then when you look at the question of why would you expect such a big change so fast, that most people who've looked at that think it's because you're mostly seeing these changes due to changes in this acute vascular effects. And the -- see, my personal view is I think of that 1.25, 1.3 relative risk that you see in the long-term coronary disease epidemiological studies, I think a big hunk of that is due to the acute exposures. It's not like cancer where there's a sort of gradual effect. I think a lot of that effect is immediate, because when you stop -- when people quit smoking, their risk of heart attack drops very quickly, which again is quite different from cancer where things take much longer.

But I mean it may be that some of this stuff is again a matter of how it was presented. But I think these things are very important as -- these acute vascular effects are an important outcome, health outcome too. I mean we could call it -- it's not a disease, I don't think. It's got an ICD9 code. But I think in the context of a lot of other things we've looked at where if you looked for acute health effects, this is clearly within that constellation of the kind of effects that we've

talked about before.

I mean the report will -- I mean I won't vote against the document if this is taken out. But I think it's an important thing to keep in there. But I've said this five times. Let --

CHAIRPERSON FROINES: I think we're talking more about the structure of the chapter rather than the --

PANEL MEMBER GLANTZ: Right. And I can work with Melanie to clarify this.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly.

PANEL MEMBER GLANTZ: If it's all mixed up together, it shouldn't be.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It looks like, just paging through, first we did the epi studies on heart disease risk, then we got into more epi studies that were looking at slightly different things, and then we started getting into the pathophysiology. Some of it should probably have been moved into a different section. I think it's pretty easy to do.

And then I have a suggestion about the table that it hopefully would make Stan happy and Paul happy and others happy. That if we -- instead of calling it --

(Laughter.)

PANEL MEMBER BYUS: Are you going to make me happy?

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: You know, instead of just saying altered vascular properties, which, you know, you can argue whether that's a clinical effect or not -- it's certainly a subclinical effect -- we might want to just say other toxic effects dash vascular -- or cardiovascular system, and then indicate that these were human studies, short-term exposures, they do see acute effects. And then keep the discussion we have in here about how that might be related to triggering an acute coronary event.

Would that be better?

PANEL MEMBER HAMMOND: I certainly think Section 8.1 could be divided up. It is a very long section. And if you divided it up and put a few subtitles, I think that that might help.

OEHHA SUPERVISING TOXICOLOGIST MARTY: A lot.

CHAIRPERSON FROINES: I guess I'm still the person who would argue that there are effects that you measure that have relevance to the mechanism that I wouldn't classify necessarily as a subclinical effect.

The inhibition of various enzymes by lead may lead to subclinical effects like --

PANEL MEMBER GLANTZ: -- hypertension. That was the report.

CHAIRPERSON FROINES: But I wouldn't call the inhibition of the enzymes nor the oxidation of LDL nor the inhibition of nitric oxide synthase nor the Glutathione GSSG ratio, all those things, I wouldn't classify those as subclinical effects. Those are at a stage before. And I'm arguing that it's a -- that what we wanted in the long run is to be able to combine the various steps of the process that ultimately lead you to the heart attack. And the complicating feature about cardiovascular disease is the chronic versus acute elements of it that add complexity to it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think that -- you know, part of the problem might be the way we put together the presentation, because we're -- we talk about it in the summary as a mechanistic basis for some of these observations might be this compromise anti-oxidant defenses and so on.

There are clearly studies that we're talking about that directly measured vascular properties. And that's in a class in itself. But that the rest could be by the miscellaneous.

CHAIRPERSON FROINES: Well, then I would put a section on saying mechanisms -- mechanistic studies that enhance our understanding of the ultimate health outcomes, and not necessarily just throw it in as a sentence or two

in the conclusion.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We can do that.

PANEL MEMBER BLANC: What you might do as the first step, Melanie, is add a -- before you divide up the first huge table -- that's not the first table, but the big table -- into sub-tables, put in an extra column there, which actually says what the health outcome is that this study is -- or health outcomes if it looked at more than one. See if you have a sense of what the actual health endpoint was. Was it acute MI? Was it atherosclerosis, you know, measured angiographically or radiographically? I mean what was it?

And then once you do all that, then why don't you see. Because what you've got -- what you're promising the reader in Table 8.0 is that you now have 18 plus 11 studies of coronary heart disease. And I guess that's the term that you used before, so that's the term you want to use now?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. We did that to avoid confusion.

PANEL MEMBER BLANC: Instead of atherosclerotic heart disease or coronary artery disease or -- it's not the most common term.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, it's

not. But it sort of lumps those things together.

We do have, I might note, on Table 8.1 an "outcome" column. So it does have like MI --

PANEL MEMBER HAMMOND: Well, that's the numbers --

OEHHA SUPERVISING TOXICOLOGIST MARTY:

-- death --

PANEL MEMBER BLANC: Anyway, and then you promise the reader six previous studies about altered vascular properties with nine additional ones, which makes you go from suggestive to conclusive. That's your big change, right, in this chapter?

So maybe one of the reasons I focused on it is because it is the one that you're going to have to defend the most. And it seems to be a bit of a grab bag. There is heterogeneity views here clearly on whether or not that is a health condition or whether it is an important series of studies that need to be included and need to be analyzed but aren't in and of themselves a health outcome. And partly you're locked into it because I guess the last document was structured that had this, and so you didn't really think much about it. You just went forward and did again what you did last time.

And maybe what in the end will solve the problem will be a paragraph in the introduction which says, "We

recognize that altered vascular properties are not in and of themselves a health outcome. However, we have treated them for the purposes of this analysis partly because they were treated that way in the last document and we wish to be consistent and avoid confusion that might arise by combining it with others, and also because it is relevant to two types of outcomes that we can't tease out effectively from the epidemiologic data. One is chronic coronary artery disease and the other is acute exacerbation of preexisting coronary artery disease."

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think that's good.

PANEL MEMBER BLANC: "We have one epidemiologic study which is quite relevant to that which we'll be discussing at some length, as you will see in Section 8.3," blah, blah, blah, blah, blah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Another thing is we could have two separate tables, outcomes CHD and stroke, which are clear, and then a separate table talking about altered vascular properties in exercise tolerance. I'm not sure exercise tolerance would be considered a --

PANEL MEMBER HAMMOND: You don't have anything -- you have nothing to put into that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- disease

or --

PANEL MEMBER HAMMOND: -- you have nothing to put into that table.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, we --

PANEL MEMBER HAMMOND: Because there are no new studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: There's no new studies. But we want to report what we did before and so on.

PANEL MEMBER BLANC: Would you live with that, Stan?

PANEL MEMBER GLANTZ: Yeah, I mean, well, I'll -- I mean they definitely shouldn't be all mixed up.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

CHAIRPERSON FROINES: There is a difference between some of the biochemical things --

PANEL MEMBER GLANTZ: Yes.

CHAIRPERSON FROINES: -- and the altered vascular properties. I mean -- so there are stages on the gradient.

PANEL MEMBER GLANTZ: Right. No, I think this can be -- I think --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We can fix it.

PANEL MEMBER GLANTZ: We'll work together and come back with something that will hopefully make everybody happy.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We can keep going on the presentation.

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now, based on the idea that this ETS is causally associated with myocardial infarction, in '97 you see the estimates up here for excess cardiovascular death, both for California and the U.S. And in our update we're indicating about 1700 to 5500 deaths in California and roughly 23,000 to about 70,000 in the U.S.

These are based on -- the range here is based on a lower odds ratio of about 1.2 and the upper one roughly -- what is it? -- 1.6, 1.8.

CHAIRPERSON FROINES: Can I just quickly go back to the previous debate and discussion.

When you work on this Stan and get something drafted, can I take a look at it? Because we're working on cardiovascular disease and air pollution all the time. And I just for personal reasons would be interested in what we're doing versus what you're writing about, because I think there are things that overlap.

Go ahead. Sorry.

PANEL MEMBER HAMMOND: On this table, I think --

when I first saw this I was going like "huh?" There's some things that seem strange. Because if you look at the U.S. numbers, the numbers go lower and higher than the '97 estimates; whereas the California numbers go lower and lower. But actually then I thought about it some, and I had some idea of why. But I think it's worthwhile discussing those reasons. You know, in other words, part -- certainly in California the estimates for lower risks relate partly to the fact that there are fewer people exposed now to secondhand smoke, right?

ARB ASSOCIATE TOXICOLOGIST WINDER: Uh-huh.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

PANEL MEMBER HAMMOND: So I think -- but it's important to say that and to say how that's done.

And I'm not quite sure why the -- and I think there's also an underlying lower rate of death from heart disease. I don't know if that's true from '97. But, you know, the trends have been lower. So that's another reason that this goes down. But that should have then made the U.S. numbers go down. So I'm not sure why the U.S. interval becomes wider. Is there a wider conference interval in the actual understanding of the point estimate of the relative risk or --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, the --

PANEL MEMBER HAMMOND: And so I just think it's worth -- you know, what are the contributors to make these numbers change? Because its confusing to look at it first.

ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, we can add some clarity to that.

PANEL MEMBER HAMMOND: I mean I have all these thoughts in my own head. But I think it should just be there.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now, if we look at these studies regarding stroke, here we have two studies, one by You, et al., one by Bonita.

The study by You, et al., is a case control study. And the one by Bonita is looking at all forms of stroke, both fatal and nonfatal.

And what they show is that -- with respect to You, spousal smoking, that is to say exposure to ETS from the spouse, is associated with -- significantly associated with stroke in this whole group. Now, whole group in this particular instance also included active smokers.

The ever smokers, this -- you see the ever exposed on the left-hand side. And it's making reference to just ETS exposure. So You, et al., finds that among just ETS exposed there is an elevated risk that is now

significant. Whereas for the whole group, which includes those ex-smokers, stroke is in fact elevated.

Bonita on the other hand finds that from both men and women there is a significant elevation in the risk of strokes associated with ETS exposure.

Now, this is -- the involvement of ETS is further emphasized over here on the right. This is an analysis looking at the effect of active smoking on stroke risk in comparison to nonsmokers with and without ETS versus nonsmokers totally without ETS.

And the important point here is that when your referent group has no ETS exposure at all, the risk is substantially higher, as opposed to this estimate in which the ETS -- or, excuse me -- the referent group includes those exposed to ETS. So this again supports the role of ETS in the stroke risk.

PANEL MEMBER HAMMOND: And I guess I would just ask how -- is the comparison group in the You or the Bonita for the passive smoking -- is the comparison a group of people who its well established don't have ETS exposure?

ARB ASSOCIATE TOXICOLOGIST WINDER: Not terribly well.

PANEL MEMBER HAMMOND: And I think that's worth -- I think that's a message that needs to kind of

keep bringing brought out. When the comparison group probably has some ETS exposure, we need to say that.

ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, that's the reason we pointed out this right here.

But you're right, I need to emphasize it more for You.

PANEL MEMBER HAMMOND: Well, I would assume that in that. But that's what I couldn't tell is looking -- at least from this, you know.

So that if you look at the -- the NS there is nonsmokers?

ARB ASSOCIATE TOXICOLOGIST WINDER: That's correct.

PANEL MEMBER HAMMOND: It's all nonsmokers?

ARB ASSOCIATE TOXICOLOGIST WINDER: In this particular -- this one is all nonsmokers.

PANEL MEMBER HAMMOND: No, to the left.

ARB ASSOCIATE TOXICOLOGIST WINDER: Oh, over here.

PANEL MEMBER HAMMOND: Are these -- I'm confused what those three bars are. Are those --

ARB ASSOCIATE TOXICOLOGIST WINDER: Oh, okay. These are nonsmokers. This is men and women. And all I've done here is separate out the men.

PANEL MEMBER HAMMOND: And they're non -- this is

ETS exposed nonsmokers compared to -- or is this nonsmokers married to smokers compared to nonsmokers not married to smokers?

ARB ASSOCIATE TOXICOLOGIST WINDER: Well, it includes that. And I believe it's ETS exposed work and home.

