MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

SOUTH SAN FRANCISCO CONFERENCE CENTER

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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Roger Atkinson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Aguila, Manager

Mr. Jim Behrmann, Liaison

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. George Alexeeff, Deputy Director

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

Dr. Andrew G. Salmon, Chief, Air Toxicology and Risk Assessment Unit

ALSO PRESENT

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

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PROCEEDINGS

CHAIRPERSON FROINES: Okay. Dr. Plopper will not be attending the meeting.

So that we will formally open the Scientific Review Panel meeting on March 14th, 2005. And we will take up the issue of environmental tobacco smoke.

I don't entirely know what Melanie's got to present. But the first thing that I would like to do is to ask the panel a question, which is -- it seemed to me that one of the primary issues that we have to address throughout the report, and in some cases more particularly, the issue of causal inference. And OEHHA has developed material in their first chapter to address that particular question.

And then there's the lengthy discussion of causal inference in the Surgeon General's 2004 report. So this issue forms a substantive basis for everything that follows.

And so at the outset I wanted to ask the panel, and particularly Gary and Paul, but others as well, if they have issues and questions about the discussion -- the OEHHA discussion on causality and decision making in the document, and are there broader issues that need to be raised at the outset?

So, Gary.

PANEL MEMBER FRIEDMAN: Well, I must admit I didn't focus on that discussion of causal inference that you referred to. But I have mentioned to Melanie that one of the main criteria for causality is strength of the association, and at the last meeting I asked that there be more attention paid to that. And they did indeed, and the breast cancer chapter drew some discussion of the strength of the association.

But I didn't think it got at the key question of whether with weak association such as their overall relative risk of 1.26 whether this could be explained by confounders, either unknown confounding or insufficiently controlled confounding. And I thought -- that's one of the main issues about weak associations. And I thought they may well have good answers to that, but it needs to be explicitly described. So that's my main concern about causality with regard to the big issue of breast cancer.

And I'm not sure whether you do this with lung cancer too, which is in the same ballpark with 1, relative risk.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I guess I would take a broader view than Gary's, that -- and more closer aligned to what you were alluding to, which is I think that the Chapter 1, which is, yes, an introduction but really is

the methods -- should be the methods section for the entire document is substantively flawed. And I feel a little bit of potential responsibility for perhaps not voicing explicitly enough at our last meeting areas that needed specific remediation, because -- perhaps I was just too global in my comments and presumed that the changes would be more substantive and less focused in that section.

It's understandable given the shear volume of studies and chapters and review that's involved in this very lengthy document. But, nonetheless, some of the area -- it's not simply causality. I think that there is a lack of transparency in the methods generally. And given how, for example, meta-analysis comes back in later sections of the document that's completely missing is an issue really from the -- not completely but substantively missing as a matter of discussion in the methods: When would meta-analysis be used, how would it be used, what would the implications generically be? I think that the issue of consultancy is very unclear. It's not mentioned actually in the introduction.

PANEL MEMBER GLANTZ: What is consultancy?

PANEL MEMBER BLANC: When external and internal consultants would be used and how they were used and what was the basis of that. And I have some -- I may have some

specific suggestions later on on how that could be addressed.

There are some other things I -- but my general -- the thrust of my comment would be that I think we should begin with going through Chapter 1; and that if we end up taking the entire session today going through Chapter 1, that might not be a bad use of time, in fact, because everything else has to flow out of that. And as it stands I don't think it's -- it's acceptable.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: I do concur, I mean in some regards. I mean I think the introduction of the Surgeon General's report is extremely clear and well written, and it's very carefully constructed and it's -- I think this is more along the line what you'd like to see in Chapter -- introductory chapter in the environmental tobacco smoke chapter. It should be as well written and clear in the two places. I mean I was struck how -- not that it isn't clear, but how well done the 2004 Surgeon General's introductory chapter is. It's beautifully written, very clear. It gives the right historical perspective. And at least from my perspective it gives an accurate analysis of how they include data and not include it and how they make associations and not. So I do agree with you.

PANEL MEMBER GLANTZ: Do we have a copy of that?

CHAIRPERSON FROINES: Of what?

PANEL MEMBER GLANTZ: Of what they're quoting -- to look at, if that becomes the standard?

PANEL MEMBER LANDOLPH: I have one if you want it.

PANEL MEMBER HAMMOND: Do you have extra copies with you?

CHAIRPERSON FROINES: We can get them copied, I guess. I don't know -- it's long.

PANEL MEMBER FRIEDMAN: I must admit, I haven't read it either. I sure would like to see it.

CHAIRPERSON FROINES: Roger?

PANEL MEMBER ATKINSON: Oh, I focused on the exposure side. And so I don't really have any comment.

CHAIRPERSON FROINES: Stan and Kathy --

PANEL MEMBER GLANTZ: Well, I'm just -- I'm kind of -- I'm actually on the Committee that's writing the next report, and had been provided with this stuff years ago. The Surgeon General's reports take forever. And the -- in fact, I drafted one of the chapters.

PANEL MEMBER HAMMOND: Not this -- this isn't that.

PANEL MEMBER GLANTZ: No, no, for the report on passive smoking, which hasn't it's often CDC land.

But the -- so we were given these same standards to use. These are the standards that the CDC has used for a long time. And those were the standards that I used in the chapter I drafted for them.

And in my reading of the OEHHA report, those are pretty much the standards I used -- or I always use. And I'm kind of surprised to hear -- I mean maybe the chapter could be written more elegantly. But I don't recall anything in reading the OEHHA report which applies any substantially different criteria from making judgments than in the discussions I've had on the Surgeon General's committee. I mean maybe I -- those committees move very slowly, and it's been a long time since there's been a meeting. But the -- but I'm kind of surprised to hear that there's a substantive -- in effect there's a substantive problem with what OEHHA did.

The other thing that I am concerned about -- and maybe again I misunderstood something -- but it seems to me that criteria for decision making that are described in this document are essentially the same criteria that we've always used on this panel. And if I'm missing something, someone should correct me.

So I mean are you -- I mean I don't quite understand. I mean I think that there are two -- there are two different possibilities here, or three. One -- I

actually thought the chapter was okay. But one is that it just simply needs to be more clearly stated. The other is that we need to make a fundamental change in the way that we make decisions, which I would be very much against because I think this panel has a good record of making scientifically high quality decisions.

The one thing I can tell you from having read a lot of Surgeon General's reports, and, as I say, helping in -- being involved in writing one of them now, is I think there's an overly reliance on epidemiologic criteria almost to the exclusion of everything else.

And that is a result I think of many years of having the tobacco companies bang on them. And I think the level of caution that has been imbued into the process is just -- you know, it's like, you know if something gets into a surgeon general's report there's not a type 1 error. But, you know, they -- I mean, for example, on heart disease, which is now widely accepted by everybody, including the CDC now, there is still no recognition of passive smoking causing heart disease in the a surgeon general's report, you know. So I don't quite understand -- I mean I don't --

CHAIRPERSON FROINES: I think that -- let me cut you off.

PANEL MEMBER GLANTZ: What's the substantive

issue here? I don't understand.

CHAIRPERSON FROINES: I think that we should not get distracted on to the Surgeon General's report.

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: I think that Paul, for example, raised -- and Gary both raised substantive issues.

PANEL MEMBER GLANTZ: Well, what are they?

CHAIRPERSON FROINES: Stan, quiet.

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: We're not going to listen to you all day if you're going to go on in a monologue. You're going to have to be sensitive to a committee process.

PANEL MEMBER GLANTZ: Okay.

CHAIRPERSON FROINES: Okay?

PANEL MEMBER GLANTZ: I --

CHAIRPERSON FROINES: All right. Let me answer you. This is going to be very difficult if you run a monologue throughout this day. And I think you need to be sensitive to the other members of the panel and stop talking when you're finished making a point and listen to other people. I will not tolerate a monologue that goes on indefinitely. It's not the way we're going to run this day.

Paul and -- and what I was trying to say was in their comments, both Paul and Gary did not mention the CDC report. I did. Craig did. The issue is that both Paul and Gary raised substantive issues about the -- about the OEHHA report. They did not talk about the issue of the Surgeon General's report. Paul raised questions about the use of meta-analysis and the transparency associated with that and he raised questions about the issue of consultancy and he raised a question about the definite -- the discussion of causality as being related to the whole notion of the methodology by which it's done.

One of the problems that has occurred over and over again in this document and to some extent in others that we've reviewed in the past, but this is where it came out more completely, is that we often don't understand what was the basis for the decision. We see a review of a large number of studies, but in the end, you don't know what was the basis for a decision. After our saying that to OEHHA, they went back and followed and developed a new approach in which they defined with some care the basis for their decision. And so that's in this particular document. But it still needs discussion, I think.

So I think that there -- let's put the Surgeon General's report aside for the moment. There are issues that have been raised that we need to discuss, which has

nothing to do with the past history or the present history. There are issues -- substantive issues that two people have raised, and we're going to pursue them.

PANEL MEMBER FRIEDMAN: I do have a -- I would like to refer to the Surgeon General's report in a different --

CHAIRPERSON FROINES: Sure.

PANEL MEMBER FRIEDMAN: -- context in terms of the kind of work we do and OEHHA does and this process that we go through to arrive at a conclusion about a toxic air contaminant.

I've been a reviewer for a surgeon general -- a chapter -- I received a single chapter from a previous surgeon general's report on a couple of occasions. They said, "Would you please review it, comment," and so on. And I'm sure they sent that single chapter out to several people. And this contrasts with the fact that we as a small group are faced with this huge document. And I think -- it would be really nice if we could get someway to get more help in terms of other readers of specific areas in which they have expertise. And I just -- I just want to express a frustration of having to deal with this huge document and being -- feeling responsible for approving it or not, when we have so little -- we're not being paid for this. That's not a big issue. But we -- a

lot of us -- all of us are very busy and we just don't have time to study these things carefully.

CHAIRPERSON FROINES: I think that point that you're raising now relates directly back to Paul's point about the role of consultancy. Because there's first the question of the consultants who OEHHA employs to do both writing and reading reviewing. And then there's the question about how does -- should the panel approach that issue?

For example, we were helped greatly by hiring Dale Hattis to review the formaldehyde document. It was his review that really formed the basis for the conclusions that led to the final decisions. So in that case, the panel used a specific consultant.

With diesel we actually held, as you remember, a conference in which we went over the issues on diesel.

And so the panel has used consultants in the past. But it's also clear that OEHHA uses consultants. And I think Paul -- in the context of the methodologic approach for decision making, one of the issues is consultancy and how best to do that, to pursue that.

Is that a fair statement of what you were -- I don't think it -- I was more narrow --

PANEL MEMBER BLANC: I mean it has to do -- and I'll come back to the -- I mean I think that Stan's

summary of possible pathways with Chapter 1 were succinct. And I would just add one other pathway to it. I mean because you said perhaps it's just, you know, okay, perhaps it just needs -- perhaps it needs to be rewritten and then a pathway in which it would somehow change the way in which the analysis was approached. But I think that there's's a fourth arm to that and, that is, that chapter -- I would like to see Chapter 1 written in a way which would allow me systematically to review the document for its science in a way that I can't do currently, because I can't trace the consistent choices that were or were not made. And that doesn't mean that I have to agree with the end analysis. I think what I'm being asked to say is is the science appropriate? Not do I agree with a conclusion which may or may not be ultimately subject to interpretation and expert may disagree.

But I have to be able at a minimum to say that I think there was an appropriate, consistent scientific approach. And for me to do that I have to understand what the stated approach is more clearly.

And, you know, for your -- the chapter that you reviewed you seem to have more confidence that you can tease that out. But I'm having trouble. And that's why I started off by apologizing, because maybe I should have been clearer at the last meeting about the parts which

don't seem so clear to me. And I certainly didn't find the explanation of what the body-of-evidence approach meant functionally to be transparent enough for me to actually then see how it was being consistently applied throughout the book.

And I would also -- well, again, I'm holding back a little bit, because I don't want to hijack the discussion. So I think from a procedural point of view the first thing I'd like to hear back from people is whether or not we should actually devote time to talking about Chapter 1. And then -- if we do, then I'm more than happy to go into some of the other details of what the things are that -- specifically.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: As one of the newer members of the Committee, I guess I'm surprised to hear this discussion. I guess I assumed that there was some general understanding that has been used by this committee in other documents. I mean is that not true? Am I misunderstanding something here?

CHAIRPERSON FROINES: I think that what happens is -- I may be not entirely correct in saying this. But I think that in some cases the data was sufficiently strong that the conclusions were relatively obvious. And in some cases, for example, with methylene chloride there was no

Epi at all, and we did use -- well, that's not true. But the Epi was limited and we used animal data as the basis of the decision. So that there have -- one could quarrel with that, you know. And I think it's true that there has never been a defined criteria for a decision making.

PANEL MEMBER HAMMOND: Okay. I guess I have approached this -- I've also served on -- instead of medicine committees where we had to make decisions on Agent Orange, you know, and causality. Things were highly political and had a lot of attention paid to them. And, you know, they have laid out sort of meeting criteria for all of these things. And I've also reviewed documents that they've done. So I've been in that position as well. And I'm also serving on the Surgeon General's committee, so we've been through that thing. So I'm aware of this. And I guess I assumed that those were the -- the sense of causality and suggestiveness, that those were following very similar kind of criteria. And that's how I've been reading the documents. I guess I was thinking that that was more or less the state of scientific art right now, the art of trying to understand data.

And I think that whether -- I don't think data are necessarily overemphasizing epidemiology or underemphasizing. I think it depends on each material what's available. And I think it's important to look at

all the evidence and to weigh it. And I do think it gets to be very difficult to -- you know, to say, okay, we'll give 42 percent of the weight to the animal studies and 37 percent to epidemiology and so much to structural -- you know, quantitative structural analysis. You know, we can't do that. Each study will have its own balance.

However, having said all of that, and thinking that that was all there, I also think it's extremely important for this committee to feel secure about the approach that was taken. So I think if people in the committee feel insecure, if it's not clear, I think it's really critical when decisions are made. But I would suggest that -- I don't know if this is out of line, but that we think of this not just in this document but, you know, kind of settle it, you know, more or less that this is the approach that will be used in other documents, so that we don't have to reinvent the wheel for everything. If that makes any sense.

CHAIRPERSON FROINES: Well, I think you're right. And I also think it goes back to a point Gary made, that I think we're at a watershed or decision point in so far as -- you know, you go along and life is easy and then you don't necessarily use the same rigor as when it gets difficult. And so when it gets difficult, you say, "Holy smokes, our procedures weren't quite as good as we thought

they were."

But now this issue comes up also exactly in terms of what Gary said in so far as we have -- I don't know how many thousands of pages there are. There's the document itself and then there is the number of papers that underlie those documents. So there's five, ten thousand pages that one could read.

And the question is: How do you take a person who is getting no compensation whatsoever for reading a document, to ask Gary to read what is essentially maybe 50 to 100 Epi studies over -- that are within this context? Or looking at -- Joe to look at mechanistic issues? In other words, we don't -- we haven't dealt seriously with the load on the panel. And that affects also then the way you end up -- how well prepared you can be for a particular document. So that I would predict that nobody on this panel, with the possible exception of Stan, has read every Epi study, nor would you expect them to do.

PANEL MEMBER HAMMOND: Well, John, I couldn't agree more with that point. I mean to me -- I have been feeling very overwhelmed in this panel. And I was a lead on silica, and silica was pretty overwhelming to me. And yet the universe of silica was very different. And we all know the passive smoking has this wide universe out there. And so it is a problem that I see on the committee.

I would point out that the OEHHA document has had reviewers, I would say, somewhat analogous to the Surgeon General's. At least that's how I interpret these terms "reviewers" on the front page. Are these people who've actually reviewed the document for OEHHA and --

CHAIRPERSON FROINES: Those tend to be internal reviews.

PANEL MEMBER FRIEDMAN: Maybe I should step in to respond to that.

These are internal reviewers.

PANEL MEMBER HAMMOND: Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And they include people who are epidemiologists: For example, Jay Beaumont, Farla Kaufman; and other individuals who have expertise in specific areas, Mari Golub for developmental toxicity. The consultants we used outside of the agency helped us actually develop the report.

CHAIRPERSON FROINES: Who?

PANEL MEMBER HAMMOND: So they did not review the document?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER HAMMOND: Right. So there were no outside people reviewing until this committee -- this committee's the first outside review?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

PANEL MEMBER HAMMOND: Okay.

CHAIRPERSON FROINES: And so the role of Johnson is?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Johnson helped us develop the section on breast cancer and, in particular, worked specifically on the meta-analyses with us and also in helping us understand what the data say there in the literature on ETS and breast cancer.

CHAIRPERSON FROINES: Stan.

PANEL MEMBER GLANTZ: I'm a little troubled by the direction of some of these comments. Because, you know, I've been on a lot of committees and peer review committees and study sections, and I think if the -- I mean we're not the authors of this report. We're the reviewers of it. And serving on all the committees I've been on, whenever we've dealt with any kind of conflict -- and I'm not talking just about this committee. You know, it's very rare that there's ever anybody there who's read everything about everything. And the reason that you have a committee like this committee is to make a collective judgment where different people bring different bits of expertise. And, you know, we have, as you said, John, on occasion, gone officially and asked outside people to review documents for the panel, which I think is a fine thing to do. I have informally on many occasions asked

people to look at stuff for me to help me in guiding my decisions.

But, you know, we don't have a formal policy of sending these documents out for review. But by the same token, we have the public commentary and the Surgeon General's report. And, in fact, none of the other committees I've ever been on that deal with similar things have the public commentary period. And, you know, one of the ways I have dealt with the fact that I'm routinely asked to look at things where I don't have a huge amount of direct expertise is to rely on the public commentary. Because I figure the people who are submitting those comments, which are almost always industry, although not exclusively, are highly motivated to point up the weaknesses in the document. And so the way I -- and I've said this on the record many times in this committee, the first thing I always read is the public comments and the response to comments. And then I bring my -- whatever additional particular expertise I have to bear.

And so I think it's a little bit misleading to say that there is no outside review. I mean the Surgeon General's reports, for example, are not submitted to the public. They're very -- we all had to sign confidentiality agreements to be on that committee.

So, you know, I sort of -- and maybe I've been

thinking about this committee wrong all these years. But I've sort of viewed our role is to sit in judgment of the case which is put before us and -- and how well OEHHA has dealt with the literature as we know it and also the literature -- and the criticisms which are raised. And I frankly have thought that's been a quite good process. So, you know -- and I've never been on a committee that's dealt with a complex issue where every member of the committee had read every relevant paper.

PANEL MEMBER FRIEDMAN: I guess just to give a personal example. You know, I had read much of the cancer thing, particularly the breast cancer because that's new and controversial. And then issues came up on the press. I said, "Jeez, I better reread this breast cancer and make sure I know what I'm" -- you know, "my conclusions are." And then I get a call from Jim Behrmann or, John, I forget who said, "Well, Paul Blanc wants you to read the cardiovascular section because of some issues there." And I just couldn't do it, you know, and I -- I just couldn't do it. I have responsibilities over the weekend, you know, as a guest faculty at a meeting yesterday and -- so I just feel frustrated.

CHAIRPERSON FROINES: Well we -- we have a problem that when we -- everything's fine as long as the data is clear and -- I mean the mistakes that were in the

OEHHA document were so clear there wasn't even a problem. We just stated them and they were dealt with.

But at least in the breast cancer case there are very widely divergent opinions that are very, very strongly held. And they are unequivocal. There's OEHHA here and there is a whole bunch of other people who disagree. And so when -- and very, very respected scientists who disagree. Not advocates for a particular interest, but scientists who disagree. And with that tension -- if you recognize that that tension exists, that forces me and Gary, particularly, because there's so emphasis on Epi to say, "We better work our tails off to make sure we understand the nature of those disagreements and what OEHHA has done, what they have done in terms of their methodology." And that means that you really have to put a lot of time in reading. And even given the -- I bet I've spent all day for the last five days reading that chapter -- that chapter and papers within it. And I'm beginning to feel like I understand it. But there's still a lot left to go.

But the issue that still arises that Paul raises is, having done all that work, the basis of how the -- how the conclusions are drawn are still not entirely clear. Why something is in at one point and then all of sudden gets dropped out is not entirely clear. Why, there's

discussions of how things are changing; but then when you look at the dates, the things aren't changing. And so on and so forth. So there are lots of issues which we'll get to later when we talk about breast cancer.

But the point is that I think the panel -- where you have significant controversy, it puts more pressure on the panel, and the issue of either consultancy within the context of OEHHA or within the panel is something that we have to consider, because we can't -- we cannot simply drain the blood from the members of this panel and expect it to be successful.

PANEL MEMBER GLANTZ: Well, but we've dealt with lots of other -- look at diesel. I mean that -- we've dealt with lots of difficult and controversial issues and lots of issues where people that were intelligent people who didn't agree. I mean I'd like to make --

CHAIRPERSON FROINES: But, Stan, we -- on diesel we had -- excuse me -- on diesel's a very good case in point. There were three workshops on diesel. We spent ten years on it, and we attended three full workshops. We had extraordinary outside input to that process. We haven't had that in this process.

PANEL MEMBER GLANTZ: Well, people -- we had -- there was a workshop. Nobody came.

But can I just ask a question, just to make this

a more concrete discussion. I think it would be very helpful for OEHHA -- I mean the question which has been raised is how -- what were the criteria used to make the judgment? And that could either be a fine criteria, which maybe wasn't described well enough for certain people's -- you know, to feel comfortable with it or there may be substantive problems with the criteria. And rather than continuing to discuss it in the abstract, I would like to suggest that we simply let OEHHA try to explain it and then let Paul or whoever else asks whatever questions they have to try to decide whether the problem is with the criteria as OEHHA applied it, or whether the problem was with how OEHHA described the criteria that they did apply. Because those are two very different situations.

CHAIRPERSON FROINES: We hadn't gotten to Joe yet. Then we can -- unless -- Paul asked a question which we haven't answered, so we'll go back to that.

PANEL MEMBER LANDOLPH: Yeah, I wanted to thank OEHHA for responding to those ten pages of criticisms I sent. And it looks like you answered most of them. I understand you can't do all the condensation I wanted. Whatever you do, don't make this document too much bigger is my request.

I would like to see -- I guess you'll get to the breast cancer data later. But I would like to see a very

concise explanation of why the Surgeon General in 2004 doesn't list any evidence for breast cancer at all and why now we're getting a lot of data; however you explain this, whether it's you're seeing more studies that they didn't see or whatever. I'd like to see a transition and a reasoning, very concisely, very short, if possible.

CHAIRPERSON FROINES: One thing I think is important is that now there are -- quote, now there are more studies. There are an enormous amount of studies that were earlier. And one has to be careful not to simply as we age us those out, right? Because otherwise half the panel would be gone if we through out the old guys.

The point I'm trying to make is that's where the -- that's where the criteria issue comes, is that one can talk about, quote, the new studies, but it has to be in the context of how do you look at all the studies and what do they tell you. Not because they're old versus new, but because there are methodologic issues associated with them. And so the -- what am I trying to say? What I'm trying to say is that the -- that's where the issue that Paul and Gary are raising I think comes up, which is how do you look at the --

PANEL MEMBER LANDOLPH: And I agree with everything that you all said. So what I would like to see

in there is just some reasoning as to how you got from where they were in 19 -- 2004, assuming they did everything right, and how we got to where we are now. Because they are orthogonal conclusions and there has to be some transitory statement just to bridge that and assess it.

CHAIRPERSON FROINES: But Paul raised the question of: Does the panel want to spend some time now talking about Chapter 1 of the OEHHA document?

PANEL MEMBER LANDOLPH: Is that the executive summary? Is that what you're calling Chapter 1?

PANEL MEMBER BLANC: No, the introduction -- well, I interpreted Stan's comments as saying that, in essence, you are in favor of that because that's part of the heart of the matter is the core methods that were used in this --

PANEL MEMBER GLANTZ: Well, I'll be very precise. I think that it's fine. I'm happy -- I'm happy with what they wrote. Okay? And I think that the -- and it seemed to me that reading through the document that they have applied a consistent set of standards which I think are reasonable. So if it were up to me, I don't think it's necessary to discuss it. But obviously you do. And I think that, you know, since in the end we're going to have to make a decision about this document, everybody needs to

be comfortable.

But the question I was -- so I'm satisfied with it as it is. Maybe I'll change my mind when I hear the discussion.

What I was saying though is I think rather than have an abstract discussion which drags on for a long time, I'd rather let them try to explain the criteria that they think they consistently applied through the report to see if you agree or disagree with the criteria. If you agree with the criteria, then it's an editorial problem. If you disagree with the criteria, then there's a very fundamental scientific problem. And it's not clear to me which of those is the situation from your perspective.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: Well, whether or not we do that, I hope we do get to the point that Joe raised, because what's -- you know, I think the situation we're in now is different from a lot of the other things we reviewed, because the public comments have generally come from lawyers or advocates for an industry that might be affected by the decision that's made.

Whereas, here we're concerned with comments from a neutral body like the Surgeon General's report or scientists we respect like Michael Thun or Jonathan Samet. And I'm really nervous, if they come to a different

conclusion, I want to -- I want to make sure that -- can I finish please? -- I want to make sure that OEHHA deals directly with their comments and why their conclusions are different from those of these respected scientists.

PANEL MEMBER GLANTZ: Right. Just for the record though, Michael Thun submitted a public comment. Jonathan Samet didn't. Several of us have talked -- I was on a study section with John on Friday. So several of us have chatted with him. And we have the Surgeon General's report -- the 2004 Surgeon General's report, which he edited. And he's also editing the -- whenever it come out, one on passive smoking, which Kathy and I are on the committee for. But that document hasn't -- that document hasn't been released. It will come out some day. And, you know, he is not the sole arbiter of what that document will say. So we can -- that's pure speculation. If you want to invite him to do something, that's a different thing.

But I think that the issues that have been raised, and I personally think dealt with in the document, around breast cancer -- the differences of opinion in the community are, you know, people understand what they are, and it's different people can draw different conclusions. I think -- And I agree -- by the way, I agree with the point Joe made about having an explicit -- and I've told

this to OEHHA. I think that there is a need to explicitly deal with what the 2004 -- for the reasons you say, what the 2004 Surgeon General report says. I think that needs to be explicitly addressed in the document and why -- you know, what's changed in the five years or so since they stopped, you know, actively collecting papers for that report. Because those things do -- they are very slow in being produced.

CHAIRPERSON FROINES: I think in this case we have -- we have a quite significant issue that's very worrisome. We have the Surgeon General's 2004 report. More importantly, we have the IARC 2002 report. That also is strongly negative.

We have Sammit's comments, and he only -- when I spoke with him, he was speaking for himself, not for this committee. He was giving me his point of view.

Michael Thun, when I talked to him, gave me his point of view, not necessarily.