PANEL MEMBER HAMMOND: Work and home?

ARB ASSOCIATE TOXICOLOGIST WINDER: Yes.

PANEL MEMBER HAMMOND: Okay. So it's at least a little better effort to deal with.

ARB ASSOCIATE TOXICOLOGIST WINDER: Right. But you're right in terms of the comparison group. It's --

PANEL MEMBER HAMMOND: But I think it's an important message that could be carried through the document. Kind of the stage can be set in Part A, you know, that the comparison group is very important. Pick a few of the good examples, even within -- maybe Part A could add that in too to say how important the exposure assessment is. But the comparison -- you're absolutely right, the bars to the right and earlier in the breast cancer used similar information that when you compare smokers to all nonsmokers or to nonsmokers who also have no passive smoking, you get different results implies that there's an effect from the passive smoking. And I think all studies should always be looked at in terms of how

good is the comparison -- how clean is the comparison group.

PANEL MEMBER BLANC: When you did your key word search in terms of stroke, what were the words that you used?

ARB ASSOCIATE TOXICOLOGIST WINDER: Stroke, ischemic, and hemorraghic. And then picked out many others that were just -- that came up in searching for ETS and cardiovascular effects, since many papers showed up in that kind of search.

PANEL MEMBER BLANC: And you use CVA, cerebral vascular accident?

ARB ASSOCIATE TOXICOLOGIST WINDER: No.

PANEL MEMBER BLANC: And did you use amaurosis fugax?

ARB ASSOCIATE TOXICOLOGIST WINDER: No.

PANEL MEMBER BLANC: Or carotid?

ARB ASSOCIATE TOXICOLOGIST WINDER: No.

PANEL MEMBER BLANC: Just as a double check, I think you -- it seems a -- the literature seems a little sparse. There were two studies that came out in 1999. You'd think somebody would have said, "Hmm, I have a data set I can analyze for that outcome."

PANEL MEMBER GLANTZ: Yeah, I think -- I mean I think that doing those extra red lines searches that Paul

suggests is a good idea. But I think it's pretty sparse literature.

PANEL MEMBER HAMMOND: Actually the Whincup paper has a stroke in it.

ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, They did mention stroke.

PANEL MEMBER HAMMOND: Yeah, they have -- it's a negative. They don't -- they actually had a negative result, but the Whincup paper has stroke.

PANEL MEMBER GLANTZ: I don't think there's been a lot done. I think it's worth doing those other checks, but...

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now, with respect to responses to comments.

This is a comment from Lee. And hes' suggesting that recent study show little association between spousal smoke and CHD, especially two largest studies in 1995 and 2003.

Well, it was never specified in the comment to what studies he was referring, but we can pretty well guess it was probably either the LeVois & Layard paper of '95 or just the Layard paper in '95 and Enstrom & Kabat's paper in 2003.

Now, with these studies we have concern with

respect to misclassification. For example, with the Enstrom & Kabat, they're looking at CPS data on a cohort of women who are -- what they're effectively doing is comparing women who allegedly are not exposed to spouse -- spousal smoking with women who are. But it doesn't take into account ETS exposures outside the home and elsewhere. So there's some question in mind as to how the control group -- how exposed they are to ETS.

Furthermore, for example, in the LeVois & Layard paper ex-smoking spouses are included in this study as though they are continually smoking. Well, if they stop in the process, this is going to skew the results toward no effect.

In addition, in Layard's study the cases were older than the controls. So had the controls lived as long as the cases, maybe they would have become cases themselves. So this particular difference in the ages here is a concern with respect to their analysis.

And as I mentioned with respect to Enstrom & Kabat, it seems very likely that the controls were exposed. And at that point in time there's a lot of smoking and a lot of ambient ETS exposure.

OEHHA SUPERVISING TOXICOLOGIST MARTY: 1959 was their baseline.

PANEL MEMBER BLANC: These papers with these

limitations are cited and discussed in the document.

ARB ASSOCIATE TOXICOLOGIST WINDER: That is correct.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. LeVois commented that the studies in the update do not find a significant association with coronary heart disease.

Well, on the contrary, several studies, Rosenlund, Ciruzzi and Whincup, all relatively recent, all of which find significant association with respect to ETS. And some are based on just report, some are based on serum cotinine. And, again, it's a significant association in all three.

The comment in the stroke studies by Bonita and You, et al., have severe limitations. And as we indicate up here, that's part of the reason that we think that these studies should be considered as suggestive of an association. But they're nothing upon which we can base any conclusion of causality.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: And this particular comment by LeVois is risk from ETS is close to active smoking risk at a fraction of the exposure.

Well, this is one of the things that's come up earlier in the discussion of carcinogenesis. And that's

the idea that ETS is not just diluted mainstream smoke. They're different constituents. With respect to the heart disease, perhaps some with the most interest are carbon monoxide, PAH's, and nicotine. They happen to be higher in the side-stream smoke.

Furthermore -- and again this has been alluded to earlier in the morning regarding the dose response effect -- the CHD response to smoking is nonlinear. So that at low levels a fairly small increase in the amount of exposure results in a relatively high increase in effect. Whereas at higher levels of exposure, this seems to plateau.

Also we've mentioned this morning regarding the nature of the particles to which we're exposed. Now, in ETS the particulates tend to aggregate less than in mainstream smoke. So that these -- in ETS-exposed individuals are getting better penetration in the lungs by these smaller particles with whatever is on those particles.

PANEL MEMBER HAMMOND: I'm not sure I find that argument convincing.

What size do the mainstream aggregate to?

ARB ASSOCIATE TOXICOLOGIST WINDER: I don't know the aerodynamic size right now. But the studies read indicate or tend to aggregate such that they precipitate

or deposit in the upper airways better than the more dilute ETS smoke does.

PANEL MEMBER HAMMOND: I guess, you know -- the other thing is ETS particles tend to aggregate to about .3, which is like the hardest size to deposit. It's the least likely to deposit, and so it's actually going to be exhaled. So you actually exhale a higher percentage of -- I mean I think that's a difficult argument to go down. I think it's a complex issue and I'm not sure I would find that really compelling, because there are other studies that show that a smaller percentage a ETS particles actually get deposited in the lung. And it's not the penetration. It's the deposition that matters.

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. And to what extent in terms of exchange of material is adhering to those particles is observed in, for example, ETS versus mainstream?

PANEL MEMBER HAMMOND: Well, I'm just saying -- I can't answer that right now. I'm saying it's very complex. I think it's taking a one-dimensional approach to a multi-dimensional problem. So if you want to pursue that argument, I think you have to pursue all those aspects.

ARB ASSOCIATE TOXICOLOGIST WINDER: Sure. Okay.

Now, further in this development we find that

cells respond differently to ETS versus mainstream smoke in the study by Wong, et al., in 2004.

This was kind of an interesting study in that the -- in many respects the mainstream-smoke-exposed cells tended to be more like the unexposed, whereas the ETS cells were radically different.

This is suggesting that the different cell types will have a very different response to ETS --

PANEL MEMBER GLANTZ: What kind of cells are these?

ARB ASSOCIATE TOXICOLOGIST WINDER: I believe these were fiberglass.

PANEL MEMBER GLANTZ: Pardon me?

ARB ASSOCIATE TOXICOLOGIST WINDER: I think they were fiberglass.

At least I think so.

And then --

CHAIRPERSON FROINES: This one seems a little abstract to me.

PANEL MEMBER HAMMOND: Can you explain that -- explain this bulletin.

CHAIRPERSON FROINES: When you say respond --

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. What Wong, et al., were doing was taking and creating a solution of mainstream smoke, so they have this extract in

solution, as well as an extract of ETS in solution. And they were exposing cells in culture to both these kinds of solutions in addition to controls, and then looking at various properties of that exposure.

CHAIRPERSON FROINES: Like what?

OEHHA SUPERVISING TOXICOLOGIST MARTY: They looked at the cells microscopically, in particular looking at the endoplasmic reticulum, which in control cells was well developed, concentrated around the nucleus.

In cells exposed to side-stream smoke containing media they showed punctate staining, reflecting fragmentation and coalescence of the endoplasmic reticulum around the nucleus. Whereas the endoplasmic reticulum in cells exposed to the mainstream smoke looked more like that of the control cells.

They also looked at the integrity of Golgi vesicles.

And they looked at the distribution of the chemokine IL8 compared to control and mainstream smoke. And the mainstream smoke looked in both cases more like the control cells. And the side-stream smoke had a higher level of effect.

PANEL MEMBER BLANC: Wouldn't it just be simpler to say that "We acknowledge that the relationship between the risks consistently associated with ETS and the risks

associated with direct smoking in terms of cardiovascular outcomes are not directly proportional. However, there are multiple plausible biological reasons why this maybe the case and we do not find it necessary to find a proportional and linear dose response in order to support this effect."

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER BLANC: "And briefly we refer you to a series of articles about the" -- "series of sources about the make-up and potential biological effect difference between these two mixes"?

PANEL MEMBER GLANTZ: Yeah, I think --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think that's actually the gist of our response in the report.

PANEL MEMBER GLANTZ: Yeah, I think -- I'd like to agree with Paul. I think all you need to say here -- I think the Law & Wald paper from 2003 deals with that issue quite, you know, directly at least in terms of platelet activity. And Terry Pechacek and Stephen Babb from the CDC had an editorial in the BMJ commenting on the Helena study, where they dealt -- it was almost like a -- it wasn't an editorial. It was like a little review dealing with exactly this issue of the nonlinear dose response relation and bringing in a lot of the stuff that had been published since then.

And I think if you just go to those two papers, that answers the question, rather than trying to build up the argument yourself.

CHAIRPERSON FROINES: I agree with Stan and Paul, Melanie, and Kathy for that matter. I think the last three bullets up there are all complex issues. And you just get yourself into a lot of speculation. And, you know, they are probably very reasonable explanations for the differences that they saw. There may have been some cell death at the site of toxicity. There are all sorts of reasons why things are different that have nothing to do with what you're talking about.

So those last three bullets are the kinds of things that I would say fit into the category that you can refer to them but not really get into a discussion of them, the way Paul -- I think Paul suggested.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We can go back and look at our response to that comment and see how it plays out with respect to what Paul just said.

PANEL MEMBER BLANC: Can I just make a time comment?

You know, unless the Panel members have a specific comment, I think that there's some really pressing things I'd like to discuss rather than going through in this format with each and every one of your

point-by-point responses, you know, to these, you know, consultant very voluminous comments. I understand that it's your responsibility. And it's our responsibility to overall see that your response is coherent, which I think it is. We could tweak it here and there. But I think that there are some more fundamental issues that warrant our consideration today. If indeed you're going to be most effective in your work in revising the document for our forthcoming meeting.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's fine. We can stop here.

PANEL MEMBER BLANC: Is that okay with the Chairman?

CHAIRPERSON FROINES: I agree and disagree. I think Paul's point about speeding things along is fine. I think that we also want to be sure that we have addressed -- the Panel has seen how you addressed the comments from the interested parties so that we have a complete understanding of those comments so that we don't give short shrift to the commenters.

So I think that to follow his model is fine. But I don't think we should sacrifice the record in that respect if we have --

PANEL MEMBER BLANC: No, I don't mean to sacrifice the record. And I'll say for my part, looking

at your slides, which summarize your detailed responses to the next 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 points by LeVois, it seems as if you've given them very full and detailed and legitimate consideration.

PANEL MEMBER GLANTZ: Can I --

PANEL MEMBER BLANC: And I feel fine that the record could show that from my point of view.

PANEL MEMBER GLANTZ: Well, I've looked through them too and think the same thing.

What I would suggest is that you go through them quickly. And then if any member of the Panel has a pressing point to make, we could make it. But I would try to go through them quickly. I also while you were talking looked through them. And I think a lot of the issues have already been addressed actually in the discussion we've had.

Why don't you just quickly run through them just for the record and to make sure nobody notices something that isn't obvious.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Well, as this comment here, they're suggesting that the endpoints that we reported are not unique to ETS and may not increase CHD.