We have the position of the National Cancer Institute on developing a review process that's different than the one we currently have. So the NCI has taken a position on the review of this document given the differences of opinion that exist. It's a comment.

And I spoke today with Kurt Straif IARC about this issue.

And so when you start to add up the number of not people who are interested because of their employment, but because who are strong scientists and you have a whole body of people who are taking a completely opposite point of view, then I think Gary's right. We need to pay attention to what are the -- what are the differences.

I didn't go back and look at the IARC report and take each study and then compare it to what OEHHA had said. But I think part of OEHHA's methodology should precisely be that they take what's written in the IARC report, compare it to what they think, and see where there are differences.

For example, there -- in the Surgeon General's 2004 report there is a criticism of one of the studies that OEHHA has taken as one of their six main studies. And the IARC -- the Surgeon General's report talks about confounding and explanation of the confounding. And so they actually suggest that that study's positive nature may not be as positive as OEHHA would have said. And that's the kind of thing, it seems to me, that we have to have OEHHA address as a methodologic issue that Paul's raising.

And so where you have these kinds of differences, it seems to me that those have to be addressed because they ultimately form the basis for differing conclusions.

PANEL MEMBER GLANTZ: Well, I don't think anybody disagrees with that. And I think we should let them do it, you know, and see what they say, you know. And then make --

CHAIRPERSON FROINES: But Paul's point is germane because we shouldn't be having a discussion about the Surgeon General's report after we've had three meetings on this topic and still say that there are differences in how that report dealt with something in 1996 than what OEHHA did. That should be in their document. That's the point.

In other words, what should be in their document is in fact the methodology they used for making the decisions. Because if you take the Surgeon General's report, you can't put it necessarily in the top six. You have to maybe question whether it should be there.

So all I think Gary and Paul are saying is: How do we approach these decisions? Or how does OEHHA approach these decisions?

Joe.

PANEL MEMBER LANDOLPH: Yeah, it almost occurs to me this is an issue, speaking of the breast cancer, one where there is a little wider distribution of opinion than perhaps we would like to see to make definitive statements. And I guess it's because maybe less well developed in time. You know, so we haven't had a

scientific consensus. It's like a Delta function. It's still a little -- the coefficient of distribution -- of the width of the distribution is still a little bit wide. So I don't have any problem with saying to you, just acknowledge that there is some width to that distribution, and that's okay. We may not be able to resolve these issues precisely here at this point in time because of the divergence of opinion of other investigators, you know, who are pretty good. So just acknowledge it and let it go at that. That's the best you can do.

CHAIRPERSON FROINES: In terms of the list of comment -- of outside agencies and groups and individuals that have commented on this issue, you also have -- which we'll try and Xerox and get you -- the editorial from the Medical Journal of Australia, which its editorial starts out, "It all depends on which studies you emphasize." And they take a somewhat negative view of the OEHHA report. And so it seems to me that these are the kinds of issues that -- that need to be addressed when we talk about breast cancer. But the point that Paul is making, we need to address the issue in a broader context in terms of approaching reports in general.

Paul, do you have a comment at this point or are you --

PANEL MEMBER BLANC: Well, I'm a little bit

uncomfortable with the way the conversation is evolving, because the specific topic of the cancer chapter in general, or the breast cancer part of the cancer chapter, is a little bit of the tail wagging the dog. I think that if we can satisfy ourselves with the generic principles, then we have a way by which all of those discussions can come into a unified context without there being an issue of, you know, is it one issue or another that's got people, you know, hot under the collar? Let it be more of a consistent approach.

Again, echoing Stan's comments that what our role is is to review the process of the science behind the document, without presuming that we have reviewed the raw data, because that's not -- that's not our responsibility nor our authority nor our expectation.

CHAIRPERSON FROINES: That's an interesting question that I asked Jim about for a legal opinion. Because if one reviews the process and says that the OEHHA report as it's presently constituted followed a satisfactory scientific process, then you would vote to approve the report, even if the consensus of the committee was in opposition, say, on the breast cancer issue. And so that there are some dilemmas there that are not entirely obvious.

PANEL MEMBER HAMMOND: John?

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER HAMMOND: I have -- I share some feelings with Paul about this concern that we're -- we're focused on one chapter pretty clearly. And I bet we can all guess why. And somehow that seems to me like the process of this committee is not following -- it's being driven by media rather than by science. And I think it is important that we go back to the science and say, "What do we want to do scientifically?" I am fully supportive of having a clear and transparent method. I think that that is really important, regardless of this study, silica, anything, but for this -- and I think that's very important.

It bothers me to have this discussion about one particular outcome right now, if -- and then if we want to talk outcomes, I guess I would almost flip it around and say since that's the only -- of dozens of effects, it's the only effect that's been discussed this morning, you know, does that mean, could one infer that this committee is totally supportive of all the other findings? And if that were true, it would be nice to kind of get that done, put aside, and then go to the one issue where there's a problem, if that's what it is. But we should actually kind of just get done with everything else if that's true. Or is there this concern that the methodology, you know,

kind of issues are a problem throughout the document and we need to -- in that case I think we should focus on the methodology questions and being very clear about that.

I think the last thing we should do is talk -- I mean in my mind, the last thing should be to talk about the breast cancer chapter at this point. Either we -- you know, either we have to figure out where are we in the whole document, you know, and we've done everything except that, and we'll go to that chapter. Or do we want to talk about the methodology and then we'll go through various things?

CHAIRPERSON FROINES: I think we should talk about the methodology till we feel comfortable with it.

PANEL MEMBER HAMMOND: And then maybe we should give OEHHA a chance to talk to us.

CHAIRPERSON FROINES: Yeah, we're going there.

And then talk about other aspects of the chapter -- of the other chapters in the document and then go to the breast cancer issue.

Are there any other comments from the panel?

I do think that we're not just talking about breast cancer. I think we're talking about how OEHHA views meta-analysis, for example, and how -- what the process is for -- I suspect that I disagree with OEHHA on meta-analysis, and I -- maybe others do and others don't.

So it's --

PANEL MEMBER HAMMOND: John, I would propose in that case that this is -- it's fundamental to the whole workings of the committee, that if -- I agree with -- was it Paul or Gary or Craig? -- who said if only thing we did today was work at -- come to a conclusion about methodology and get that clear -- and, again, it may be that we all would agree with what they did, that they just didn't say it well or clearly enough; or we disagree with what they did. But if we came to some conclusions around that today, that would be a productive meeting.

CHAIRPERSON FROINES: Good.

PANEL MEMBER BLANC: It was me.

I agree.

PANEL MEMBER HAMMOND: I thought it was.

Thank you. It was Paul, by the way.

(Laughter.)

CHAIRPERSON FROINES: Judging from the reaction to what you said and then Paul's reaction and then Gary's reaction and Craig's reaction -- even Roger was smiling -- let's assume that for the most part people agree with that notion.

Do you have anything more to say before we ask Melanie or George or both to comment?

PANEL MEMBER BLANC: No, that's fine. Get them

started.

CHAIRPERSON FROINES: All right. Melanie has also seen a document that I sent to the panel, which listed a number of topics, of which go to the same kinds of issues.

Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: There's a couple issues.

It's not clear to me what it is that Paul or anyone else doesn't like about how we laid out the criteria that we used. So that's one issue. So a little more specificity there would be useful to us.

In Chapter 1, because this document relies heavily on epidemiology, we essentially indicate that we looked at several sources, which described typical criteria for causality used by epidemiologists. And that --

PANEL MEMBER HAMMOND: Could you please refer to the pages.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

PANEL MEMBER HAMMOND: So we can just follow along with you. And then -- I think would help clarity.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Section 1-4 starts on page 1-9, at least in my copy. I hope it's the same in everybody's.

Where we talk about a weight of evidence approach being used to describe -- the body of evidence on whether or not ETS exposure causes a particular effect. Since there are many, many, many Epi studies ETS, that was primarily what we focused on in describing specific health outcomes. But we also looked at other sources of information on biological plausibility. For example, the whole body of literature on carcinogenesis of constituents of ETS, which should play a role in your decision on whether an endpoint makes sense or not.

We used traditional criteria for causality, such as the Hill criterion. And if you go to different sources, you get basically the same underlying criteria, although the discussions of the utility of those criteria vary source to source. But essentially looking at -- and then on page 110 we described that a little, saying that the criteria for causality include things like biologic plausibility; the strength of the association; any dose response relationships that are evident from the data; the consistency of the association across studies, across geographic regions, across different populations and even across different Epi methodologies; the temporality of association, in other words does it make sense -- the time between exposure and effect, does that make sense for the effect under consideration? And then the coherence, which

in our mind is a little bit like biological plausibility: Do all the data stick together or does -- is there something in their which would make you think that the Epi study is measuring something different than it thinks it's measuring?

We had some discussion at the last meeting in terms of: Well, is one study good enough, two studies good enough, ten studies good enough to determine that something is causal? And we would very much hesitate to put that in, because that is way too prescriptive for epidemiology, in our opinion. Each endpoint has a different database, different numbers of studies, different quality of studies. Clearly determining that something is causal has an element of judgment. You cannot get around that. I think in the past in the toxic air contaminant program, in some cases we've relied heavily on animal data because that's what we had. We still continue to believe that if animal data show an effect and you have no reason to believe it doesn't occur in people, then those data are useful.

CHAIRPERSON FROINES: But, Melanie, if I can just make a comment about that, which will come up again later when we talk about other things.

But there is a definition of what constitutes a toxic air contaminant. And there is a definition which

constitutes causality with respect to the science of an issue. The criteria for what's a toxic air contaminant is very liberal in that sense. Most -- a lot of things -- many things would fit, but that the same substance might not meet an establishment of causality of effect based on the science. So that one has to keep in mind that there are policy differences that are actually real. And when you get into -- you know, in the National Toxicology Committee on Carcinogens, which I chaired, things don't make the top list unless there's epidemiologic evidence. Animal evidence doesn't -- can't bring it to that level.

Under Prop 65, an animal evidence can bring it to the top level. And those are differences in definitions, as a toxic air contaminant definition is very, very loose in that because they were trying to maximize protection.

So I think one has to be careful to be clear on what's the science and what's the policy.

PANEL MEMBER FRIEDMAN: I'd like to raise a specific question based -- we had a conversation the other day, and I think it was either you or Mark Miller who said that you have a section on how you decide which are the, quote, influential studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER FRIEDMAN: And is this it on the bottom of page 1-9, general consideration made in

evaluating individual studies include study design appropriateness of the study population method used, et cetera? Is that the section? Because I was looking for it and I couldn't find it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. That is our --

PANEL MEMBER GLANTZ: I just --

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- overall statement. What Mark was referring to was the specific studies that we thought had done the best job of exposure assessment for the breast cancer chapter. So that is the first section under the discussion of the association between ETS and breast cancer is where -- that's where that whole terminology came in.

PANEL MEMBER GLANTZ: Actually I find that very confusing terminology, that --

PANEL MEMBER FRIEDMAN: Yeah, because I was searching for that after in that conversation. Would you mind -- I'm sorry to divert again to breast cancer. Could you just tell me the page that that's under or that that's on, I should say.

PANEL MEMBER GLANTZ: While Melanie is looking for the page, I think that term "influential studies" should be purged from the report.

PANEL MEMBER FRIEDMAN: Yeah, I agree, that

"influential" is not the correct --

PANEL MEMBER GLANTZ: Yeah, I think what they're trying to say is studies with the best quality exposure assessment. Is that what --

PANEL MEMBER HAMMOND: Or you could say most informative studies.

PANEL MEMBER FRIEDMAN: Yeah, or the most scientifically --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I totally regret using the word "influential" because everyone has hated it.

PANEL MEMBER BLANC: Well, let's get a little bit more specific -- and I'm going to come back to some of my other comments -- but wait --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I answer Gary's question first?

PANEL MEMBER GLANTZ: Let her answer Gary's question.

PANEL MEMBER FRIEDMAN: What's the page where that is?

OEHHA SUPERVISING TOXICOLOGIST MARTY: On page 7-132 under Section 7414. And we are discussing essentially the study characteristics that we think are important for looking at effects of ETS. And this was with regard to the breast cancer issue, because there are

a number of studies that don't show an effect. But the exposure assessment was very poor -- poor to very poor. And it's an important issue for us in terms of determining whether we think there's an association, suggestive or causal, between ETS exposure and breast cancer. So that's why we were more specific in there, because of this issue of having a lot of negatives -- or null studies.

PANEL MEMBER FRIEDMAN: So it's the four points starting on page 7-132 and ending on 7-133? Those are the criteria that you used?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. And it's on top of the general criteria up front of, is it a good study for other reasons, not just the exposure assessment. So it's on top of those criteria described in the sentence you were reading.

PANEL MEMBER FRIEDMAN: So --

OEHHA SUPERVISING TOXICOLOGIST MARTY: So looking at study design, sample size and so on.

PANEL MEMBER FRIEDMAN: So would you be able -- with each of the studies that you quote -- you know, which you're going to pick another term, but which you now call "influential, be able to say, "We picked this one because this" -- you know, be able to specify exactly what --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER FRIEDMAN: Okay.

PANEL MEMBER HAMMOND: You could maybe make a table If you needed to. But --

PANEL MEMBER GLANTZ: You really like tables.

CHAIRPERSON FROINES: Well, I think that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: There is a table.

CHAIRPERSON FROINES: Paul, go ahead, because I think you're going to raise the other side of the coin.

PANEL MEMBER BLANC: Well, just in regards to this one here's what I'm trying to talk about methods. You're saying you will weight studies. What you're actually saying is that in certain instances you will weight studies 1.0 and other studies zero. You're saying you will exclude studies from analysis if in certain -- for certain analyses there will be sensitivity analyses or sub-analyses, which will exclude certain studies and include others altogether. Not weighting them or at least weighting will be one or zero.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, that's not what we meant by saying that.

PANEL MEMBER BLANC: But isn't that what you do functionally in certain analyses? Certain analyses -- you exclude certain studies from certain analyses, certain meta-analysis, for example --

OEHHA SUPERVISING TOXICOLOGIST MARTY: If you're

looking at meta-analyses, there are criteria for inclusion of studies in meta-analyses. And we did exclude some studies, both positive and negative studies -- positive and null studies because we thought we were concerned about methodologic issues for those studies. But that's a little different than what we're talking about in Chapter 1. When we say we are weighting studies more heavily, I'm talking about more in a qualitative fashion of this study makes more sense because of the study design than this other study. That's what we meant there.

PANEL MEMBER BLANC: Whereas what you mean in the other section that you were referring to in the cancer -- in one of the subsets of the cancer study was more a -- was not a quality weighting, it was an exclusion-inclusion? Would there be situations where studies would be excluded or weighted to null? I'm not just talking about whether there's heterogeneity that allows you to do certain aspects of meta-analysis. I'm just talking about analyzing certain groups of studies together and not others. Is there an A priority or consistent decision methodologically about that or does it vary from outcome to outcome?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I think if you're doing meta-analysis, you always have some inclusion-exclusion criteria based on the study design, if

that's what you're getting at. When we're looking at things in a fashion to say, well, you know, I -- this study doesn't show an effect. But probably the reason it doesn't show an effect is because of methodological flaw, number one. That is what we mean when we say weighting the studies as we go through each health outcome in the studies that are focused on that health outcome.

PANEL MEMBER GLANTZ: Well, aren't there -- I mean I think there are kind of three different things that are getting a little bit mixed up here, if I can -- I mean I think that -- and if I'm wrong, correct me. But one thing -- the way I read Chapter 1 -- and I just looked through the Surgeon General's discussion of causality. And I don't think you're doing anything differently than what they say they're doing is my understanding.

But I think one is the question -- when you talk about weighting the evidence and considering which studies are influential or important when you're making the qualitative judgment in the end, which I think is what Chapter 1 is trying to talk about, I think that the -- which I think is one issue. The other issue, which is the point you're bringing up now, Paul, is that when you do a meta-analysis, how do you weight the studies in the sense of mathematically weighting them in the calculation? And that -- there are two kind of sub-questions to that. One

is whether you include the study or not in the analysis, which is a 0-1 kind of thing. And then there's another more technical question of how do you -- once you've included them, what weight do you assign?

I think what OEHHA has done here, in dealing with the second two questions -- and, Melanie, if I misread your report, correct me -- I think they followed a very cautious approach throughout the report. One is they used the random effects meta-analysis I think everywhere, which is the most conservative kind of meta-analysis to do and I think the correct one to do here because there is study heterogeneity.

And then the other thing -- so I think that was appropriate. And then the other thing -- and again correct me if I'm wrong -- what they did was they cut the data in several different ways. The first thing they did is they said, "Okay. We think there are some good studies and some not so good studies, based largely on the quality of exposure measurement." And they make the argument that the poor quality exposure measurement bias is the results toward the null. And then they said, "Okay. We're going to take every one of the studies and put them into an analysis whether we think they're good or crappy."

And if I say anything wrong, stop me.

And then they said, "Okay. When you do that,

when you put every single study in, including ones which you think are biased toward the null, you still find a statistically significant elevation in the meta-analysis."

And then they went on and -- so to me when I read the report, I think that's a pretty strong argument that there's an effect, not talking about the magnitude of the effect.

And then they went on and they said, "Okay. There are several different ways that people have proposed looking at the data differently. And one of the things to do is to say we're going to take what we viewed as the highest quality studies," which was these four criteria on page 132. And when you do that, you end up with a higher risk estimate in a second -- that's a second analysis. And they actually I think did several, cutting it in different ways.

And I mean I think that that's an appropriate thing to do. I think that it's pretty -- it to me it was clear what they were doing and why. And I think that the concern of being selective in the studies that you include in a biased way, if they hadn't found a significant elevation when they looked at all of the studies, then I think that would be a of concern. But since the analysis including all the studies found a significant effect, then I think it makes sense to do the subsidiary analyses. I

mean I don't -- I mean -- so to me, when I read what they did, I thought it was reasonable and, in fact, very cautious. But I mean obviously you --

PANEL MEMBER BLANC: I'm not talking about -- but I'm not talking about the breast cancer thing. Only talking --

PANEL MEMBER GLANTZ: Well, but that was the approach they used throughout the --

PANEL MEMBER BLANC: Well, no, they don't say here that for some -- no, that's not true. They don't -- there aren't other chapters, for example, or consistently chapters where there are a consistent re-estimation of an effect in some kind of meta-analysis approach that attempts to limit it to studies of better quality.

Now, maybe that's because -- and, again, let me come back to saying how I can -- I'm trying to understand what you did consistently. So perhaps it's only for those things where you were going up a notch. If you were finding -- if you were simply reaffirming what had been found in the previous document, you didn't find it necessary to do that. So only consistently for areas where you were going into new territory where something was going from inconclusive to suggestive or suggestive to conclusive you did the following things that we might not necessarily do. We attempted in all cases to do a

meta-analysis. When we did the meta-analysis, we attempted to do both the meta-analysis with all studies that had data available for meta-analysis and we did a meta-analysis with studies limited to studies which we felt were less likely to be subject to bias towards the null for the reasons that we had previously alluded to on the page.

In fact, the meta-analysis doesn't appear here at all in the introductory chapter, any comment on using meta-analysis, how it will be used, when it will be applied, when it won't be applied. It's just on a case-by-case basis as you go through the chapter. So, you know, I have no way of knowing as I read something, "Well, okay. Now, they didn't do a meta-analysis here. Is that because it was superfluous, the data didn't exist, you know, it wasn't adding anything, it wasn't necessary to add anything?"

So that is an example. And I certainly think that -- you know, Gary hit on another thing that I had already made a note to myself about was this thing about the quality of the studies and what does it mean and what does it not mean. Does it -- when you say weight, it's -- you know, it's with quotation marks and it means that -- it doesn't mean that something will be ignored, but it may mean that you will, you know, more strongly emphasize

certain studies or not.

And I would be happy to go on to some other things which I think are issues for me of a similar vein. But I hope this gives you a flavor of where I'm going, that I -- if this were a "method" section for a paper, I couldn't understand the paper if I was looking here -- if what I was looking for here was some road map that will tell me what is the consistent approach that will be used throughout this document. In other ways you're very explicit. You know, you talk about "We're basing this volume on the previous volume. We're not going to rehash studies that were already in the previous volume unless," you know, the following things are going on, "at which point we may go back to a study."

Am I -- is this making it clear what my -- where my --

PANEL MEMBER GLANTZ: So I guess the question is: Is there a substantive problem here or is it a problem of presentation? Do you think you're doing the kind of things Paul is talking about or do you think you did them? Or is he bringing up things which would represent a fundamental change in what you were trying to do in the report? And maybe you -- if you could clarify these things.

CHAIRPERSON FROINES: Can I make just one comment

before you answer, because I -- I do think that the issue of what are the better studies is -- you think through. But the other side of the coin of the, quote, "weaker studies" or the ones that you somehow -- they somehow disappear is not clear, because to the degree that those tend to represent the null studies, you need to be careful about defining how and why those studies, which would tend to lead to a different conclusion, in a sense disappear from view, which is very worrisome to me at least and probably to others.

So Paul's comment about 0-1 I think is an accurate statement. And it's the -- where is these -- where is the between 0 and 1 and how does one deal with that? Because to the degree that null studies disappear, that's a potential -- that suggests a potential for bias as well.

PANEL MEMBER GLANTZ: But it's important to point out though, John, that they did an analysis where they didn't exclude anything. And so the way I think about what they wrote in here is they did an analysis where they included everything and found -- regardless of their measure of study quality --

CHAIRPERSON FROINES: Well, we could debate that, because --

PANEL MEMBER GLANTZ: Well, no. They're in

there.

CHAIRPERSON FROINES: I understand. I'm looking at it right now. And I also look at the heterogeneity and I -- it's not so obvious. And it's one of the reasons a lot of people don't like meta-analysis, and especially for defining causality. So that it's not quite that simple, Stan, that they did it all.

PANEL MEMBER GLANTZ: Well, no. If you look in the report, they did an analysis including all the studies, at least as best as I could tell. And then -- and that to me in reading the document is sort of the most important single fact that's in there. Then they went on and did these subsidiary --

CHAIRPERSON FROINES: I think they did a study that had specific exposure characteristics that they put all the studies in. There was no document -- There's no table where they put all the studies in.

PANEL MEMBER BLANC: Well, we can -- again, I think we're --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Actually there is a table.

PANEL MEMBER GLANTZ: Let's let them answer.

CHAIRPERSON FROINES: Where?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. First of all --

PANEL MEMBER BLANC: Well, but I don't want to go into right now a discussion of the breast cancer subsection of one chapter. I'm trying to get at generic points. And then we can come back to some of these other questions. Because if you say at the beginning that "This is what we're going to do with meta-analysis," and if you say, "This is the importance. We will or will not get to meta-analysis. This is the situations that we will use meta-analysis and this is how we will use it when we use it," then it's a simple thing for me to figure out, you know, Stan's point versus John's point and for me to see whether or not from a scientific point of view that use of meta-analysis is appropriate.

CHAIRPERSON FROINES: Well, I was just saying, I think that the -- one of the issues has to be how do we deal with negative studies, whether they're --

PANEL MEMBER BLANC: Well, we can come back to that in a different way.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Can -- just a couple comments in response to Paul's comments.

I think your point about meta-analysis and that there's nothing in Chapter 1 about it, we can fix that, because we should describe why we did a meta-analysis when we did it.

We only ended up doing two meta-analyses: One on childhood asthma and -- which involved 85 studies. And it's not presented in depth in here. That's because we have a totally separate project that's doing that, and it's going out -- it's being submitted for publication. The other endpoint that we used -- or that we did a meta-analysis for is the breast cancer in ETS exposure endpoint.

PANEL MEMBER BLANC: So let's take an example.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So then -- and actually the meta-analysis were done to help us understand what the data are saying, not to say whether it's causal or not. A positive meta-analysis makes you feel better about saying that there is an association. But it's not the only reason that we said there was an association for any endpoint.

PANEL MEMBER BLANC: But you don't say that either, do you? You don't say here in part of our --

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's the stuff we need to put in.

PANEL MEMBER BLANC: Yeah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's the stuff we need to in.

PANEL MEMBER BLANC: And why would you not, for example, on something like adult asthma onset, which has

been more controversial than childhood asthma onset and where I believe you're upping the ante to causal from suspect?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Suggestive.

PANEL MEMBER BLANC: From suggestive, I mean. Is that right? Am I getting the right step up?

Why would you not have done an analysis there? Because you felt that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, it's mostly a resources issue. We didn't think that that was going to be a particularly controversial decision either just because of the number of studies and, you know, the continuum of having induction exacerbation of asthma in young kids, older kids, and then adults and adolescents.

PANEL MEMBER BLANC: So, for example, that would be a place where you could explain a priority, why you did or didn't do. You know, issues of manpower, I'd be frank about it. That's in the human resources issues of -- that not in all cases it was not a -- not only was not a requirement to establish causality in your view or to go to causality from suspect or whatever -- I'm sorry, I'm blacking on the word -- but in fact --

PANEL MEMBER GLANTZ: Suggestive.

PANEL MEMBER BLANC: -- suggestive, but in fact

is not used as a sole criteria. And then if you say it's not used as a sole criterion, then you better explain what kind of criterion it is used at. I mean is it -- you don't mean to say it's not used at all?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No.

PANEL MEMBER BLANC: So to support causality.

So one of the discussions we had theoretically last time was in fact: What is the role of a meta-analysis? And is it a marker of consistency or is it a marker of strength of association? And it's kind of a theoretical question.

And I don't think you have to, you know, give -- write an epidemiologic theoretic text, but I think you better -- you need to say what it is that you were thinking as you did these things.

I think that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We also described meta-analysis that were already published in the literature for a number of other endpoints.

PANEL MEMBER BLANC: Well, that's right. And this is a really small thing, but again it sort of highlights. When you have your tables and you list studies, some of the chapters you list separate numbers for studies that are original studies and studies that are meta-analyses. And some of them you have a little

asterisk and you say, "Includes three studies that are meta-analyses." Just those little things show a kind of inconsistency, which it has a cumulative effect of not suspending one's disbelief.

So that's a little editorial comment, but it does come back to this.

Now --

PANEL MEMBER GLANTZ: Could I -- I just wanted to ask a point of clarification to see -- because I think there's a point of agreement here, but I just want to try to make it explicit. I mean when I look at a meta-analysis, I look at both as a measure of consistency and an attempt to get an estimate of the magnitude of effect. Those are two different things. But you can use meta-analysis to help you with both of them. I mean is there any different -- do you agree with that?

PANEL MEMBER BLANC: I don't know. I mean I think that there are elements of both, but I --

PANEL MEMBER GLANTZ: But they're two different purposes --

PANEL MEMBER BLANC: Well, they're two different purposes. And what I don't know is -- or what I have a gut-level feeling that would be a bad idea is if you used it to do both simultaneously; that in the same argument, if you said, "Well, I don't really have consistency

otherwise and I don't really have a strength of association otherwise, but I have a meta-analysis which has both and, therefore, I've met two of my Bradford Hill criteria in one fell swoop."