And the point of this one is that in fact these

endpoints that we reported -- that are listed here are supported by other researchers being associated with cardiovascular disease.

And ETS increases the measurement of these endpoint.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Says there's a smoker misclassification likely in Rosenlund and most ETS studies.

And we agree that it -- if you have a smokers in control group, that would bias the results toward the null.

And if smokers are in the exposed group, that would inflate our apparent risk.

But the point is that these population-based studies when they have studies looking at misclassification level, this is generally relatively low. In this case a study by Nyberg, et al., it's running 1.2 percent. And at that level if that's applicable to Rosenlund, that wouldn't affect the results substantially.

PANEL MEMBER HAMMOND: And one other point that I would add and, that is, that for heart disease the relative risk is relatively small. Lung cancer, which where you really have much more of a serious impact, there's a high relative risk if you've got a smoker in

your exposed -- in your nonsmoker group that's exposed to passive smoke. And that's going to have a significant impact, but not when the relative risk is small. Even if they're there, they're not going to have a significant impact.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Here it's saying Steenland, et al., were inconsistent in the inclusion of ex-smokers.

This and the next slide they're mainly criticizing Steenland's general analysis. But his analysis included here three different -- or excuse me -- four different ones, three which looked at the effect of the spousal smoking, which examined all source.

He tended to limit his analyses to those in which the couples were both participating in CPS-II. So they can validate the exposure both by self-report and by spousal report. The idea is that this would tend to give a more certain discrimination of who was actually exposed and who wasn't. That analysis resulted in significant risk.

Also the small increased CHD risk associated with marriage to current smokers but not ex-smokers.

And then an increased risk with ETS from all sources. But only home exposure in males was

statistically significant.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: This says here that Steenland's focus on never-smokers married to current smokers at baseline ignores relevant data.

We're saying again that this -- he excluded exposure to former smokers because CHD risk does appear to drop rapidly after cessation of exposure. And in these studies listed here, Steenland, Raitakari, and Rosenlund, the risk decreases rapidly after cessation of exposure to ETS as well.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: It says here the CPS-II data do not show evidence of decreased risk after cessation of ETS exposure. So criticism of use of ever-smokers is not justified.

The list is related to the slide before this. And the CHD risk is attenuated after ETS exposure. So including ex-smokers would tend to skew the results toward the null.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Steenland's analysis of concordant exposure data excludes subjects not reporting home ETS which likely meant no ETS exposure. Therefore the data did not reflect true CPS-II exposures

and the analyzed subjects may be a biased subset.

Well, this is speculation on the author's part because the analysis of the concordant data was only one of several analyses. And these several analyses did find significant associations. But it's also the analysis it would be most likely to give the least misclassification. And that the assertion of the data represent no ETS exposure is just speculation.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. This is the Enstrom & Kabat studies. Analysis of CPS-I data for California may be more valid than the studies based on CPS-II.

Well, as I mentioned on one of the earlier slides, we have some real concerns about the background exposure to ETS in that group that was analyzed by Enstrom & Kabat. And that when you -- there's several curious things about this study. And one example is that the spousal smoking in that study reportedly increased with education, which is contrary to what most studies find, in that individuals with more education tend to smoke less.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Oh, yeah, this is the same group.

Further in that study by Enstrom & Kabat there

was no update on the spousal smoking during this 26 years of follow-up from 1972. So this has the same problem that we've reported on many of these other studies that says exposure at baseline and then not during the follow-up. So we figured there maybe substantial chance of misclassification there.

The age of the never smoking women at baseline in that study decreased with increasing spousal exposure -- spousal smoking.

Well, this is important because during the study period the CHD mortality in general fell about 5 percent for every four years. So as a result of these women being younger that had the higher ETS exposure, that effect would be counteracted by the fact that there's a decreased CHD mortality compared to the older controls. And we would not expect that the control for age in this study would necessarily compensate for that. So we have some concerns that the results were biased or nil.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: This comment says weight of evidence for causal ETS-CHD association has gotten weaker. Our report ignores studies not supporting the conclusion. And laboratory studies are not convincing regarding mechanisms.

We disagree. We say on the contrary that newer

studies do continue to support a causal association. And we cite here, for example, the Whincup study.

We mention here the fact the study by Wong, et al., suggesting a difference between ETS versus some mainstream smoke.

And we think the studies that they're concerned that we're ignoring are the ones by Le Vois and Layard that, as we mentioned before, have some serious concerns about the program.

OEHHA SUPERVISING TOXICOLOGIST MARTY: In which we did not ignore. They're in the document.

And that's it for Chapter 8.

PANEL MEMBER BLANC: I'd like to ask -- I know that there was discussion at this point switching to the ARB presentation relating to Part A, I guess it is? The exposure assessment?

But I would like to make a request to the group if we could have the discussion which I assume did not happen this morning on the general approach to causality, suggestiveness and inconclusiveness, unless I missed it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It didn't happen. We have a --

PANEL MEMBER BLANC: That it happen now, because I'm probably not going to be able to remain here until 4 o'clock.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We have just a few slides relevant to that.

PANEL MEMBER BLANC: If that's okay, with the Chair's indulgence.

CHAIRPERSON FROINES: I'm afraid so. I know -- hopefully we can finish this in a half hour and have an hour for Jeanette.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It should be fairly quick.

CHAIRPERSON FROINES: We certainly -- I think that it's important, but I think we can probably get through it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: This primarily relates to our description of -- no, we do not have handouts, I'm sorry to say. We weren't sure we were going to actually even talk about this today.

But it basically goes to Chapter 1's description of what we are saying is the basis for describing something as causal. And I'm looking for that.

It's on page 1-9 in the gray-covered document.

And the bottom paragraph of page 1-9 we somewhat -- we're somewhat short in our description. Dr. Blanc sent us a document from the Institute of medicine, which said it much more clearly, and which we feel is certainly applicable to how we looked at all of these

studies. So we are suggesting adding a few sentences to that paragraph on the bottom of page 1-9.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: And this slide, the first sentence is what is already in the document. And the second italicized sentence is what we want to add, which we think more clearly states what we actually did when we looked at all of the studies.

So what we're saying is it's causally associated when there's a positive relationship and the effect can't really be attributed to chance, bias, or confounding. The sentence you want to add is: "The evidence must be biologically plausible and satisfy several of the guidelines used to assess causality such as strength of association, dose response relationship, consistency of association, and temporal association."

So I think that makes it more -- makes it a little clearer what we've done.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: IOM has a few more layers than we actually used when we were looking at these studies. We have conclusive, suggestive, inconclusive.

The bottom part of that page starts where we

discussed when we say something is effect that we consider to be suggestive. And that is for which you could interpret it as causal. That could be credible. But we don't have the same amount of confidence that chance, bias or confounding is not playing a large role.

So we added two more sentences there to indicate what we mean by that. So, for example, at least one high quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Alternatively several studies of lower quality show consistent positive associations and the results are probably not due to bias and confounding.

So, you know, hopefully that is a little bit clearer description of how we differentiated between a causal effect and a body of evidence where it's suggestive of an association.

PANEL MEMBER FRIEDMAN: The first sentence in italics sounds like it could be consistent with a causal association. I think it would help me if you specified what's missing -- what is missing that would make that not be a -- regarded by you as a causal association? You mean the fact that the criteria such as strength and so on were not considered or --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, they may have been considered but may not have satisfied

several of the guidelines. So, for example, if we're talking about a causal association, we have some biological plausibility evidence and we also have the strength of association, dose response, consistency and temporal association all satisfied.

PANEL MEMBER FRIEDMAN: So I think it would help me if you said in terms of the suggested one that, "but it lacks those things."

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. So make a clearer differentiation.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, what we're saying is that I think we can't really rule out chance, bias or confounding.

PANEL MEMBER BLANC: What does rule out mean to you?

PANEL MEMBER FRIEDMAN: When you say one high quality study, you know, is free of bias and has controlled confounding, that sounds pretty persuasive to me. So what's missing?

PANEL MEMBER BLANC: Multiple studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Multiple studies, exactly. To some -- you know, if you have one study it's really hard to hang your hat on it.

PANEL MEMBER FRIEDMAN: You said that there's

only one study or something --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right, if you have study. But it's pretty hard to hang your hat on it, particularly if you have other studies that didn't show that effect.

PANEL MEMBER HAMMOND: So I guess -- yeah, I mean -- I agree with Gary. I think you do have to be a little clearer. So whether it's to say, for example, one, only one, rather than at least one high quality study? Or is it that, for instance, it doesn't suit -- if you go back a slide, it doesn't suit biologic plausibility or it doesn't answer several -- it does not in fact answer several of these guidelines, is that what you're saying?

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's basically what we're saying.

PANEL MEMBER HAMMOND: So maybe it's -- and actually I think strength of association I think is becoming, to my mind -- I know that's been out there for a long time. But I think that we're kind of moving beyond that now. We're looking at low level effects. And I don't think that one has to have a relative risk of five for it to be believable. And I actually feel that that's an old criteria that is no longer valid.

OEHHA SUPERVISING TOXICOLOGIST MARTY: But I think --

PANEL MEMBER FRIEDMAN: But it does -- a low relative risk does leave open a greater chance of confounding, explaining it. So I think in your --

PANEL MEMBER HAMMOND: But if people have addressed it, that's what you have to look at.

PANEL MEMBER FRIEDMAN: Right. I think it has to be addressed. We still believe it even though it's low level because --

PANEL MEMBER HAMMOND: You certainly have to do more to address those issues when it's a low level. But I don't think strength of association is actually as important as some other issues.

PANEL MEMBER FRIEDMAN: If it's there it's just like -- like CRAIG was saying for a dose response, if it's there it really helps a lot.

CHAIRPERSON FROINES: Wait, wait, wait, Kathy. I want to stop.

We have one issue on the table, which is the difference between 1 and 2.

PANEL MEMBER HAMMOND: That's what I'm talking about.

CHAIRPERSON FROINES: I know. But people are now into the details. And I want to talk about dose response obviously. And so -- but I'm holding back. I think we should address this issue of what's the difference between

1 and 2 and then move on to the other topics, like strength of association.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I think that the number of studies clearly always comes into play, the number and quality of the studies. We already --

CHAIRPERSON FROINES: But what is the --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We've already described that in the paragraph above when I'm talking about that.

CHAIRPERSON FROINES: What does the number mean? Because with diesel we had 50 studies, and we've made decisions on methylene chloride with one study. And so I don't know what more than one study means unless you mean confirming study or -- or what are the criteria?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Let me read the paragraph above that on page 1-9, and maybe that will help people understand what we're saying.

We say, "A weight of evidence approach has been used to describe the body of evidence on whether or not ETS exposure causes a particular effect. Under this approach the number and quality of epidemiological studies as well as other sources of data on biological plausibility are considered in making a scientific judgment. Associations that are replicated in several

studies of the same design or using different epidemiological approaches or considering different sources of exposure are more likely to represent a causal relationship than isolated observations from single studies.

If there are inconsistent results among investigations, possible reasons are sought such as adequacy of sample size for a control group, methods used to assess ETS exposure, range and levels of exposure. And results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound.

"General considerations made in evaluating individual studies include study design, appropriateness of the study population, methods used to ascertain ETS exposure as well analytic methods such as the ability to account for other variables that may potentially confound the ETS effect.

"Increased risk with increasing levels of exposure to ETS is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidenced against a causal relationship."

And then we would have these two sentences and then those sentences. So, you know, I -- we don't want to sit here and say you have to have ten studies or you have

to have five studies or you have to have thirty-five studies. You know, it's clear that there is some judgment based on the science that goes into your decision.

PANEL MEMBER BLANC: For practical purposes now in retrospect though, can't you go back, look at all of your decisions and say there is no -- the minimal number of studies that we have used to classify any health endpoint as causally related in this document is 5, is 7, is 4, whatever it is? Isn't there some minimum if you actually went through?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, we have the number of studies that have been considered both in the '97 report and this report. I mean we could go back and say, yeah, there was a minimum of 15 or whatever it is.