PANEL MEMBER GLANTZ: No, but there are tests -- you can do tests of heterogeneity as part of a meta-analysis. I mean I don't know if we're getting into a semantic debate. I actually brought two textbooks on meta-analysis because I thought this would come up.

I mean I think that when you do a meta-analysis, you can test your heterogeneity, which at one level consistency is: Are the studies homogeneous or heterogeneous? The second thing -- and when they are, you should be using a random effects model, which they do. And then -- but if you are finding the -- when you say to me consistency, it -- to me it's talking about basically the width of the confidence interval that you estimate from meta-analysis. When you talk -- the other point is the magnitude of the point estimate, which is the measure of effect size. And then you put those two things together to do a test of significance.

So I think in fact when you do a meta-analysis, those are the things that pop out of the analysis.

There are three different -- there are three different things that you can say when you do an analysis:

Is there a homogeneity or heterogeneity?

How much variability is there in the conclusions of the studies? Which is going to be measured by the standard error of the confidence interval.

And what's your estimate of the -- of the coin estimate of the effect size? Which is magnitude of the effect, which is a different question than the level of -- to me when you say consistency, it means you do the study 27 times and you get the same number 27 times. That would be your most highest level of consistency.

PANEL MEMBER FRIEDMAN: Could we substitute the word the size of the "association" for size of the "effect"? Because once you say "effect," people start assuming you're talking about --

PANEL MEMBER GLANTZ: Okay, sure. If you want to say size -- the point -- yes, I don't have a problem with that.

PANEL MEMBER FRIEDMAN: Thanks.

PANEL MEMBER GLANTZ: Although in most books they talk about effect size.

PANEL MEMBER FRIEDMAN: But I mean you're talking --

PANEL MEMBER GLANTZ: But what we're talking about is the point estimate that pops out of the analysis.

PANEL MEMBER FRIEDMAN: Right. But, I mean when

you say effect, people have started thinking you're talking already about causality. And I really worry about that.

PANEL MEMBER GLANTZ: Oh, I guess, except that -- well, the point I'm trying to make though is that these three things are all tied -- you do one analysis, and it gives you information about all three things. And what I'm trying -- and that's what I thought I heard you say and that's what I heard Melanie say.

So would it be an accurate statement to say that, you know, by spelling that out in the introduction to say, "We" -- in the appropriate places, "We" --

PANEL MEMBER BLANC: It would be helpful -- I think it would be helpful to have them comment as to -- explicitly as to what their view is and to be very specific about how much weight or not weight you -- in the quotation marks weight sense, how influenced your thinking might or might not be in a weight of evidence causality decision in terms of what an internal or external meta-analysis may or may not show. And that may also have to do with not just the meta-analyses that you did, but meta-analyses that you found in the peer-reviewed literature, which is relevant to -- even though you yourselves only did two meta-analyses, in effect you did try to find them if they existed relevant to the topics at

hand. And it's not clear -- you know, if there was a consistent approach to how that might have influenced or not influenced your thinking, that's not spelled out either.

And I think another very important and related topic, which is not dealt with at all in the introduction and tends to come up only in specific contexts, which may need to be done -- reiterated is whether or not OEHHA has an opinion about cohort versus case-control studies in the topic at hand, in the general topic at hand, and whether it's different for cancer as opposed to noncancer respiratory effects or whether you have a generic overarching sense of the cohort studies or not.

You've spent a lot of time in the introduction talking about classification and misclassification, which I also want to come back to. But you don't really ever talk about a dichotomy between cohort and case-control studies. Your implication functionally in certain parts of the book is that there's almost no way that a cohort study could be as good as a case-control study for exposure classification. I mean that's kind of the implication, is theoretically it's possible; but in practice, less likely. But you don't -- you don't explicitly say that.

And also in terms of consistency of results, does

it matter to you or not matter to you whether there is consistency across both case-control and cohort studies? Or is that all for you a question of exposure assessment in ETS? So --

CHAIRPERSON FROINES: Paul, I think the first point you made, which I agree with, you talked about -- went into talking about meta-analysis. But I think the point itself is generically important as well.

PANEL MEMBER BLANC: Yes. About cohort versus case-control?

CHAIRPERSON FROINES: No, before that, the point you were making earlier. We'll leave it on the record so it's clear.

PANEL MEMBER HAMMOND: I'm sorry. I don't want --

PANEL MEMBER BLANC: No, I have other comments. But I don't want to just speak for --

PANEL MEMBER HAMMOND: I want to get back to something. When Gary had talked about strength of association versus strength of effect, I agree with that should be strength of association. But I actually would like to go on record as saying I think we ought to question that particular criteria in the Bradford Hill. I think that that's something that comes from the fact that that was a set of criteria that was set up 50 years ago,

right -- I mean 40 to 50 years ago, and at a time when we were looking at relationships between exposures and disease that had five- and ten-fold factor -- relative risks of five or ten.

We are now living in an age where we are concerned about effects when there's a 20-percent increase risk and a 40-percent increase risk. And we have much better techniques available to us, both statistical and epidemiologic and exposure assessment, so that we have the potential of being able to detect those.

I think that strength of association -- and there's no intrinsic scientific reason that all associations have to have relative risks or odds ratios of 5 or more at all. Some things could in fact -- if we knew absolute truth and God came down and told us the truth -- and the truth might be for some agents that there's a 10-percent increase risk or a 50-percent -- the reality is it's easier to detect the large effect. But if you have a large enough study, if you have controlled for factors well enough, then one can detect small enough. Look at air pollution where we're looking at a few percent, a handful of percent. So I think it's a time we actually step away from that as a criteria.

PANEL MEMBER FRIEDMAN: I agree with you that there definitely are weak associations and weak causal

effects. And, you know, if you can show them in a randomized trial, then I'm very happy. But when you find them in an observational study, you still have to worry about uncontrolled confounding. And I think they -- even though I agree that some of these weak associations exist, I think they have to explicitly address the possibility --

PANEL MEMBER HAMMOND: I totally -- I would totally agree that the study is going to have to be much more carefully conceived and conducted to be able to yield information about a small effect. But if a small effect exists, it's more likely than not to be -- to lead to a negative result of a true effect than a positive result of a not true effect. I always get type 1 and type 2 backwards, you know, which ones -- but, you know, which errors --

PANEL MEMBER GLANTZ: Type 2 -- you're talking about type 2.

PANEL MEMBER HAMMOND: Yes, type 2 is the more like -- we worry about type 2. But I think type 1 is actually the error that happens more often.

PANEL MEMBER GLANTZ: No, you have it backwards.

PANEL MEMBER HAMMOND: I've got it -- see, I said -- I knew I'd get it backwards. But, anyhow --

PANEL MEMBER GLANTZ: You worry about type 1, but type 2 is --

PANEL MEMBER HAMMOND: I'm worried about false negatives. But people tend to worry about false positives more.

But, regardless, I think we agree that to detect -- to have an epidemiologic study yield information on a low effect requires an extremely well done study with lots of things that have to be there, and you have to look at it carefully. But there's no intrinsic reason that all exposure disease relationships have to be large. And that's what the Bradford Hill criterion on that implies.

PANEL MEMBER FRIEDMAN: But if they are large, don't you feel more confident that they're really causal?

PANEL MEMBER HAMMOND: Well, you feel -- yeah. But that doesn't mean that -- I don't think that being small makes me -- you know, it's just that there's less likely to have a chance. But that's already taken care of in some ways with a confidence interval. See, I think the confidence interval, which is another criteria, already takes care of that issue.

PANEL MEMBER FRIEDMAN: Well --

PANEL MEMBER BLANC: Well, you know, I don't -- for my part, I think the way that they could tie those two arguments together, and it has to do a little bit with the order of the -- the sequence of the various parts of Chapter 1. But clearly in the discussion of attributable

fraction and population of attributable risk, that's where you can talk about -- you know, an odds ratio of 1.15, when an exposure is ubiquitous, can have real public health consequences. And, you know, I think that that brings that point.

But since you put that discussion prior to the discussion of the standard measures of causal association, it's perhaps the sequence that's held that up. But I think that -- apropos of Kathy's comments, I think this whole section, which starts at the top of page 110, which you've added -- which you added in response to the comments of the panel last time, it starts off by trying to do what we asked, which was to explicitly address the traditional causal criteria of the Bradford Hill type.

But what you end up doing is sort of setting up this very bizarre straw man. First of all, Bradford Hill criteria were not developed for an infectious disease model and it's an absurd implication to start off with suggesting that. And, you know, the issue is not whether Koch's postulates are bad or something. I mean it's just a sort of straw man discussion.

And to have then this, you know, sort of lengthy quote from Lillian Feld -- and Lillian Feld prior to actually saying what the -- you know, what the traditional model is, well, first say what the traditional model is

and how close you are to it or are not to it, and then to the extent that you differ from it, you could, you know, make your arguments about, you know, what are some of the rationale, the peculiarity of secondhand smoke, the challenges of some of the outcome measures you're looking at. I don't know what the issues as you see them may be, but you don't say them.

And then going forward, I think that you're -- you have tried -- I understand and I'm sensitive to the fact that you don't want to layer -- set yourselves down to saying that it will take exactly 2.5 studies for us to say that something is suggestive of an effect. But you're so vague here that it actually makes matters worse rather than improving them. So I think your additions weaken rather than strengthen what you're trying to say. You say, for example, at least one high quality study reports a positive association that is sufficiently free of bias, including adequate control and confounding.

This is in relationship to a suggestive association.

I doubt that there's actually a place in this document where you say something is suggestive because of just one study.

PANEL MEMBER HAMMOND: But I think the comment was made at the last SRP meeting that this committee had

used one strong epidemiology study. Was it formaldehyde? But I think, John, you made the comment that this committee had used just one Epi study in the past.

CHAIRPERSON FROINES: I don't think so.

PANEL MEMBER BLANC: Not for this kind of thing. I mean we may have used it in the --

PANEL MEMBER HAMMOND: To determine to see if there was a toxic air contaminant.

CHAIRPERSON FROINES: No, we used basically one study, the NTP bioassay for methylene chloride.

PANEL MEMBER GLANTZ: No, there are times in this panel, which is -- what you've said that -- I mean you don't use it all by itself -- but where one strong epidemiological study is the thing --

PANEL MEMBER HAMMOND: -- is all that there is.

PANEL MEMBER GLANTZ: Yeah, or might be all that there is.

PANEL MEMBER BLANC: Well, then now you bring up a very good point, because now we heard it say, what do you do when you have one strong study that's positive and five studies that are negative? I mean you've got to say something about how you're going to handle conflicting findings in the discussion where you talk about suggestive and --

PANEL MEMBER HAMMOND: I think that that's true.

CHAIRPERSON FROINES: I don't think we've ever adopted something based on one study.

PANEL MEMBER GLANTZ: Well, there -- but there are times that we've said we're going to do the unit risk based on one study. That's happened.

CHAIRPERSON FROINES: That's different --

PANEL MEMBER GLANTZ: Well, I just worry --

CHAIRPERSON FROINES: -- considerably.

PANEL MEMBER GLANTZ: -- I mean, you know -- I mean I don't -- I think all of the things you're saying are fine, Paul. But I mean do we really -- I mean it a little bit sounds like you're asking to write a textbook.

PANEL MEMBER BLANC: I'm writing -- write enough methods so that I can read their document and come to a decision as to whether it's scientifically appropriate. And I'm trying to say that I don't have that information enough to feel comfortable doing that yet. I do --

PANEL MEMBER GLANTZ: Well, what would ideally -- rather than have -- because they're clearly -- and this was a subject that was discussed at some length at the last meeting, I think, or maybe the one before. And they've made an attempt to do this, which you're pointing out problems with from your perspective. I mean what would you like them -- I mean I'm very frustrated listening to this conversation, because it's -- I mean I

think that it needs to get much more specific. And I mean I think we could either have OEHHA, say, try to explain what the criteria are and if there are things you don't like, then you'd -- very specifically to say --

PANEL MEMBER BLANC: I think I'm being pretty -- now you're -- I'm going to take umbrage with this.

I think I'm being pretty darn specific in my comments. I mean maybe somebody -- yeah, I guess I need feedback.

Melanie, do you feel like I'm being specific in my comments?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, I do.

PANEL MEMBER GLANTZ: Okay. Well, then I retract what I said.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I was going to say I think there's a lot of things you've said that we can readily clarify and add in to Chapter 1. And we did -- some of these additions we took right out of the IOM criteria. So, you know, we did do some specific additions. But in listening, I'm starting to understand more what it is that's missing.

PANEL MEMBER BLANC: And, again I apologize. But clearly I wasn't clear enough last time --

PANEL MEMBER BYUS: Let me perhaps make a suggestion. I mean I understand what you're saying, and I

agree with you.

Perhaps in this introductory section here, as you outline your criteria, all of them that you used, give examples back into the document -- specific examples of how you apply them --

PANEL MEMBER BLANC: As you will see in Chapter 5 --

PANEL MEMBER BYUS: As you will see in chapter whatever. And refer to it, "Here's this where we did this," consistently all the way through giving examples. And that way it refers to the methodology that you're going to apply all the way through. Because when I read it -- and epidemiology is not my field. But as I read each section, I am -- I constantly am asking myself exactly those questions.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, I think --

PANEL MEMBER BYUS: You see what I'm saying?

So that's just a concrete example. And I think that would provide a lot of the information. I'm not saying you -- I think you actually did apply it for a lot -- you know, appropriately. But it's unclear that you applied it consistently throughout. And this is where I'm saying -- I hate to refer to the Surgeon General report and I won't refer to it. But it provides the Method" section that you can then apply. Give some examples. And

they do. They do give examples. And it was very illustrative to me. It was very informative for me to follow when you do that.

OEHHA DEPUTY DIRECTOR ALEXEEFF: I was just going to -- George Alexeeff at OEHHA. I was just going to say I think the comments are helpful, the ones we've talked about today, in terms of the specificity. And just in terms of over -- or looking over, arching over all the compounds this chem panel has looked at, you know, by far maybe 90 percent or 95 percent have looked primarily at the animal evidence. And in those cases there's a lot of the issues that we don't deal with in the epidemiologic evidence. And the criteria for animal evidence has been fairly explicit for the last 20 years in terms of number of studies and the other information that comes in.

In contrast -- and in the past we have dealt with -- you know, whether it's methylene chloride or other compounds -- where there's been animal studies and a little bit of Epi information. But for the most part it's either been non-informative or just helpful.

And now what has happened, with diesel exhaust we moved to a slightly different situation where it was primarily based -- there was a lot of animal evidence, although that was in great dispute. But in that case we had human evidence and we -- but we only focused really on

one endpoint, lung cancer. Okay? And there were, you know, oh, about 40 studies that we looked at on the one endpoint. There was a bladder cancer issue, which we basically said was not conclusive, so we kind of moved it away. And we spent a lot of time on that one thing.

Now we've come to this next situation where -- with ETS, where we're -- now, let me just go back off one more step.

There really are not as far as I can tell, except for the Bradford Hill criteria, but there's really not useful helpful criteria out there like with IARC. Here's how you weigh these to figure out exactly what the level of suggestion is. So in part we're -- this panel is helping us define how we're going to weigh this information in a more specific manner. Also since our process is very public, it would be different if the panel was just deliberating, deciding amongst yourselves, do you think, you know, it's a go or not a go. Instead we have to lay out the criteria as a public agency. What are the criteria we're using in order to say it meets a certain level of evidence? And that's something -- so we're breaking new ground. So it is hard work for all of us, hard work for us, it's hard work for you folks. We appreciate all the effort you're trying to -- I mean you're giving us and all the information you're giving us.

CHAIRPERSON FROINES: I think that -- I think one thing, the fact that we haven't done it before doesn't mean that we shouldn't do it now. I think --

OEHHA DEPUTY DIRECTOR ALEXEEFF: No, I think we have to do it now. I think it's groundbreaking helpful information you're giving us, because we're trying to see how explicit do we have to be in order to reach a conclusion that really hasn't been laid out very well --

CHAIRPERSON FROINES: Well, see, I think that there's another benefit to doing this. And, that is, when we were doing diesel, George, the -- if you remember, there was a long paper by Roger McClellan that went through all 40 Epi studies. And by critiquing them, he was able to basically conclude in the end that all of them were irrelevant and that there was no evidence for an effect.

And so it's -- epidemiologists often lose the forest for the trees, as we know. And that the advantage of what we're doing means that you have another tool to use when it comes to evaluating papers like that, because then one can look at them and say, "This paper is not quite adequate."

OEHHA DEPUTY DIRECTOR ALEXEEFF: Right, yeah. So I'm just being -- sort of expressing, you know, positive response. Thank you, you know, because these comments are

helpful. Although it's -- you know, obviously this process is very difficult trying to figure out at what point -- because I think clearly we have -- we only needed -- we only would need one endpoint to label something a toxic air contaminant.

So I mean we're focusing really on the scientific criteria for the specific endpoints, which is going to help us for any other compound we work on in the future. Not only that; we're dealing with noncarcinogenic endpoints as well, which is also another new area for us.

PANEL MEMBER BLANC: So I'd like to go to another area of Chapter 1 then also, which is again methods related. And it begins on 1-4 measures of exposure in epidemiologic studies, and it continues on until you get to animal studies.

There is a lot of emphasis on misclassification here. And I see later in the document why you want to lay some groundwork on misclassification. But somehow tied into misclassification there is concern about confounding, which is never called the issue of confounding and there isn't a separate distinct discussion of confounding.

And there's also a lot of talk about really lack of precision in exposure gradation as opposed to misclassification between exposed and not exposed. I mean in its crudest form there is a misclassification between

saying some people are not exposed, as if it's zero, and some people are exposed, as if it's one.

And then there are issues of level of exposure that relates to later dose response inferences that you may be wanting to make among different gradations of exposure.

And then there are issues of things which are confounding variables that are linked to exposure and linked to effect.

And they're all muddled up together in these pages. And I'm not clear that it's clear to you when you're talking about one and when you're talking about another and what the implications are for your interpretation depending on them. And it comes -- it turns out to be rather critical in certain of the endpoints that you're looking at and maybe it's less critical in certain others.

It certainly seems to be a critical issue when you're trying to look at effects that would also be related to direct smoking versus secondhand smoke versus trivial-to-no smoke exposure of any kind.

PANEL MEMBER HAMMOND: You know, that actually was a major point that I had wanted to make about this. And, that is -- I'll take one piece of that -- and, that is, the term "misclassification" is used for two entirely

different concepts. You're not the first. This is happening all through the literature, so it's natural it would happen.

And I know that if you think about it -- I know you'd know the difference, but it's even in the text they get intertwined. And one paragraph talks about one and then the other and then back and forth. So the first -- I'm even going to be simpler and say one is the misclassification of smoking status itself, which has been a big issue --

PANEL MEMBER BLANC: You mean active smoking --

PANEL MEMBER HAMMOND: Active smoking. Whether or not someone who claims to be a nonsmoker was in fact a smoker.

All right. And that is -- you know, there's a whole literature on that. I don't need to tell you that. But I'm just pointing out there's this whole literature, this whole amount of material on that topic, which is very important. It needs to be addressed. One needs to say things like "This is particularly important for something like lung cancer, where you have a very high relative risk. It's much less important when the relative risk is low." And that needs to be dealt with in and of itself. And it should be very clear that's what you're dealing with.

And then the second issue is the question of, for true nonsmokers, the misclassification of their passive smoking status. And even in -- do we dare say it? -- in Chapter 7 --

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- Section 7-4 perchance?

PANEL MEMBER HAMMOND: Funny I should mention that?

PANEL MEMBER GLANTZ: What'd you say?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Section 7-4 perchance?

PANEL MEMBER HAMMOND: Seven-four, in fact. Now I have to find where it is.

What happens is you actually start speaking about one of those misclassifications. The next paragraph goes to the second, and then you go back to the first.

CHAIRPERSON FROINES: What page?

PANEL MEMBER HAMMOND: Well, that's why I -- I had my cheat sheet with the pages someplace. Then I mislaid it. So I'll find it. And I will get that for you.

It's the section you deal with the exposure assessment.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. It's actually Section 7-0.

CHAIRPERSON FROINES: Well, do you think --

PANEL MEMBER HAMMOND: Oh, is it back at 7-0?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think so.

PANEL MEMBER HAMMOND: Oh, yeah. Here it is, right. It's on page 7-9. Okay?

And just let me get this out.

CHAIRPERSON FROINES: Seven dash what?

PANEL MEMBER HAMMOND: Page 7 dash 9. Recent data on misclassification of smoking status.

So the first paragraph starts talking about this.

The next -- the second paragraph starts talking about the exposure of nonsmokers.

CHAIRPERSON FROINES: Kathy, I'm sorry --

PANEL MEMBER BLANC: Seven dash nine.

PANEL MEMBER HAMMOND: Page 7 dash 9.

PANEL MEMBER BLANC: Chapter 7 page 9.

CHAIRPERSON FROINES: I don't have it. I have it 7-109, 110, or what have you. I don't have a --

PANEL MEMBER HAMMOND: Go earlier in the document.

CHAIRPERSON FROINES: Oh, very early in the --

PANEL MEMBER HAMMOND: Early in the document.

PANEL MEMBER GLANTZ: Chapter 7 page 9.

PANEL MEMBER HAMMOND: Yes. Our 7.0.1.2.

CHAIRPERSON FROINES: I got it.

PANEL MEMBER HAMMOND: Anyhow, you can see through here where you've actually switched back and forth between these different concepts. And I know you know the difference and it's -- there was some -- I think it is an area of great concern.

When I served on the U.S. EPA committee that was considering passive smoking, I actually brought up this issue of the true nonsmoker being misclassified, their exposure status, if you only used the spousal smoking status, for instance. And it's very, very important. It's very near and dear to my heart. And of course it underlies a lot of what you do later.

But I think you have to take these two different things -- in fact, I would love it if we got away with the term of "misclassification" for the smoker who claims to be a nonsmoker question, if we could find another term that. I don't know if you can or not. But that's a misclassification of your subjects in the first place. They should never be in the study for those studies.

But in any event, they need to be dealt with very clearly as separate sections because they have very different implications. The problem of the misclassification of smoking status leads to a bias upwards, a positive bias, whereas misclassification in

passive smoking exposure leads to a bias towards the null. And, you know, unless someone really knows this literature well, it's very confusing.

PANEL MEMBER GLANTZ: Well, do you think -- I mean do you think it would be helpful in Chapter -- I mean we don't want to turn Chapter 1 into a 3,000 page monograph. But do you think it would be helpful in Chapter 1 to have a section talking about exposure -- basically I guess subject misclassification, which has I think been pounded into the ground a lot in the literature. But the other one, which I agree with you is a very important point, is exposure misclassification. And introduce those as separate terms to then be used consistently through the report, and then in Chapter 1 to have a discussion of -- I mean I think the subject in this classification thing has been well -- there's some big literature.

But to actually talk about the difficulty of exposure misclassification, the fact that that bias issue toward the null and then that would become one of your criteria -- getting back to what Paul's saying, that would be explicitly presented at the beginning in the chapter of one of your criteria for the quality of a study, of a given study. I mean do you think that that's a good idea? Is that a bad idea?

PANEL MEMBER HAMMOND: Well, actually, yeah, I've actually felt -- you see, I -- Bradford Hill didn't work with exposure assessment people. So he didn't put in his criteria. And I would include -- I will substitute for strength of association, quality of exposure assessment. And I'm actually really serious about that. I really think that quality of exposure assessment is far more important than strength of association.

PANEL MEMBER BLANC: Well, he actually started off as an occupational epidemiologist in the --

PANEL MEMBER HAMMOND: But they don't all do --

PANEL MEMBER BLANC: -- in cotton dust exposure realm. So he may have been more sensitive to that than you --

PANEL MEMBER HAMMOND: Actually the dose response relates to that, but --

PANEL MEMBER GLANTZ: Well, but I mean the people -- you know, I've sort of tried to put forward a specific suggestion to try to bring all this --

PANEL MEMBER BLANC: Well, it's consistent with what I'm saying. They already have three pages on misclassification. And I think that they don't have to increase --

PANEL MEMBER HAMMOND: That needs to be clarified --

PANEL MEMBER BLANC: They don't have to increase the length of that section. It just needs to have separate parts. I agree with Kathy's suggestion, which I hadn't really focused in on. But over and above that, I think within -- you have to talk about when in the classic sense -- in the first sense of misclassification, that is to say whether somebody's secondhand smoke exposed or not. You need to be clear about when you're talking about misclassification and when you're talking about imprecision in exposure measurement, presuming that they really are ETS exposed. But were they exposed at home only versus at home and at work.

And then talk about confounding, which is blurred up in here. And it's not the same issue. Clearly you care about it. But it isn't -- and I think it should warrant its own little subsection, but it's not in there.

So I don't -- I think the length is already there. They've already given a lot of emphasis. But it's ill-spent emphasis.

PANEL MEMBER GLANTZ: Well, then do you think -- that sort of gets into the issue that somebody touched on earlier of, you know, the issue of cohort versus case-control studies. And then in some cases the case-control studies can actually be preferable because of improved exposure assessment. I mean is that -- which is

an argument they make later in the thing and --

PANEL MEMBER HAMMOND: Yeah, I was going to make that -- I don't know if you want to move there yet or not because -- if you were on track.

PANEL MEMBER GLANTZ: Well, I'm just raising it as a question. Is that a point that -- because that's an argument which figures prominently later. Is that something that ought to also be addressed in Chapter 1, do you think?

PANEL MEMBER BLANC: Absolutely. And I think that what -- in terms of the order of things talked about, I think there needs to be a separate section about -- or separate subsection not of the -- not of this -- addressing the issue of case-control versus cohort studies. Within that discussion you certainly are -- since it's a point that are you going to make later on, you should make the point about whether or not you would raise up the value of cohort -- of case-control studies higher than might be in certain other generic approaches for the following reasons.

But there are on things you have to talk about in a discussion about case-control versus cohort. Certainly you have to talk about reporting bias. But I think also you need to talk about the issue of how difficult it is to have appropriate cohort study in a long-term cancer

outcome. And that's probably why those studies have poor exposure assessment, because of the length of follow-up. And often they just have some measurement of exposure at one point in time. I mean things are all connected.

But I think you need to acknowledge that the general risk assessment bias or weighting that's out there is towards cohort studies and that to the extent that you're going to go against the flow, say that up front and say why that is so that it's not, you know --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Buried in Chapter 7.

PANEL MEMBER BLANC: What's that?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's buried in Chapter 7 is what you're saying.

PANEL MEMBER BLANC: Deeply buried.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's there, believe me.

PANEL MEMBER HAMMOND: Yeah, I think if --

PANEL MEMBER GLANTZ: But it's in Section 7.4.6.3Q.