PANEL MEMBER HAMMOND: I would be careful though. I think you want this statement to stand for other risk assessments you do for other materials. So, you know, as John said, you might have another compound for which you have one superb study that looks fabulous and fulfills every criteria you can think of. And you don't want to say that you're locked in because we happen to have five wonderful studies here, as we set five as the criteria.

Well, you should do it intellectually like what you think is actually necessary to come to that

conclusion.

PANEL MEMBER BLANC: I'd sort of take a middle ground, where I would do one but I would leave the door open that, you know, just doesn't preclude that, you know, fewer studies might serve that purpose. But there's certainly not a scenario where you see where one study in fact would be sufficient; is that correct?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I wouldn't be comfortable with that.

PANEL MEMBER BLANC: Would two?

PANEL MEMBER BYUS: I disagree. I think one -- these days, especially with these low risk studies, one large study funded could be conclusive, and it would be virtually impossible to reproduce --

CHAIRPERSON FROINES: Well, we made a decision to --

PANEL MEMBER BYUS: -- if it was good. You know what I mean?

CHAIRPERSON FROINES: We accepted the risk assessment for naphthalene based on one health input in animals.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right. I think that's a different -- that's a different issue. Are we talking about risk assessment now or are we talking about epidemiologically?

CHAIRPERSON FROINES: No, but the committee also was saying that the qualitative evidence of it being a toxic air contaminant was adequate, you know. I mean in other words the qualitative issue was being dealt with as well as the quantitative one.

PANEL MEMBER HAMMOND: Actually -- I mean that gets -- your comment just got me to think about it. This is a section on weight of the evidence. So it's not like just what epidemiologic studies are sufficient to make a judgment, as is implied in your italicized section here. We add to the epidemiology other data such as toxicology data, which is biologic plausibility -- I mean there are many other things that go into it.

It is there. It's in your -- or it's been one before. I'm sorry. I'm in the wrong slide. But in the conclusive one, italicized section.

But it actually -- and that's when I think of weight of evidence is were adding epidemiology, toxicology, all our knowledge of the world. And yet the way it's written actually here -- and, you know, the discussion is focused very much in epidemiology. Of course it's important. But I think it's important to keep this sense that one good epidemiology study along with good senses of biologic plausibility, a dose response function, consistency of -- you know, all these -- if all

these things -- I can imagine one study that would be very convincing to all of us.

PANEL MEMBER GLANTZ: Well, see, I -- the problem I -- I want to expand on that, because I think that -- I mean every time I hear the term "biological plausibility," I think of ye olde English, because the idea of biological plausibility, I don't know when that all got cooked up a long time ago, but that was before we had a tremendous amount of mechanistic understanding or experimental toxicology and things like that.

And so, you know, these criteria are really based almost exclusively on statistical and epidemiological considerations. And we're way past that on a lot of these things. I mean if you look at the whole discussion this morning, if you look at the discussion about heart disease, you know -- so it would be nice to, you know, instead of talking about biological plausibility, to me when you talk about the weight of the evidence is you look at the epidemiology if you have it. And, as John said, we've often dealt with things where we don't have any human epidemiology. You look at what you know about the mechanistic effects of the compound in question and any biological effects. Rather than biological plausibility, I would say biological effects. And to me, you know, when I look at these things, it's sort of when you step back

and look at the whole picture, the question is: Does the evidence hang together?

You know, do you have -- do you have, you know, things where you're showing effects, not to reopen an old -- the discussion we had before. But, you know, when you look at heart disease, we see these changes in oxidant loads, oxidant LDL affects the dose, things you have on Nitric Oxide Synthase, which affects vascular reactivity and the development of atherosclerotic plaque and acute events, and then you see it in the epidemiology. So the whole -- you have this whole train of evidence going from very molecular things and mechanistic things up to where you can see something at the level of an entire population. And that to me is like -- that's like really nice when you have that.

Now, often we don't have that full range of evidence. And so to me the question is like how -- and I don't know how you would put this in these words, but sort of how long is the chain and how strong are the links. And that to me is how you make these judgments. So I think that -- you know, and is what evidence you have internally consistent, you know. So I don't know quite how you would write that.

But I'd like to see this move away from such sort of a traditionalist strict epidemiological statistical

paradigm, which was developed before a lot of these other more experimental tools were even around.

OEHHA SUPERVISING TOXICOLOGIST MARTY: You know, I think -- I'd like to point out too on page 110 that we discussed this issue in the context of the Toxic Air Contaminant Program, which, you know, Dr. Froines just pointed out we have naphthalene based solely on animal data, we have perchlorate. I mean there's like a ton of them that we've already identified as text.

We point out that because the epi data are extensive for ETS, they serve as the primary basis on which findings of ETS effects are made. Experimental data are also reviewed to determine the extent to which they support or conflict with the human data. In some cases studies of ETS constituents in animal -- experimental animals are used to support the weight of evidence judgment. As noted above, this is standard practice in risk assessment.

In many instances in the toxic air contaminants program chemicals have been identified as TAC's and emissions have been regulated based on animal toxicological data alone. This is important in the public health setting because often times adequate epidemiological data do not exist.

So I think that -- what I'm trying to say is

basically what Stan just said, only much more articulately --

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- that there's a whole chain of events, you know, and a whole --

CHAIRPERSON FROINES: We're going to let this -- assessment's going to take ten more minutes. And then you're going to take what was said here, unless somebody makes a specific suggestion, and work on it and bring it back next time. So we have ten more minutes and then -- because I'm not going to keep ARB from...

I want to strongly support Stan's point of view in this, Melanie. Because when I served on and chaired the NTP Carcinogen Committee, every time a chemical came up, various intervenors came in and said, "There's no dose response information. There's no dose response information. There's no exposure information." Well, the fact of the matter is when you go out there and look at who collects exposure information, for the most part it isn't collected routinely. And so we always have to -- we always have the problem that there's inadequate exposure information.

So then we set our ourselves this criteria of dose response, which we can never adequately meet, for the most part, except in the very, very most expensive and

best studies. So, yes, I agree with you about dose response. But we already talked earlier about it doesn't -- everything doesn't just keep going up. And so we need to understand that -- whether it be strength of association or dose response, we have to have a modern understanding of what reality's all about in order to make decisions. Otherwise we get our own rhetoric -- we get trapped in our own rhetoric. And what happens is we become criticized for inadequacy of, for example, exposure information that isn't routinely collected.

And so it seems to me that the epidemiologists did very well with tobacco smoke because they get such a -- an enormous dose. They have very, very powerful findings. But for most things that we deal with, the levels of exposure in the environment are so low as to be very -- that we're always forced to extrapolation because we can't measure in the regions where people are actually breathing the chemical. So what does strength of association mean in a lot of circumstances? We simply can't get to it.

So I think that we have to be very careful not to set ourselves up with a goal standard which we're going to have consistent difficulty in meeting and develop criteria for decision making that is realistic within that particular context.

PANEL MEMBER BLANC: Well, I think I would differ to an extent. And, that is, that I think it is important, as you have tried to do, to lay out what is generally considered the traditional approach to causality. I think it would help you to the extent that it's publicly available to actually cite explicitly what the IOM approach has been. Perhaps if the EPA has struggled with a causality guideline, you might look at what they have.

I think it's not absurd to even go back to sort of the classic tobacco-related diseases, hypertraditional causality framework. And then having done that, talk about those ways in which that, as in an overly prescriptive or overly narrow version of causality, is to an extent not applicable to this situation. I think that's the context in which you could have your discussion about cigarette smoking in relationship to -- direct cigarette smoking relationship to the outcomes. I think you weaken your direct cigarette smoking argument by not saying first, "Well, in general, yeah, we do think that it's supportive when cigarette smoking is related." You go immediately into this sort of backpedaling, well, but it's problematic and there's this and there's that. But in fact, you know, you don't start off by saying, "Well, yeah, you know, generally speaking, yes. But here are a few caveats. We don't expect to be linear. For some

things there may be a threshold." So it's well understood, you know, gathering epidemiologic data is, you know, indicated -- and this is particularly the case for certain health outcomes such cardiovascular disease -- see Chapter 6 -- as you'll see in Chapter 8, whatever it is.

And, similarly, I think that this is the area in which you should have your generic discussion of the issues of defining exposure for the purposes of the referent group, since this is something that's come up again and again and again in your analyses: Is your referent group actually free of secondhand smoke exposure or not? And how do you know it? And is a -- you know, Stan's points from earlier today about even though traditionally cohort studies -- longitudinal cohort studies are argued to be more free of bias, for your purposes longitudinal studies which don't have multiple measures of changes in secondhand smoke over the observation period are perhaps less useful than retrospectively ascertained exposure data. And I would lay out all of the generic issues that you've struggled with the various epidemiologic and non-epidemiologic analyses. And I think this is also the point in which you should make clear what drives you to do your own meta-analyses and what role you believe they serve in raising the threshold perhaps from suggestive to

causative.

You know, by implication it's not that nothing could be causative without a meta-analysis. However, when there is a meta-analysis, you believe it is further substantive strengthening in the area of consistency of results, particularly if there are multiple studies but all of them have fairly small populations because of the nature of the endpoint being studied. And therefore pooling data substantively increases the power or the analytic power to answer the question. And I think if you use these pages to do all those things, it would first of all free you up from a lot of gobbledegook later on, because you could just simply say, "Refer to perform to" -- "We performed a meta-analysis as part of our causality evaluation (see Chapter 1)."

CHAIRPERSON FROINES: Paul, I certainly would support what you've said almost completely. But I still reserve -- I still think one has to have a section where you talk about limitations and realistic considerations. Otherwise you're stuck with Bradford Hill. And Bradford Hill just doesn't work under circumstances that we live in. And we have to have ways of making decisions. So that I would agree that everything you said can go as a front piece. But I think there needs to be some sort of paragraph or paragraphs that talk about some limitations

as well. And that doesn't have to be defensive?

PANEL MEMBER BLANC: No, no. In fact you can set up Bradford Hill as a kind of strawman where you say, "We love Bradford Hill. It's great for the following reasons:" But of course there is this other problem and this problem and so on. And so, you know, we've tempered our application of it to be consistent with the reality. Although actually this particular body of subject matter is heavily epidemiologic as it turns out for most of the endpoints that you're interested in.

PANEL MEMBER GLANTZ: Yeah, but, you know, I don't want to prolong this. But in terms of breast cancer though I think the toxicology studies contribute a lot though to the conclusion of causality. The fact that there are elements -- you know, that there are elements in the smoke that we know are delivered to breast tissue, that they are causing cellular damage in breast tissue, and that they are mammary carcinogens in animals. And I think those facts add a lot to the epidemiology.

CHAIRPERSON FROINES: I would even argue that given what we have in tobacco smoke, it should be the burden of the person who wants to not consider it a carcinogen to make the argument. Because we have lots of epidemiology showing human carcinogenesis from those chemicals. And so the burden shouldn't be on us to prove

at some level. But given the way the process works, we are going to take that tack basically.

PANEL MEMBER GLANTZ: Right. But what I'm just saying is is that to me when you look at the breast cancer data, the toxicology is more than just, quote, biological plausibility. I mean I see the toxicological evidence as very, very strong all by itself. And the fact that you have this strong toxicological evidence in combination with what I would call reasonably good epidemiology is what I think justifies a causal conclusion.

I think that the epidemiology on its own without the toxicology might, but it's much, much stronger when you put the two of those together.

CHAIRPERSON FROINES: And given that you're talking about toxicology, that leads us right into Jeanette's talk, discussion.

So thank you, Melanie. Thank you everybody from OEHHA.

PANEL MEMBER GLANTZ: I think you get to come back later.

CHAIRPERSON FROINES: Jeanette, you want to take five minutes to give our guy a chance to take a break.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: We can go till 4:15 I think, Jeanette. As long as there's a cab outside at

4:15.