PANEL MEMBER BLANC: These are all like Star Trek dates. I'm standing there like log entries, Captain's log --

PANEL MEMBER HAMMOND: But if you -- if you do all of this -- I think the point is if you do all these

things that Paul and the rest of us are suggesting in Chapter 1, then when you get to the -- and you do it very clearly, first of all, it could be laid out conceptually without it being like, "Oh, this would be a nice criteria" -- it may look to people like, "This might work for me in this particular setting," and rather lay it out as a -- on principle kind of issue. And then when you need it in a chapter, you say, "As we said in Chapter 1.3.Q1W," you know, this and that.

And I do think that there should be a section on the case-control versus cohort, but before -- that should be preceded by some of these other issues. So I would say that if you clearly made the case for why it's important to do good exposure assessment and how the lack of good exposure assessment leads to misclassification, which then will under -- will bias towards the null, then when you get to the case-control and the cohort, you can simply cite that argument as one of the advantages of case-controls.

PANEL MEMBER GLANTZ: Which I bet Kathy would even help you, right?

(Laughter.)

CHAIRPERSON FROINES: But I think it's -- I think you have to look at the advantages and disadvantages broadly, because there are clearly a lot of issues that

are not only the --

PANEL MEMBER HAMMOND: Oh, no, no, no. I think you should. But the thing is you can lay out -- you don't have to kind of keep repeating the arguments if you've -- I'm trying to say, if you make a certain case and do this systematically really as Paul is trying to lay it out, then when you have a particular argument you can refer back to that section where it's well developed. You don't have to make it in pieces all over --

CHAIRPERSON FROINES: I think that there are power issues and there are obvious bias issues. It seems to me that we're talking --

PANEL MEMBER HAMMOND: Oh, there are lots of issues that go into it. I don't mean to say that's the only one. But I was just trying to make that as an example of the --

PANEL MEMBER BLANC: Can you tell me in your opinion how important is this precision issue, leaving aside the 1-0 misclassification? Do you think that the precision --

PANEL MEMBER GLANTZ: Precision of what?

PANEL MEMBER BLANC: Of exposure quantification within the group that have secondhand smoke. And what are the ways in which you think that, that that matters?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, it

matters if you're trying to come up with information on a gradient in-dose response. That's the most important problem.

PANEL MEMBER BLANC: And do you have the luxury of doing that very often for some -- are there some things for which it's more important than others within the document? Or do we think it's a -- do you think it's a particular issue to cancer outcomes or -- I mean because if you do -- or cardiovascular outcomes are less important for cardiovascular? I mean you come back to it in cardiovascular because there's this whole issue -- when you talk about doze responses not being monotonic. Obviously it doesn't matter if it's monotonic if it's a yes-no. So for the ones where it's -- except that you have the implication about comparing it to active smoking.

So it is a complicated thing. But I think you're going to have to tease out and give it -- and give examples, you know, prequels to what's coming that you think are pithy cases in point perhaps.

PANEL MEMBER HAMMOND: You know, I think what you're asking for, Paul, is really good. It will make it a very good document. But I think it's also going to be much better than anything that's out there. By the time this is all done it's going to be a treatise on how to handle this incredibly complex data. And I think it will

be better than the Surgeon General's report.

CHAIRPERSON FROINES: One problem is we also have to bring in the biology, whereas a monotonic dose response relationship doesn't really necessarily occur. The increase in effect as a result of an increase in exposure is not necessarily what we always see. We see things going like that, and when -- and so when you start to get a drop-off of a response because you have cytotoxicity occurring instead of, say, inflammation or something, the -- so it is more complicated. And the higher dose may -- well, it's the estrogen issue all over again and a million others.

PANEL MEMBER BLANC: Well, can I come to that?

Actually here's another thing that's missing from the methods, which is: What are your criteria for stratification or sub-analyses? In all cases where available, you would like to look at childhood versus adult effects? Or is it only for lung disease? In all cases, do you think it's necessary to look at gender stratified data if they were available for all outcomes, or do you think it's only for certain kinds of outcomes? What I think would be important is in the introduction lay out a rationale in advance for why there might be reasons in certain instances to look at stratified -- women stratified by premenopausal versus postmenopausal. I mean

if there's a precedent for that in other -- in certain types of chronic disease or chronic health outcomes -- certainly for heart disease that's the case. I'm not actually aware that -- in the cardiovascular disease section on secondhand smoke, are there studies of secondhand smoke in women and heart disease of the stratified by premenopausal --

PANEL MEMBER GLANTZ: Yeah, there are. I mean it turns out -- gender turns out not to be a factor. You know, people have looked at that. We looked at it. And the risks are pretty much independent of gender.

I mean I think though that the -- I mean --

PANEL MEMBER BLANC: Again, on consistency, just -- sorry to interrupt. But it's just a sort of laying out of consistency rather than an ex post facto we did this in this case.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think the stratification issue is much more driven by what's been done, what's published in the literature, than anything else. The premenopausal-postmenopausal, even for the breast cancer, we didn't start out seeking that. We just noticed, "Hey, look at all these studies that are doing this and seeing a different result."

PANEL MEMBER BLANC: So Then perhaps what you should say in your methods is if the body of evidence

indicates that analyses -- the multiple analyses employed certain stratification approaches to data based on the biology of the endpoint that we're looking at, we then analyzed the stratified body of evidence if there was one, for example.

PANEL MEMBER GLANTZ: Well, you know, I think that's what they did. I worry a little bit though, I mean, about laying -- I mean I think most of the criteria that you're talking about are going to be clarifying -- actually have the effect of shortening the document probably, which would be good.

But I think you're getting a little bit too prescriptive here. And the reason is, I -- as Melanie said, I mean I think if you look at the breast cancer thing, you know, the people who did the studies decided to stratify a menopausal status because people who do research in breast cancer think menopausal status is important.

And I think if we were to try to establish a general principle for when things should be stratified and when risks should be stratified, you're going to impose a criteria on the rest of the book, which may not be necessary or appropriate, you know. I think that the -- because in heart diseases, I said, for example, people have studied genders -- affects of gender, and there

doesn't seem to be one. And, you know, do we want to say to OEHHA, "You've got to go back and reproduce all of that stuff"? I mean I just don't think that's --

PANEL MEMBER BLANC: Well, I don't think they have to do a stratified meta-analysis of heart disease in secondhand smoke. I do think that if there -- of the studies that you cited, especially since the last document, you're reaffirming the finding that you already had. But if -- I think that if eight of the ten new studies that looked at women stratified by age and -- or, no. If what you were assessing were general -- if most of the studies stratified by gender and there was no gender effect, I think there should be a sentence there saying, "By the way, you know, eight of these ten studies stratified by gender, and there was no gender effect." And if you feel that that's then worthy of a comment in the discussion about -- you know, that although estrogen status seems to be important in heart disease, it doesn't seem to be important in secondhand smoke and heart disease, you know, that's fine. I mean that's your editorial judgment. But I do think that kind of thing -- it's not adding length. I'm not suggesting you go out and do your own meta-analysis on that.

CHAIRPERSON FROINES: Paul, how close are you to being finished with specifics?

PANEL MEMBER BLANC: Not that close.

CHAIRPERSON FROINES: Shall we break for lunch now and then just come back to it?

PANEL MEMBER GLANTZ: Could we -- I mean since this is going on, can we like work through lunch?

PANEL MEMBER BLANC: We don't have as much support personnel as we usually do.

PANEL MEMBER GLANTZ: Well, the concern I have is I know that OEHHA brought Ken Johnson down here from Canada, who is one of the, in my view, great experts in the breast cancer issue. And I think we -- it would be nice since he's here -- and there was a comment earlier about the need for expertise -- to make sure we have enough time to let them deal with the issues that he's very knowledgeable about.

PANEL MEMBER BLANC: I don't object to that. I think what we should -- if I hear what you're saying is it would be helpful for us to map out before we break what is our anticipated agenda and how we --

PANEL MEMBER GLANTZ: Okay. Yeah, I just -- because this seems to be going on. I mean this has been a nice discussion. But I really would like -- I mean I know because I asked Melanie to do it -- to address this point that several people have brought up about why -- you know, what's changed since the 2004 Surgeon General's report. I

think it would be -- on breast cancer. And I think it would be very good to allow that to be presented while Ken is here.

And I don't what else -- I mean a lot of these issues that have been discussed about exposure assessment, case-control versus cohort, stratification, I mean those are -- I mean Ken has done some of the original studies as well as the meta-analysis. And I think we just want to make sure there's enough time to ventilate that before everybody runs off to the airport.

So I don't know if that means trying to get a quick lunch and come back or break this discussion, have that, and then come back to this. But I think it would be a real shame to not have the benefit of him being able to address these questions.

PANEL MEMBER BLANC: Can we work backwards?

John, what time are you expecting us to break for the day?

CHAIRPERSON FROINES: Jim.

MR. BEHRMANN: There are three persons on 4 o'clock fights. We can move them later, if necessary.

CHAIRPERSON FROINES: That unfortunately doesn't answer Paul's question.

MR. BEHRMANN: We need to break at 3 presently.

PANEL MEMBER GLANTZ: Three o'clock.

PANEL MEMBER GLANTZ: Unless people are willing to move their flights later.

PANEL MEMBER LANDOLPH: Sure.

PANEL MEMBER GLANTZ: Are people willing to move their flights later?

CHAIRPERSON FROINES: It's not clear that people from Riverside can easily do that.

PANEL MEMBER BYUS: How much later?

MR. BEHRMANN: There's flights every hour?

CHAIRPERSON FROINES: To Riverside?

MR. BEHRMANN: No, no. They're flying to LAX -- they're going to LAX and then to Ontario.

CHAIRPERSON FROINES: So, Craig and Roger, what do you want to do? Do you want them to look for later flights? Do you want to stay with what you've got?

PANEL MEMBER BYUS: An hour later would be all right.

PANEL MEMBER BLANC: Yeah, that's right. What I want is --

PANEL MEMBER BYUS: As long as you can get us on there.

PANEL MEMBER BLANC: I have about 30 minutes more I think on this. And I think the big question -- or it's not a question -- I think the big thing that would sort of take a time pressure off the Committee is the

acknowledgement that we're not going to be coming to a decision today about the document and, therefore, we don't need to have that discussion. And that being said, I think we will certainly have time for Dr. Johnson's presentation specific to breast cancer. Because I'm certainly not prepared to decide on this document absent seeing a revised Chapter 1.

CHAIRPERSON FROINES: So --

PANEL MEMBER GLANTZ: Well, could I?

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER GLANTZ: Could I just suggest that we do the following then, because -- what I'd like to ask is that we table the Chapter 1 discussion, and then discuss the material that OEHHA and Dr. Johnson have as soon as we come back. And then when that's done, return to the Chapter 1 discussion.

PANEL MEMBER BLANC: Sure, sure.

CHAIRPERSON FROINES: Well --

PANEL MEMBER BLANC: I don't have any problem with that.

CHAIRPERSON FROINES: How long do you think the Chapter 1 discussion's going to occur? We're not going to vote today.

PANEL MEMBER GLANTZ: Well, no. I accept that. But what I'm just saying is, you know, I think there have

been -- there are two sets of issues here.

There's sort of general philosophical points and issues of presentation of the criteria, which is what we're talking about. And I think all the discussions, the changes that are being talked about will make the document better and make it shorter.

Then there's a whole bunch of very specific ways that these criteria are applied in the context of breast cancer. And I'm just very concerned that that -- we have an expert here who is one of the people that -- when we talk about consultants, he was one of the consultants. And I think we want to make sure that discussion isn't rushed, you know.

You know, we can all get together --

PANEL MEMBER BLANC: That's fine, that's fine, from my point of view. I'm not objecting to that.

PANEL MEMBER GLANTZ: What I'd like to do is have that be the next, and then we come back and finish this up.

PANEL MEMBER BLANC: It may even inform the discussion more on Chapter 1 what specific examples --

CHAIRPERSON FROINES: Melanie, then that would mean that we would start after lunch on the breast cancer and then go to Chapter 3 and 4?

PANEL MEMBER BLANC: No, no, that I don't accept.

I'm willing to hear the discussion from the guy from Canada -- from Dr. Johnson from Canada. Sorry.

DR. JOHNSON: I can come back every month. It's not a problem.

PANEL MEMBER BLANC: But I don't want to then go through this other presentation. I would like then to finish my comments.

PANEL MEMBER GLANTZ: What I'm suggesting is I'd like to have the breast cancer discussion and then go back -- Chapter 3 and 4 we can deal with later.

CHAIRPERSON FROINES: The level of subtlety of your argument is not lost on anyone.

PANEL MEMBER GLANTZ: I don't understand -- I'm sorry.

CHAIRPERSON FROINES: So we will go to -- we'll break. We'll go to breast cancer. We'll go back to Chapter 1. Then probably at the next meeting I would guess we'll go to the next 3, 4 and 5.

PANEL MEMBER BLANC: But in the meantime, if it's possible, to do 3 instead of 4, that would help because -- I mean if you have to leave by -- you want us to leave at 4, we'll --

CHAIRPERSON FROINES: Melanie, I was -- can I just ask one question?

In terms of Chapter 8, I did not see the word

oxidated stress or inflammatory responses or oxidation of lipids at all in that whole chapter. It seems like that chapter represents an earlier version of the science in this field. And so I -- it's something that I think needs attention, because it's sort of like there's all this stuff emerging, but it's not in the chapter.

PANEL MEMBER GLANTZ: We just got a paper published reviewing all that. I'll give it to you.