CHAIRPERSON FROINES: We're in business.

(Thereupon an overhead presentation was Presented as follows.)

ARB MANAGER AGUILA: We're in business? Okay.

Well, good afternoon to the Panel. I'm Jim Aguila with ARB. I realize it's kind of late in the day. We'll try to get through this as efficiently as possible here.

But we actually have the ARB team here this afternoon to kind of talk about some of the issues and questions that were raised last time. And to my right I have Robert Krieger and Jim Stebbins. And to my -- or actually to my left, to your right. To my right is Bruce Winder, who's going to cover some of the biomarker information.

So Robert will take us through most of the presentation and then I'll kind of chime in on the particulate matter discussion.

MR. KRIEGER: Okay. Thank you, Jim.

Today ore presentation will focus on the comments that you presented at the November 30th meeting.

Next slide.

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MR. KRIEGER: As discussed at the November SRP

meeting, you, the Panel, had several comments on the report which we'll address now.

The first comment deals with your concern over the regards for the statewide ETS PM outdoor estimate. This is the number that we had previously in the report that we submitted to you that estimated a state -- overall statewide concentrations of ETS fine PM.

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MR. KRIEGER: To address this comment we actually did a Los Angeles-area-only estimate based on several studies that we'll talk about here. We felt that this estimate better reflects what most people are exposed to in urban areas. And we felt that this could be kind of tagged along top of some of the estimates that we already have in our report.

As a reference point ARB staff used the results from the Schauer and the Rogge studies to estimate the 2003 Los Angeles ETS fine PM outdoor ambient background concentrations.

Cigarette sales data, taken from the Board of Equalization, and cigarette emission rate data, taken from several studies were used to determine the percent reduction in cigarette emissions from the data presented in the Schauer and Rogge studies to 2003 year.

Next we applied this percent reduction to the

1982 fine ETS PM estimates that were presented in the Schauer and Rogge studies to calculate the annual average Los Angeles fine ETS particle concentration.

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MR. KRIEGER: This next slide shows actually the calculations that we used to get to this level. The top half of that graph shows the statewide emissions for cigarettes in California -- or actually in California, the statewide. And it shows that the percent reduction in actually just cigarette sales was about 59, 60 percent reduction. The ETS emission rate was based on -- that was based on the 1982, was 20.4 milligrams per cigarette. That was based on the Schauer and the Rogge study.

Actually that number came from a Hildeman study in 1991. But that emission factor we believe decreased. We have newer data that shows that the emissions from the cigarettes are at 13.4 milligrams per cigarette.

You take the total difference between the two cigarette sales and the emission rate and you come to roughly an estimate about 73 percent reduction. And we just simply -- from that point we simply took that percent reduction, applied it to the 1982 data set emissions or at least ambient calculations to come up with a 2003 fine PM estimate ranging from about .06 to .10 micrograms per cubic meter.

Next slide.

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MR. KRIEGER: The SRP also had a comment on the percentage of indoor cigarette smoking that makes it outdoors. That was a comment that was made by Dr. Blanc. And Dr. Hammond raised this issue as well. And we'll address that in this next slide.

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MR. KRIEGER: As we mentioned before, there is limited information -- or limited information is available to allow an accurate estimate of indoor to outdoor ETS emissions. No direct measurement of indoor versus outdoor cigarettes consumed in California have been done. But there are several actually data sets that are available that we could make kind of a reasonable assumption the percentage of cigarette that is smoked indoors makes it to the outdoor environment.

Some of these are based on the current laws that limit most smoking in public indoor places, like the AB 13 that was adopted in 1988. The work place, bars and restaurants, et cetera.

Also the 2002 California adult tobacco survey data from the Department of Health Services indicates that about 95 percent of Californians report a smoke-free indoor work environment.

About 50 percent of all the smokers live in smoke-free homes. That means all the smokers that reported in the survey, the people that reported that they smoke, 50 percent of them said that they just smoke outdoor only when they're at home. They do not smoke inside. So about half of those.

And about 80 percent of all California homes are smoke free for children.

There's also several ventilation studies that deal with generally fine PM's, small fine particles. But there's one in general that deals with ETS particulate matter. That's the Rogge study from 1994. They present a range -- or he presents a range of 50 to 80 percent cigarette smoke ventilation occurs when you smoke indoors that actually makes it to the outdoor environment.

--o0o--

MR. KRIEGER: So using these assumptions, we put together a couple of scenarios which we can show -- or reasonably estimates that most of the cigarettes are -- actually most of cigarettes smoked indoors makes it to the outdoor environment.

From the top we take a typical adult lifestyle. And that's from a person -- it could be a smoker's lifestyle, or any lifestyle really, spending time at work and at home. The average habit from a smoker is about 15

cigarettes per day, those who smoke only.

Fifty to Eighty percent -- it was the number that was used in the previous slide -- of the ETS ventilates indoor to outdoor.

With those assumptions here we go through Case 1. And Case 1 we just wanted to show that if you're a smoker and you follow the rules of the work place exposure and not smoke indoors, you're smoking outdoors the majority of day, and if you do not smoke at home, virtually a hundred percent -- and it may vary a little bit -- but virtually a hundred percent of your smoking occurs outdoors.

What we want to point out here is that Case 2 is the scenario where the smoker does not smoke outdoors but smokes, let's say, 50 percent -- or smokes at home the rest of the time or the six hours of the time, but at a 50 percent ventilation rate. So 50 percent of the cigarettes smoked actually is smoked indoors, 50 percent makes it outdoors.

So we add those two together. And with the total cigarettes they smoked per day we come up with an 80 percent calculation or rate that smoked indoors make it outdoors. And so we believe that this would sort of comprise maybe the lower end of a range for emissions that would actually make it from the indoor environment to the outdoor. It could be much higher.

And this is for smokers only too. For nonsmokers it's -- we assume it's much more higher than 80 percent.

PANEL MEMBER FRIEDMAN: Can I ask a question?

MR. KRIEGER: Yes.

PANEL MEMBER FRIEDMAN: Maybe I don't have this correctly. But you said that 20 percent -- 80 percent of children live in smoke-free homes. And isn't it true that about half of smokers -- I mean that the percentage of the smoking adults in California is about 20 percent -- about 20 percent or 18 percent?

MR. KRIEGER: That's correct.

PANEL MEMBER FRIEDMAN: And if half of them don't smoke in their home, then there should only be about 10 percent of homes with smokers.

ARB MANAGER AGUILA: Okay. I think that refers to the nature of the survey itself. And what they did is they surveyed homes. But homes may have more than one child. So that's not really factored in.

PANEL MEMBER HAMMOND: There's another factor too. And, that is, that something like 40 percent of children have parents who smoke. So in other words smokers and nonsmokers don't have the same percent of -- the children aren't evenly distributed among smokers and -- all right. So it doesn't follow that. So it turns out the higher percentage of children have a parent who

smokes than the percent of the adult population who smokes.

PANEL MEMBER FRIEDMAN: I'm surprised.

PANEL MEMBER HAMMOND: You can start working out the scenarios, but it -- yeah.

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MR. KRIEGER: The next slide.

The comment is actually an easy comment to address. It dealt with Dr. Blanc's comment on the Eisner study. We presented in a final slide, which you will see here today too, that we presented an outdoor number that was taken from the Eisner study. And he asked us to go back and confirm whether this was an ETS-monitored measurement or not. And in doing so we did -- the next slide.

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MR. KRIEGER: Just a summary real quick. The Eisner study dealt with actually 50 subjects who were part of the asthma study. They used passive samplers to measure personal exposures to nicotine. They actually had a category that had 12 that it had only outdoor exposures only. So there was a category for outdoor exposures only. And they reported concentrations from the outdoor ambient environment to be .025 micrograms per cubic meter nicotine. And it's important to note too -- and I will

show this on the last slide too, our summary slide -- that the results are consistent with all the other studies, measurements and estimated results.

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MR. KRIEGER: Another comment that was brought up by Dr. Froines mentioned about our ARB air monitoring study -- near-source nicotine, our monitoring study. And I will present some of the findings from that study in the next few slides.

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MR. KRIEGER: The ARB staff conducted an ambient air monitoring at outdoor smoking areas for nicotine, in part to address some of the gaps that existed in outdoor measurement studies.

To obtain data on current levels of ETS in ambient air where people spend part of their day the ARB monitored nicotine concentrations at several outdoor smoking areas in California. These sites included sampling at an airport, college, public building, office complex, and an amusement park.

At each of the study sites sampling was conducted for nicotine over a three-day time period during typical business hours, usually between 8 and 5 p.m. Two of the days were devoted to eight-hour samples; six one-hour samples were collected on one of the sampling days. QA/QC

samples were obtained for this study.

The estimated quantitation limits shown for the eight and one-hour samples is the level that we have confidence in showing the nicotine levels that we measured.

Sampling was done by ARB's monitoring laboratory staff and analyzed by UC Davis's trace analytical lab.

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MR. KRIEGER: Here we have -- next few slides have a couple pictures of our actual sampling equipment.

During this monitoring period nicotine was collected with XAD-4 absorbent resin by pulling air through the sampling cartridges you see up there at a rate of 15 liters per minute. The sampling cartridges contained about 30 milliliters of XAD-4 resin.

Analysis was conducted by a gas chromatography with mass selective detector. And the pump is shown on the right too as well with the tubing.

Next slide.

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MR. KRIEGER: This next slide shows a picture of our actually monitoring set up. The slide on the left shows the -- kind of the typical height of our monitoring device. The slide on the right shows that -- the importance of this slide is actually to show where the

monitors are located. And you see the one on the right, which obviously is the airport there you can tell, is located right outside the baggage claim area where several people congregate. And smoking occurs right next to the monitor. So we would expect higher, you know, ETS levels to occur there.

The picture on the bottom left is from the college. And -- well, at that time there's no smokers there. But there were a few.

And the one on the right's the office building.

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MR. KRIEGER: This slide shows in a graphic form -- and the next slide will be a table with the same results. But some of the results here. The results of our monitoring show that actually the number of cigarettes smoked on the right correspond to the levels found in the areas -- and the levels are on the left, the concentration levels. So basically the number of cigarettes smoked corresponds to the levels that you see on the table.

The background concentration are in red. I don't know if you can read that. And the kind of green color is actually the mean concentrations for each one of those sites.

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MR. KRIEGER: This table shows actually the

concentrations that were presented in the graph.

Be important to note here too that some of those levels that you see in the slide before, especially like the office complex, the number of smokers that smoked on the right seems to be -- you know, there are a fair number of smokers that occurred in that eight-hour period. But the concentrations were not as high. And some of the factors such as wind speed and actually location of the monitors had some effect on the monitoring results. But in general you'll still find the correlation between the number of cigarette smoked in any kind of area corresponds to the concentration.

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MR. KRIEGER: Here's the same slide, but we're just talking about one-hour samples here. You'll see the samples correlate almost identically to the eight-hour samplers, just the slight number of decreased concentration, decreased smokers.

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MR. KRIEGER: This slide shows the results similarly. And on the slide too I wanted to point out that the number of samples taken are up in the second column, data presented. The range presents the number of samples that were taken in each one of those sites.

So we had a fair number of samples taken

throughout each one of the monitoring sites.

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MR. KRIEGER: That's all I -- oh, we have one last slide. And this is actually the pretty important slide which will become part of our Table 5 of my report.

This slide summarizes the data we have found on the outdoor levels of ETS exposure.

The results from the studies themselves are indicated by the black text. And the estimated levels of either nicotine or fine ETS PM are shown on the blue text.

The estimated levels were calculated by using an adjustment factor for the conversion of nicotine to the fine ETS PM. And the ratio we used for this calculation was eight. And that was supported by data by Nelson in 1994 and Martin in 1997, who tested a number of cigarettes for fine ETS and nicotine as well. So we had the ratio that occurred from nicotine to fine PM.

And as you can see on the slide there, both columns actually match up fairly consistently. And the levels are not too far off from even the estimated concentrations. So there's like a convergence there between all the data that's presented in our outdoor estimates.

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MR. KRIEGER: Any questions on that?

Okay. Next we'll turn it over to Jim Aguila, who will be presenting the particle part of this presentation.

ARB MANAGER AGUILA: Okay. The last SRP meeting that we had Dr. Froines was kind of curious about our discussion on the particulate matter and ETS, and recommended that we take another look at our information that we had in the report to see if we couldn't have a little more comprehensive explanation and summary.

And so we've done that. We went back -- since the last meeting we went back and took a look at the papers. And there was actually quite a bit of detail, that at this point we're proposing to add to the report. So what I'll do is I'll go over the information as we plan to present it in the report.

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ARB MANAGER AGUILA: And basically it's important to note that some of the discussion this morning -- and it was kind of talking about some of the composition of mainstream, side-stream and what is ETS. That is important to point out. And we do have that in the report now. But we're taking another look at it and we'll look at it in terms of differentiating between side-stream and mainstream. But right now we have it listed in our report differentiated between gaseous components and particulate matter components. So we'll continue to have that in the

report.

And then also for people who read our report who aren't as familiar with analytical methods, we plan to add at least a little section in the report to explain how PM research is conducted. There's term-of-art words like mass mean diameters and median diameters and the like that people may not be familiar with. So we'll take this opportunity to kind of explain how research is done.

But, more importantly, it's probably more important to talk about what actually happens to ETS. And as it turns out, it is a very complicated mix that undergoes a complicated aging process as well.

And then, finally, to tie it together in terms of what does it mean to the outdoors.

You know, we intend to have a conclusion indicating what we feel are the relevant aspects of PM research that would be helpful for somebody who's interested in looking at dose and dose response and the like.

Next slide.

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ARB MANAGER AGUILA: Basically in our discussion we proposed to introduce PM as it being comprised of solid, semisolid land liquid aerosol particles in addition to particles that have some attached organics in there.

But more importantly it's important to point out that in general ETS does fall within the ultrafine and fine particulate matter range. And I think this kind of talks a little bit to what was discussed earlier regarding ETS's role in terms of overall air pollution.

So we would make a point to point out that, you know, it is kind of overlapping between the two. Not to mention that, you know, ETS has several carcinogens. And of course there's literally thousands. We put 50 here because that's what we found in our literature. But I'm sure there's probably more.

Not to mention as well that there's also many that are reproductive toxicants and possibly even developmental toxicants too.

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ARB MANAGER AGUILA: As far as the PM research is concerned, you know, we'd just like to point out that just the nature of how PM is generated, it leads to a nice normal distribution and that's typically how it's viewed. Most of the studies typically look at particle mass. But there's also other studies that have looked at number counts, that is, the number of particles per cubic centimeter or meter, in addition to the actual length of the particle itself.

But, by and large, when you talk about

conclusions of some of these studies, they're put in basically statistical terms in terms of median modes, standard deviation and the like. So we'd like to point that out in our report, especially since we're going to be presenting some data that would be in that form.

It's also important to note that, you know, over time detection methods and techniques have changed. And, in fact, there's studies that we looked at that have actually done comparison work to point out that, depending on what kind of analyzer you use, there could be differences and, in fact, stark differences in some cases. And then also to point out the differences between research that's done on mainstream versus side-stream. There are differences in terms of its, not only the chemical make-up, but also the particle mass distribution as well.

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ARB MANAGER AGUILA: As far as the aging process goes, typically what we point out is that the ETS would dilute rather rapidly in the air in most cases. But depending on the conditions that its generated in, there's a number of chemical reactions that could occur. The ones listed on the slide here are simply the main ones that we were able to find in the literature.

And of the list there, probably the coagulation

would be most important in the mainstream smoke where you have an artificial setting in drawing a puff where you actually create a situation where you're actually promoting coagulation.

Evaporation is also very important as well and the condensation.

But in addition to chemical reactions that happen to the plume, there's also external things that can happen like the absorption and desorption. This is something that Dr. Froines had brought up at the last meeting. ETS is very sticky stuff and it does stick to walls, but it doesn't always stay there. It also desorbs as well. So we point that out.

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ARB MANAGER AGUILA: Here we have an example of some work that was done by Brenner. And basically what we're looking at here is a histogram that will show the temporal effect of what happens to PM -- ETS PM over time.

This particular study was done in a 30 cubic meter chamber. And it's a measure of mainstream and side-stream. And basically what it shows is that over time not only do you have a reduction in the number of particles, but you also have a reduction in the diameter of the particle as well.

And what we're showing here is we're showing two

different diameters. We're showing what we call a particle -- a median particle diameter, which is based on simply the number of particles that are there. You take the median number and, you know, that's the diameter that's shown there. And then on a mass basis, we're also showing the diameters based on the mass of each particle as well.

So what we're pointing out here between the two slides is that over time, in this case it's 230 minutes, we have a quite a large change in the average diameter. In the case of the particle it goes from .11 to .22, roughly a doubling of size. And likewise in the mass case, you are having some increase in the average mass diameter. But If you look at the number of particles, there's less of them. So it does go down.

But I think the salient point of this slide is not only just to point out the temporal effect, but also to point out the fact that even though it undergoes these chemicals processes, the diameters are still less than PM 1.

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ARB MANAGER AGUILA: In this slide this is an example actually of a study that looked at condensation effects. This is an interesting study in particular, because what they did in this study is actually they

captured mainstream smoke and was able to filter the mainstream smoke so you have only the gaseous component of ETS, which the author terms as smoke vapor. And this was kind of an interesting analytical apparatus that they used here.

But basically it was a 50 milliliter syringe where they stuck a cigarette on the top of it and pulled a plunger and were able to generate smoke. And they looked at that smoke in two ways. One way they looked at it was through light scattering techniques. And another one was just an optical counter -- a Lasik optical counter.

And the bottom line here what you see is that basically after about 100 second or 150 seconds the particle number stays relatively flat until you get to about 500 minutes -- or seconds. Excuse me. But the diameter of the particles do increase over time. And the authors theorize that this is mainly due to condensation of particles.

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PANEL MEMBER HAMMOND: How large was that chamber?

ARB MANAGER AGUILA: It was 50 milliliters lit ease

PANEL MEMBER HAMMOND: Fifty milliliters?

ARB MANAGER AGUILA: Yes, it was rather small.

And the author -- by the way, on the previous slide the author also theorized that one of the chemical processes that could be happening is the combination of NO2 with isoprene. So they note that as one of the chemical reactions that would lead to this increase in diameter effect.

Next slide.

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PANEL MEMBER LANDOLPH: To come up with the particle diameter, what did they use, low angle forward scattering --

ARB MANAGER AGUILA: Actually they used a horizontal and a vertical scattering technique and they compared the light intensity of the two measurements. And based on theoretical calculations of angle of defraction, they were able to determine the response curve between the ratio of the horizontal to the vertical light scattering intensity to this theoretical graph that allowed them to actually plot the diameters on that.

CHAIRPERSON FROINES: I don't understand something. You said that they attribute the increase in diameter to isoprene NO2, is that what you said?

ARB MANAGER AGUILA: Yeah, the combination of NO2 and isoprene was one of the chemical reactions that they noted in the paper.

CHAIRPERSON FROINES: Well, wait. There's no chemical reaction we're talking about. I assumed that the increase in diameter occurs basically by coagulation and condensation, not by chemistry.

ARB MANAGER AGUILA: Yeah, I simply mentioned that because it was mentioned in the paper. But, you're right, there's other reasons why --

CHAIRPERSON FROINES: Vapor is -- you know, is a molecule.

PANEL MEMBER HAMMOND: Well, those kinds of reactions will actually give you smaller particles, not larger ones. So I think John's right.

ARB MANAGER AGUILA: Okay. Well, we'll make sure we get that straight.

PANEL MEMBER HAMMOND: Well, it's probably not important for where you're going.

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ARB MANAGER AGUILA: Okay. This is the next slide here. This is another study. Ingebrethsen, who looked at particle evaporation.

In this case this was a side-stream diluted with air in a -- and an optical particle counter was used with an electrical mobility analyzer.

And in this particular study we're looking at the time relationship to mass mean diameter. And what it

indicates is that there's an initial dip, which the author explains as an evaporation effect happening. Before other chemical processes take over, that actually would increase the mass mean diameter. But essentially this is important within the first 100 minutes or so.

PANEL MEMBER LANDOLPH: Well, you know, that last side, I was trying to thinking of what confused me. The particle concentration is on a log scale. The diameter is on a linear scale. So you see the diameter going up fast. And you see that the particle number looks like it's decreasing slowly, but actually it's on a log scale, so it's going down much faster.

ARB MANAGER AGUILA: Yes. And actually that's a good -- I appreciate that you pointed that out, because this actually is a bit of an artifact of how they took the measurement. Because what you're seeing there is you're seeing the tail-end of the smoke that's in this 50 milliliter syringe. So, you know, the authors basically state that there's probably a limit to the detection accuracy once you get that far out.

PANEL MEMBER LANDOLPH: Thank you.

CHAIRPERSON FROINES: Well, it's probably pretty turbulent and you're not getting much drop off by growing. So it's a phenomenon of the production of the particles probably more than anything else.

PANEL MEMBER HAMMOND: In my humble opinion, it's pretty irrelevant to anything that's happening from the environmental tobacco smoke anyway. The 50 milliliter chamber's so concentrated -- it's just such a -- so I wouldn't even waste to spend much time on it.

ARB MANAGER AGUILA: Yeah. I think the main purpose of showing the slide is just to indicate that this phenomenon does occur, and it would occur in any environment. But, yeah, you're right, we couldn't probably draw any quantitative result from this.

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ARB MANAGER AGUILA: Okay. Was there any questions on the previous slide?

Jim, you want to go back.

CHAIRPERSON FROINES: The thing that's interesting of course is -- if you take a billiard ball and as these things coagulate you start to have these fractals with the billiard balls all hooked together, where the composition on each one stays about the same, as opposed to the idea of things evaporating and growing on individual balls. I mean so that the bio-availability of chemicals on these particles as they grow is an interesting question.

PANEL MEMBER HAMMOND: Yeah, it's quite a contrast, say, to diesel where you might have this

elemental carbon core and on the surface have PAH's condensing. That's the point you're trying to make?

CHAIRPERSON FROINES: And so as you take two diesel particles, it's not as though all those PAH's then become monolayers on top of what already exists. But you get this factal kind of thing that Sheldon Freedlander shows pictures of, you know. So that the actual number of monolayers of absorbed compound stays relatively constant, which means that they may be. It means we should be regulating on the basis of surface area, I think.

PANEL MEMBER HAMMOND: But I think it's less of an issue for tobacco smoke.

CHAIRPERSON FROINES: Why?

PANEL MEMBER HAMMOND: I think it's more uniform.

CHAIRPERSON FROINES: You think so?

PANEL MEMBER HAMMOND: I think so. I mean I -- don't guess an elemental carbon core.

CHAIRPERSON FROINES: It's so sticky, you mean?

PANEL MEMBER HAMMOND: I mean there are differences, but I doubt it, as -- in that sense, as different on the inside and the outside as a diesel particle would be.

CHAIRPERSON FROINES: I'm still in favor of regulating on the basis of surface area.

(Laughter.)

ARB MANAGER AGUILA: Well, just in general, I'd like to summarize here and just state for the record that we are changing the report. We'd like to add a lot more detail. Basically the information that we presented today was the bulk of the new information that we'd present in the report. And I think the main take-home message here would be that ETS really is a -- it's an air pollutant, a concentrated air pollutant, as I heard earlier this morning, that kind of -- it has an overlap between ultrafines and fine particulate matter. And even though it's subject to quite a few chemical processes, it still tends to stay in the same range.

CHAIRPERSON FROINES: What's at the core of going just -- Kathy. What's the core of tobacco smoke? It's not carbon obviously. Although there must be some carbon.

PANEL MEMBER HAMMOND: Well, I mean -- one of the examples I gave you was something that had no particles to start out with, right? And so it was entirely condensation -- for those particles that were formed was entirely condensation of vapors, semi-volatile organic compounds.

I'm not actually familiar with an analysis of -- a surface analysis as opposed to the core analysis. But I think there's a lot more of what it is is a condensation of smoke as opposed to there being these elemental carbon

cores. There probably are little bits of tobacco leaf, I guess. But I don't really know.

ARB MANAGER AGUILA: No, I think that's our understanding as well. And it's really obvious in the literature when you study semi-vol -- and how they dilute. It's pretty obvious that they're condensing and forming.

CHAIRPERSON FROINES: Well, you have -- a tailpipe of a vehicle is like a hot tube, right? And so you have all sorts of chemistry going on within the hot tube. And then there's what happens when all the vapors come out and condense and form particles.

So you have particles in the tailpipe or exhaust and you have particles that are formed after the exhaust comes out. So there are two. Now, do you form all sorts of particles -- you smoke -- the hot part of the cigarette is at the end. Now, we're talking about ETS here, so it's more complicated.

PANEL MEMBER HAMMOND: The hottest part is when the smoker's smoking the cigarette and they're inhaling so they're pulling oxygen here. So that's like 300 degrees warmer than when it's smoldering. And during that time most of the particles actually go into the smoker's lungs. That's one of the differences in mainstream to side-stream. But when it's smoldering it's only 600 degrees roughly. So it's a little different. But you

still would have vapor phase semi-volatile compounds that will later condense.

CHAIRPERSON FROINES: But the particles that are formed in the cigarette are -- do they have -- what is their core?

PANEL MEMBER HAMMOND: Partly -- if they're totally condensations, then they would be the same as -- that would be uniform, right?

And then the other, I don't know. But I was suggesting it could be unburned tobacco. I don't know though.

MR. KRIEGER: Yeah, there is a percentage of elemental carbon in the smoke --

PANEL MEMBER HAMMOND: It's a tiny percent --

MR. KRIEGER: It's a very tiny percent, but there is --

PANEL MEMBER HAMMOND: One or two percent.

MR. KRIEGER: Yeah.

PANEL MEMBER HAMMOND: It's only one or two percent. And I don't think that that's -- it's not like diesel.

MR. KRIEGER: It's not like diesel. Diesel's much more elemental carbon.

ARB MANAGER AGUILA: And I mean as far as being able to compare the combustion effects of a vehicle versus

a tobacco column, which is what we refer to it, they could be different because in a vehicle you have the catalytic converter, which is supposed to create chemical reactions in the engine before it gets exhausted. And there's a possibility that some of those reactions might occur after it leaves the tailpipe. But you wouldn't have anything like that with tobacco.

CHAIRPERSON FROINES: We should run some tobacco smoke in our tox systems and see what it looks like.

PANEL MEMBER GLANTZ: I just had one question.

All this stuff was about particulates. What about the gas phase? Is there anything to say about that?

ARB MANAGER AGUILA: Yeah, actually we do cover it in the report. The reason why we covered PM is because that was a question that was specifically brought up last time. But actually the report does have a discussion of the gaseous components, including a table of what -- you know, the chemicals that have been identified either through Prop 65 or ARB or IARC.

PANEL MEMBER GLANTZ: I know -- I remember the table on the particulates -- the amount of particulate pollution put into the air. Is there anything you could do for the gas phases? Or does that get even like harder?

ARB MANAGER AGUILA: Right. Well, we were talking about that. And we are aware of at least one

study where people looked at emission rates. And to the extent that we could look at a cigarette and what chemicals are being emitted from the cigarette, we could compare gaseous components that way. But there's pretty limited data. I think that's pretty much what we had in mind looking at that. And also that same data set also looks at side-stream versus mainstream as well. So we could look at those separately as well in terms of their generation rates per cigarette. So that's more like an emission factor. It doesn't really tell you much about the concentrations or anything. But at least it will tell you from a cigarette where the relative differences among different chemicals. It's not in the report now, but we'd be happy to put that in.

PANEL MEMBER GLANTZ: I mean I don't want to create a huge amount -- I mean this is something I know very little about, but I wouldn't want to create a huge amount of extra work. But if you could give -- I was pretty impressed with the emissions that you quantified there. And if you could add something about some of the gas phase emissions, that would be entertaining. I don't know that it's worth a huge amount of work. But if you can do it easily, and it would make sense -- Kathy is holding her head.

PANEL MEMBER HAMMOND: Well, no. I'm thinking,

if the left hand can talk to the right hand at ARB, and probably they're all the -- they're probably on the same bodies in between. There's a report that they recently did on indoor air pollution that I happen to be a little aware of. And there was some discussion about --

PANEL MEMBER GLANTZ: Wasn't Peggy Jenkins in the --

PANEL MEMBER HAMMOND: And there was some discussion there, you know -- and this is well known -- that in smoker's homes there are higher benzene levels in the homes than in nonsmokers' homes, you know. But those are the kinds of things that would be relevant. Obviously the cigarette smoke as the benzene loads.

ARB MANAGER AGUILA: Okay. Would that be something relevant to a discussion of absorption and desorption? Because we are aware of a couple of studies where they did look at benzene, they looked at nicotine.

PANEL MEMBER HAMMOND: Oh, I thought we were talking about something different. I thought we were talking about -- Stan was trying to talk about the composition of the emissions. And that's where I was kind of going with that.

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

PANEL MEMBER HAMMOND: The only trouble I'm thinking is since -- there's a lot that's been written on

that. I mean is that something you want to also reproduce here?

PANEL MEMBER GLANTZ: Well, it depends how much work it is. I mean I just -- I mean my main focus in looking at the document was to Part B. But in reading through Part A I just thought all this was very interesting. And I was impressed with what some of the numbers were. And I think it would be -- you know, there's a lot of other toxins in the smoke that are in the gas phase.

CHAIRPERSON FROINES: Vapor.

And some people even think some of those are the most biologically active. So to the extent that you could without doing massive amounts of work give some sense of the levels of emissions, I think it would be interesting. I don't think it will make a huge difference in whether the report is approved or not. But just in the interest of completeness, if you could do it easily, I think it would be worth doing.

And I think Kathy brought up a different point about the indoor air and the load of benzene and things like that and indoor environments where people are smoking. And, again, if that could be added in without too much trouble, I think it would be interesting and make the report more valuable.

ARB INDOOR EXPOSURE ASSESSMENT SECTION MANAGER JENKINS: Peggy Jenkins, Air Resources Board.

I think we can do that very easily. Dr. Joan Daisy from Lawrence Berkeley Laboratory actually did a study. It was under contract to CARB. But she did look at direct emissions and also aged emissions in a chamber setting. But also attempted to do kind of some realistic aging. Unfortunately some of the side-stream aging results weren't crisp. But I think the initial emissions were very good. She looked at aldehydes. Actually quite a few of our toxic air contaminants were -- I think she had about 17 toxic air contaminants that she looked at.

And one interesting result she did have was kind of an increase in formaldehyde over time, which was not totally unexpected, but I don't think it had been measured. So there are a few studies -- a couple of others like that that she cited we could certainly include in a report without any difficulty. And I don't think it's in there right now.

CHAIRPERSON FROINES: Are those smoking studies?

ARB INDOOR EXPOSURE ASSESSMENT SECTION MANAGER JENKINS: This was a smoking machine chamber study of mainstream and side-stream and initial and aged.

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ARB ASSOCIATE TOXICOLOGIST WINDER: One of the

comments that came out last time was regarding the biomarkers of exposure. Prior to disgusting some of those I wanted to cite some of the characteristics that we're interested in having in our biomarkers of exposure. These include specificity. We're looking for compounds which indicate tobacco smoke exposure versus exposure to, for example, nicotine from other sources, water, medicinal, food, this kind of stuff.

In our assays or in the assays that we use we would like to see a certain amount of sensitivity that allows us to distinguish reliably small amounts of what the compound is in accessible matrices. That is to say, things like hair and saliva and this sort of thing that we can easily get to.

And these need to be able to distinguish fairly large range of exposures so we can distinguish individuals with a low level ETS exposure versus casual smokers, for example. And the substance of interest needs to have an especially long half-life and stability to be able to be detected at these low levels.

Next slide please.

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ARB ASSOCIATE TOXICOLOGIST WINDER: So in the document we talk about several of the compounds that have been reported in studies as biomarkers of ETS exposure.

Now, I've not used most of these, and these are the reasons. For example, carbon monoxide in the measure of carboxyhemoglobin as an indication of the exposure to carbon monoxide has been reported in several studies. But carbon monoxide exposures occur from a variety of different sources. So in and of itself this is not a particularly useful indicator of ETS exposure.

Thiocyanate, which is derived from hydrogen cyanide and smoke, also occurs to a certain extent in the diet. So once again it's difficult to distinguish between individuals who are exposed and not exposed to ETS.

Now, the next category of protein and DNA adducts, some of that discussion we've had this morning, are quite a number of these that have been reported. They're used for indicating a certain amount of exposure. But what is this connection to ETS versus active smoking? Usually we can't distinguish on the basis of that.

Now, there's one example that is somewhat different and that's the 4-aminobiphenyl. As Dr. Hammond mentioned this morning, it is roughly 30 percent higher, which means 30 times higher in side-stream versus mainstream smoke. This is one of those compounds it looks like it might have some use, but it's really not been used widely. So from the standpoint of ETS exposure, this is not particularly useful.

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ARB ASSOCIATE TOXICOLOGIST WINDER: One that's looking a little more promising is the NNAL/NNAL-glucuronide. Now, this is a compound that's metabolized from NNK, that is to say a carcinogen that results as the consequence of combustion in nicotine. Now, this is -- in the use of this it's possible to distinguish between ETS, active smoking, and then exposure to other non-tobacco nicotine sources. But, again, this isn't widely used at this point. I think it's becoming more widely used. But for our purposes it hasn't been around long enough.

And the next two, nicotine and cotinine, these are the two substances that are most commonly used in this particular respect.

Now, nicotine is abundant and it's relatively specific to tobacco. Although it is present in certain dietary components. And We run into a problem with individuals who are taking nicotine in the form of patches or gum or something like this. So in that sense it becomes a little more difficult to distinguish active smoking, ETS exposed, et cetera.

Now, it has a very short half-life in body fluids, so it's useful for determining very recent exposures. And in a matrix like hair, it has a much

longer half-life. So this is useful from the standpoint of measuring -- for seeing exposures over several weeks to months.

Perhaps the most useful one in this context has been cotinine. Now, as I mentioned here that this is relatively abundant, that is to say 70 to 80 percent of the absorbed nicotine is reportedly converted to cotinine. This number derives from studies by both Dempsey and Benewis. Now, this has been well developed for a variety of matrices, hair, urine, saliva, this kind of thing.

And it's good principally for recent or continuous exposure. And one of the things that was mentioned last time was some concern that, well, what if he had episodic exposures. Well, in that case our measurements of cotinine could prove to be the same. On the other hand in conjunction -- if you use it in conjunction with nicotine, wouldn't even address that issue. Most of the studies that we deal with have not measured both, nicotine and cotinine.

Also, as with nicotine, since nicotine is found in a variety of foods, the cotinine levels will to some extent be influenced by that, not substantially.

PANEL MEMBER FRIEDMAN: Could you give a few examples of the foods that it's found in?

ARB ASSOCIATE TOXICOLOGIST WINDER: Well, tea,

tomatoes, things like eggplant. All these contain small amounts.

PANEL MEMBER GLANTZ: I think though this is a -- this is something that the tobacco companies have made a big deal out of. And Jim Repace some years ago had a letter to the editor. And I think it was BMJ. Kathy's laughing. But it turns out that the food because of the tomatoes and eggplant, I think are the two foods that have it, that eggplant parmesan would be the --

(Laughter.)

PANEL MEMBER GLANTZ: Except that when you cook it, most of the nicotine boils off. So you'd have to eat it raw. And Repace --

PANEL MEMBER HAMMOND: How many pounds you had to eat --

PANEL MEMBER GLANTZ: Yeah, Repace figured out it was several pounds of eggplant -- raw eggplant parmesan every day in order to get the levels typically seen in a passive smoker. So it's true that there is some nicotine in foods, but I think this is a pretty hypothetical problem.

PANEL MEMBER HAMMOND: Well, in the M. Haynes study where they actually had diet information as well, you know, basically again did not see increased levels in people who had the foods that are most thought to be the

problem. So it's really -- it's kind of a red herring.

CHAIRPERSON FROINES: But it's a good substance to use on Fear Factor.

(Laughter.)

PANEL MEMBER BYUS: Again, this is a joke.

(Laughter.)

CHAIRPERSON FROINES: The eggplant industry will be after us, right.

(Laughter.)

PANEL MEMBER BYUS: You know this.

PANEL MEMBER GLANTZ: The raw eggplant industry.

ARB ASSOCIATE TOXICOLOGIST WINDER: Next slide please.

PANEL MEMBER GLANTZ: That was a joke too.

--o0o--

ARB ASSOCIATE TOXICOLOGIST WINDER: So based on this, that we recognize the cotinine, nicotine and NNAL, they're probably the best biomarkers so far demonstrated. But of these, only cotinine and to some extent nicotine had been widely used and the first to be able to use in our studies with respect to ETS exposure. And so for that reason -- this is the reason we rely on cotinine for targeting at this kind of stuff. And the rest of the biomarkers, some of them may have some potential use in the future but at this point are really not of much use.

Any questions?

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: Well, I think that you've all done a lot of work, and I commend you for the work you've done and move this along quite a bit.

I think it's particularly -- since there are a lot of issues here that you've dealt with, maybe quickly -- you've put a lot of energy, for instance, into talking about some things like the formation, the complexity, which they're all there, but I actually think they again are kind of a little bit red herrings. I mean I suppose you have to address them because they're out there. But, you know, the fact that it's very complex doesn't make it not real, and the attempts to study it require very artificial situations like 50 milliliter chambers, you know, that just don't reflect what happens in reality. So it's -- we shouldn't get bogged down on some of those issues.

I think more to the point is the attempt to make some estimates of what are background exposures. These may be the most important things, you know, later. And I think you've done some very nice things where you've pulled together multiple sources of data, and I think that this is very important. So on the one hand you've made estimations from the source apportionment work that was

done by others that you cited as one of your slides -- it would have been your nineteenth slide -- that summarizes that. So you have Schauer and the Rogge data where you've made estimates of the background levels of ETS and then you've tried to extrapolate those down for the reduced rates of smoking. And then what's interesting is when you kind of compare that to some measurements that you all made in your monitoring and Mark Eisner made in his study, if anything I would say what you might note is that your estimates are actually maybe underestimates, because the observed values in your studies and in the Eisner studies, which were personal samples for seven days, were all actually higher than the numbers that you estimate. So, if anything, you're underestimating.

But I think that you've got a relatively robust number. I mean we're looking at -- to be agreeing within a factor of 2 is pretty astounding, I think, and that's where we are. The caveat -- that's a background level. And then the caveat's not to lose the idea of the hot -- well, I'm going to -- the area where people are smoking, when people are smoking outdoors, that near there you can have higher levels.

PANEL MEMBER GLANTZ: I think that you call hot spot.

PANEL MEMBER HAMMOND: But meanwhile the

background level, that's this other issue that you're exposed to, even when you think you're not near a smoker, is not insubstantial. And I think that you've got an amazingly robust estimate of that coming out of -- kind of triangulating it. So I commend you for that.

So I think you've done a nice job.

CHAIRPERSON FROINES: Other comments?

Why does passive smoking ETS cause cardiovascular disease?

PANEL MEMBER GLANTZ: Why?

PANEL MEMBER HAMMOND: Which chemical, you mean?

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER GLANTZ: Well, I think it's a whole lot of different things. I think the particulates have a lot of effects in terms of triggering inflammatory responses.

CHAIRPERSON FROINES: In the lung?

PANEL MEMBER GLANTZ: Probably in the lung, but releasing C-reactive protein, which then has cardiovascular effects. There was a very nice study done in Canada some years ago where they took fine particle air pollution out of the air and stilled it into I think it was rabbit lungs and got atherosclerosis. Controlled study. So the particulates I think are very important.

The particulates seem to cause reductions in

heart rate variability that are associated with acute events, heart attacks. I think the stuff we talked about earlier about oxidant loads are important. Acrolein is an important oxidant with a long half-life in blood. A lot -- most of the oxidants don't have lung half-lifes but some do. And there's a lot of acrolein in cigarette smoke. The 1-3 butadiene and benzopyrene have both been shown to be atherogenic on their own.

So there's a whole lot of different, you know, mechanisms that are at work here. I mean I think probably one of the most important pathways is the stuff that was being talked about earlier about the oxidant loads reducing the amount of available NO, which screws up all kinds of things related to endothelial function. But all these different things are happening.

I don't think that nicotine is particularly important. So there's a whole lot -- because there's so many pathways that lead to cardiovascular disease, there's a lot of places to stimulate those pathways in bad ways, and cigarette smoke acts through a lot of them.

CHAIRPERSON FROINES: So the reason I asked that question with you guys from ARB sitting there is precisely the answer I got, which is -- and Donaldson from England in terms of air pollution suggests the same kinds of things, namely, that you have deposition in the lung which

produces inflammatory responses and then the inflammatory responses produce cytokines and immunoglobulins and a whole range of things and -- in other words, the particle doesn't necessarily have to reach the heart to act in this way.

So that the size distribution, the characteristics of deposition, and so on and so forth become very, very important in that respect.

PANEL MEMBER GLANTZ: Yeah. And the fine particles are the worst.

CHAIRPERSON FROINES: Yeah. And acrolein's a very interesting compound because it is an alpha beta unsaturated aldehyde undergoes electrophilic addition to form irreversible products and -- now whether -- what -- presumably that's a reaction with thiol groups and so it's a protein -- it affects proteins. And so thiols are going to -- may inhibit the nitric oxide synthase. So a lot of things can happen.

So, anyway, so that both vapors and particles are probably important.

PANEL MEMBER GLANTZ: Yeah. And actually that was why I'd asked the question about trying to get some estimate of the vapor phase loads too, because those are important for some of these effects. It isn't just the particulates.

CHAIRPERSON FROINES: A butadiene is more likely to be a carcinogen rather than cardiovascular implications. So that different chemicals --

PANEL MEMBER GLANTZ: Although butadiene does -- it's atherogenic.

CHAIRPERSON FROINES: Yeah.

So thanks, everybody. That was very useful.

Joe.

PANEL MEMBER LANDOLPH: I just have some minor editorial comments I'll transmit to you and not take up any time here.

Very nice job.

CHAIRPERSON FROINES: I assume that there's no -- I didn't mean to -- Stan and I were talking. I assumed that there weren't other -- people would have jumped in if there were other comments.

So, Melanie, we'll see where we can get this next time.

PANEL MEMBER HAMMOND: John, Just a process question.

Do we see another version of these things? Or are we just kind of done with them now or what?

CHAIRPERSON FROINES: I'm assuming that Melanie's going to try and get us a draft, as well as ARB, by -- certainly by the end of February so that we have two weeks

ahead of time to take a look at it for the March 14th meeting.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we have to do that in view of the number of reorganizations, et cetera, that we're going to be doing to those chapters. So I think it's important in this case. We don't always have a draft -- a whole new revised report. But I think we need to in this case.

CHAIRPERSON FROINES: So it's important for people who have comments, just like Joe just said, to get them to Melanie as soon as possible.

And so we will assume that by March first we'll see a draft so we'll be prepared for the meeting. And if that's the case, we may be able to take a vote in March and we should be able to discuss findings.

So we'll draft some findings. And I say that, knowing Gary's to my right and has very strong views of how long those findings should be.

(Laughter.)

CHAIRPERSON FROINES: So we're going to have to figure out what the --

PANEL MEMBER GLANTZ: And then Paul is to your left with opposing views.

CHAIRPERSON FROINES: And I understand that too.

But we'll try and have -- we'll try and put

together some findings for discussion and hopefully be at a place where we can take a vote unless there's violent disagreement.

PANEL MEMBER FRIEDMAN: Will the new draft show -- you have, a track changes feature so we know what's added?

ARB MANAGER AGUILA: Yes, strike out, underline.

PANEL MEMBER FRIEDMAN: The same thing with the OEHHA version?

PANEL MEMBER GLANTZ: It may be hard though if you happen to strike out --

PANEL MEMBER HAMMOND: It may be this thick.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly. I think where there's -- for example, Chapter 6. Paul wanted lots of reorganization, which we've already almost completed. If we did that in track changes mode, it would be unreadable. So, you know, it's just wholesale switching of sections is what happened.

PANEL MEMBER FRIEDMAN: Somehow if we could have some kind of guidance as to what changes to focus on rather than rereading the whole thing.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, exactly.

CHAIRPERSON FROINES: You could send them both ways, with track changes and without track changes, and

let the reader decide.

PANEL MEMBER HAMMOND: Be electronically.

CHAIRPERSON FROINES: Electronically, yeah.

PANEL MEMBER GLANTZ: What I would suggest is -- I think there are parts of the report where the changes are going to be fairly modest. And I think that could be done with the track changes. I think for like Chapter 7, the stuff we were talking about this morning -- and if they do the kind of editing you'd suggested, Gary, I think it would be pretty cumbersome.

So maybe what you could do, Melanie, is if it's just -- if you're reorganizing something when you send a -- maybe you could send like a memo with the report saying in Chapter 6 the major change was this way, it was reorganized. Or, you know -- and then if there are parts where the changes were so extensive that you actually rewrote big hunks of them, just say sections 7-1 through 7-10 were extensively rewritten and you need to read the whole thing, or something like that.

PANEL MEMBER HAMMOND: And maybe on top of that, I would say a track changes for any changes in the executive summary or the summary or conclusions. Those should be very clearly done probably.

CHAIRPERSON FROINES: I just had one general comment. There was a fairly spirited debate between a

number of people with vis-a-vis cardiovascular. And Stan actually -- paul made the original comment and I made -- and I followed up. And when Stan articulated the whole process, beginning to end for cardiovascular disease, he did it very effectively. That I think Stan should work with you on to get that into the document, because it does go from the biochemical, biological to the downstream processes to the health endpoint. And the more we can get on that level, the better off we're going to be because it gives us the linkage between mechanistic findings to health outcomes.

So I would urge you to drag out of him everything that he knows that can help that --

PANEL MEMBER GLANTZ: I already said everything I know.

CHAIRPERSON FROINES: He said -- he volunteered. I'm just --

PANEL MEMBER GLANTZ: No, I'm happy to help.

CHAIRPERSON FROINES: -- putting it as a -- clearly he's got it here.

PANEL MEMBER GLANTZ: Just read the transcript, because I said everything I know.

That was a joke.

CHAIRPERSON FROINES: We hope it is.

(Laughter.)

CHAIRPERSON FROINES: Because you certainly sounded more -- can we get a motion to adjourn?

PANEL MEMBER HAMMOND: I move we adjourn.

PANEL MEMBER LANDOLPH: Second.

CHAIRPERSON FROINES: All those in favor?

(Hands raised.)

CHAIRPERSON FROINES: It's unanimous.

Thank you very much, folks. This was a very good meeting and very useful.

Oh, and I just really want to say, a couple -- some of the Panel members have complimented both ARB and OEHHA on the document. But just coming from the Chair I want to say that this is really an extraordinary amount of work that's been done and it's very, very well done. And so everybody should feel good about where we are. We've had two meetings and we've come a very long way. And we'll bring it to closure next time, I hope.

(Thereupon the California Air Resources Board, Scientific Review Panel meeting adjourned at 4:10 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 13th day of January, 2005.

JAMES F. PETERS, CSR, RPR
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