CHAIRPERSON FROINES: It's 12:29. So 1:15.

(Thereupon a lunch break was taken.)

CHAIRPERSON FROINES: Okay. We'll call the meeting to order for purposes of the record. And I think that we passed the baton from Paul and Gary and Stan and others to Melanie.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We had a presentation at the last meeting on our cancer chapter, including the breast cancer section. And I didn't want to give that entire presentation again, so I somewhat shortened it. And then I wanted to mention the things that we added between the last meeting and this meeting, and then a couple points that were in Dr. Froines' E-mail to the panel that were issues of concern that we could address.

So just to remind everybody, there are a number of case-control studies on ETS exposure and breast cancer. Most were positive. Many were statistically significant, either overall or in specific strata. The case-control studies with the best exposure assessment also had the highest risk estimates. There are several cohort studies that looked at ETS exposure in breast cancer, and most of those have null results.

There are three that are positive either overall or in substrata. The most recent one is Hanaoka, et al., which was published in print a couple weeks ago, but on line I think in January -- December. This is a prospective cohort study done in Japan; in our opinion, has the best exposure assessment of all of the cohort studies. And it showed significantly elevated risk for passive smoking in premenopausal women and, incidentally, also for active smoking.

And then we did look at a meta-analysis of the ETS breast cancer data, which indicated significantly elevated risk from ETS exposure and gave us a couple of estimates overall and then stratified --

CHAIRPERSON FROINES: Melanie?

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- which I can get into.

CHAIRPERSON FROINES: Can I stop you for a

second.

This notion of most with no results. Three positive either overall or in substate. Can we at some point when we get back to Paul talk about these issues about how one deals with the concept of substate? Because there's a fair amount of that as you go through the document.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: And it may -- we may be comfortable with it and we may not be. I calculated that there are ten studies -- cohort studies since 1999, of which eight are null. So all the modern studies except for two -- all the modern cohort studies have -- eight out of ten are null studies. It gives you a different impression than that gives.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, it shouldn't, because our numbers -- we're looking at the same studies, you are. So maybe you're missing Hanaoka. I'm not sure.

CHAIRPERSON FROINES: No.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Which is just published.

Well, we can get into more detail on that.

CHAIRPERSON FROINES: And the one I'm looking at, is this for premenopausal? Because he's not -- it's a

null study according to my -- when I look at it.

DR. MILLER: Who?

CHAIRPERSON FROINES: Hanaoka.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Hanaoka? No.

CHAIRPERSON FROINES: Relative risk is 1.1.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's overall. And he does two things. He looks at overall and he looks at premenopausal.

CHAIRPERSON FROINES: Yeah. I thought this was overall.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's significantly elevated risk for premenopausal women. There was one early, early cohort study that had an elevated risk overall.

I have to get the Hirayama, which is a 1980's study.

Okay. So that's one that we're including that is before 1999.

I think we can get more into that. But I would like to --

CHAIRPERSON FROINES: It's a null study.

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- to give the whole presentation.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: The issue keeps coming up over and over about cohort studies versus case-control. And cohort studies are typically considered better studies because they avoid a lot of biases. These are three non-U.S. cohort studies which show some indication of elevated risk. Hirayama was overall. Hanaoka was premenopausal. And Jee -- Mark, I don't remember.

DR. MILLER: It's overall.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It was also overall?

Okay. So that was also overall.

CHAIRPERSON FROINES: What was the third one?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Jee. It's a Korean cohort.

PANEL MEMBER BLANC: Spell the author. I'm sorry.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's J-e-e.

PANEL MEMBER BLANC: Yes, yes, 1999.

PANEL MEMBER HAMMOND: Well, I mean isn't one characteristic -- I'm sorry to interrupt you. But isn't one characteristic of -- it's almost like an exception that proves the rule. The three cohort studies that show the elevated risk are non-U.S., they're Asian, they come

from countries where women don't smoke, that their primary exposure almost certainly would be from their husbands. And, therefore, that assessment is actually a part pretty good exposure assessment. So it's almost an exception that proves the rule from your bottom line.

DR. MILLER: We think that's likely true. They're all Asian studies.

CHAIRPERSON FROINES: Well, there's some potential publication bias in that as well.

PANEL MEMBER HAMMOND: Well, but there's a whole issue, you know -- when Hiray -- you know, we could go back to a lung cancer story just -- I'm sorry to take your time. But may I just say something?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, that's okay.

PANEL MEMBER HAMMOND: You know, Hirayama published originally showing that the wives of smokers in Japan had higher rates of lung cancer than nonsmokers. Then the American Cancer Society did a study in the U.S., and they said, "No, it's not true for American women." And we had many years where the cohort studies in the U.S. for lung cancer were negative. And it's really been the case-control studies that have been most informative in lung cancer. The -- study, right?

So I think that we -- this is actually -- this is

not a new thing. It's not unique to breast cancer. It's a story that 10 years ago, 15 years ago we were hearing about lung cancer. And lung cancer isn't an issue, they were saying. And the only place it was showing up was in the Asian studies where -- where, in fact, as an exposure assessment person I would say to you, you know, that in a society where women don't smoke and women don't work, then adult women's major exposure to passive smoking would be based on their spouses' -- their husbands' smoking. They don't have occupational exposure. And, that when they're with their friends, they're not smoking.

CHAIRPERSON FROINES: Well, actually that's not true. The women in China have very high exposures indoors to cooking with charcoal pots.

PANEL MEMBER HAMMOND: I'm talking about cigarette smoke.

CHAIRPERSON FROINES: I understand that. But the question of there are confounding exposures in China that are very scarce --

PANEL MEMBER HAMMOND: That becomes a whole another story. And I was specifically speaking about the quality of exposure assessment to tobacco smoke. If you want to talk about confounding issues, that becomes another issue as well, which again may be better controlled in the case-control study.

CHAIRPERSON FROINES: Just one question, Melanie. And the three cohort studies that you refer to that you say show elevated risk, according to what I'm looking at, none of them are statistically significant. So that you would classify them as -- show elevated risk. Well, they don't -- there are no studies, it seems to me.

PANEL MEMBER HAMMOND: What table are you looking at please?

CHAIRPERSON FROINES: Table 7.4.1B.

PANEL MEMBER HAMMOND: What page?

CHAIRPERSON FROINES: 7-127.

PANEL MEMBER HAMMOND: All on the same page.

DR. JOHNSON: I have something explicitly on that from my manuscript that's in press now and the analysis.

CHAIRPERSON FROINES: Well, that may be true, whatever you have in your manuscript. But I'm asking a question about which we have in our report.

DR. JOHNSON: No, no. This is -- okay. Exactly addresses that.

CHAIRPERSON FROINES: Okay.

DR. JOHNSON: Among the Asian cohorts -- just one paragraph. Among the Asian cohort studies three of four suggested a relationship with secondhand smoke. The Hirayama cohort found an overall risk of 1.32, not statistically significant, but observed a relative risk of

1.73, 90 percent confidence interval, 1.12 to 2.6, for Japanese never smoking women whose husbands smoke more than 20 cigarettes per day.

The South Korean cohort, the Jee study, found an overall relative risk of 1.2 for wives of ex-smokers, 1.3 for wives of current smokers, and 1.7 for wives of current smokers who had lived with their husbands' smoking at least 30 years.

In the Hanaoka cohort, again overall none -- 1.1. Premenopausal Japanese women had relative risks of 1.6 for any history of residential exposure, 2.3 for current occupational or public exposure and 2.6 -- sorry -- 2.3 for current or occupational public exposure, and 2.6 for a residential history and public or occupational exposure. So in each one --

CHAIRPERSON FROINES: But my point here is, I don't give a damn about what's in that paper of yours. But I do care about what I could look at as a reviewer of this document. And that's not correct according to this table. So if -- those figures should all be some place.

OEHHA SUPERVISING TOXICOLOGIST MARTY: They are scattered in different tables throughout the document. And we had a table that we wanted to present the overall results in. And that's what we did in part so that we don't appear to be cherry picking literature.

PANEL MEMBER BLANC: Well, I think that -- maybe I can bridge the gap here a little bit. I think what's -- the issue in the slide that's up here, as opposed to the table, which, you know, could perhaps have other kinds of detail, is that when you say a sentence like several cohort studies, most with null results, three positive either overall or in substrata. In fact, they're only positive in substrata. There isn't one of the cohort studies that's positive overall. They're only positive given certain definitions of what the referent group is, right? I mean, I don't know what you mean by overall. The implication of overall --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. And we didn't differentiate between statistically significant and elevated risk either in --

PANEL MEMBER BLANC: Oh, positive means a positive direction. Well, but actually a lot of your studies are in a positive direction, if that's what you were meaning.

So, you know, that's a question about what you present here. But since we're -- it's such a contentious thing, I think you just have to be really meticulous. And I think that same -- that same cautionary level of being meticulous, you know, may come up at times in the text. So it's really -- you sort of have to bend over backwards

to make sure that no one could misinterpret what you're saying, you know, could come back and misread what you're saying as being, you know, a spin meister and not -- you see what I'm saying?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, I do.

CHAIRPERSON FROINES: I think that in the news reports and in other comments, the notion of selective selection, selective picking of studies and results is an issue that's been raised. We have to be particularly careful so that what the -- what's being used to draw the conclusions is very clear. And when I look here and see this, that raises doubts, because it seems, for me, as a reviewer on this panel, and that's what you need to be worried about, is that people like me who are not epidemiologists look at this and say, "No, these are three null studies."

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right. We did try -- then I'll get to that in a second. But we did try to take the information of where those positive substrata were and put it in in specific parts in our discussion.

CHAIRPERSON FROINES: But it's got to be easily accessible. We can't have to -- one of the problems with the document is you've got so many numbers in so many places that it's very difficult for a moderately

intelligent person to sort through it. Smart people could do it all right, but the rest of us are stuck.

PANEL MEMBER GLANTZ: Well, speaking as someone who sorted through it -- that's a joke.

But I mean one of the problems that you have when you look at these breast cancer studies is people have -- there's a broad consensus I think that breast cancer interacts with certain other things like menopausal status. And so the studies that have been done have stratified in different ways. Most of them have -- not all, but most of them have stratified on menopausal status, which seems to be the most important.

PANEL MEMBER HAMMOND: Well, isn't there an understanding that breast cancer's a different disease pre and postmenopausal?

DR. MILLER: No.

PANEL MEMBER GLANTZ: Well, there's -- I mean it may be, Melanie, that this may be another place where it's a matter of -- and of how you frame things. And it may be that you should just start out saying that stratification in these studies based on some important issues is something you should start with.

See, to me, when the -- given that the risks seem to be higher premenopausally to postmenopausally, most of the studies show that, that the throwing -- that not

stratifying again biases the result toward the null, reduces the overall estimate of the effect size. So to me, the things you're talking about actually strengthen their argument, because the analysis is based on data sets that probably should be stratified. And in fact in one of the various drafts of something I saw there was a statement about the data is particularly strong for premenopausal -- premenopausally. So I mean it may just be how the thing is presented. But it may be -- you might want to -- since that seems to be a major dividing line in these studies, you might want to just start out with that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. We do say that in several places, that --

PANEL MEMBER BLANC: Yeah, let me ask another technical question, which I don't know whether -- you may want to defer this until the presentation, if there is a presentation, from your consultant. But if a study presented more than one relative risk estimate, and if it wasn't -- and if there wasn't an overall relative risk estimate, how did you choose which one to use for the meta-analysis?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, in that case we used the overall -- we did two separate meta-analyses. One was --

PANEL MEMBER BLANC: No, I know about the

menopausal, yeah, yeah. I'm talking about the -- you know, I just noticed that in the brief comments that were just made, for example, the Jee relative risk was 1.3 compared to current smoking husbands and it was 1.15 compared to formerly smoking husbands or something. I forget what the numbers were. There were two different --

DR. JOHNSON: One point two for ex-wives -- sorry -- wives of ex-smoking husbands; 1.3 for wives of current smokers; and 1.7 for wives of current smokers who had lived with their husbands smoking for at least 30 years.

PANEL MEMBER BLANC: And was there a relative risk for all smoking husbands, whether they were current or ex, in that paper?

DR. JOHNSON: I assume so.

PANEL MEMBER BLANC: Because the risk that appears here in the table is 1.3, the risk of the current husbands. Was that a typographical error here or was there --

DR. JOHNSON: No, that's probably the overall summary.

DR. MILLER: That's probably the overall summary. What we can -- In general --

PANEL MEMBER BLANC: It can't be for this --

DR. JOHNSON: One point two, one point three, one

point seven.

PANEL MEMBER BLANC: Well, 1.7 was the subset, wasn't it, of the smoking husbands?

DR. MILLER: You know, it's really -- it would take a -- you have to go through study by study. I can tell you what we did in general.

You know, in general the estimate, whether it was the overall estimate or the premenopausal estimate, there was an attempt in the studies that didn't give a total number. If it was only presented as either current or former smoking husbands, for example, those were combined. And in each -- you would have to go to each study to see how that was done. I mean, and it depends --

PANEL MEMBER BLANC: You had to provide --

DR. MILLER: -- it depends when you go to these papers, you know, you may have different numbers from different tables, depending on how things were broken down. And so we tried to get the most complete number that would reflect the entire population, and that was -- and when in question, we took the most conservative estimate or the lower risk estimates.

And I mean there are a number of comments at the bottom of those tables that start to address how each of these things were done. And we have additional ones that are not in this particular version. But that, you know,

kind of go through each study and where those numbers came from.

CHAIRPERSON FROINES: Can you understand why sometimes when you're trying to read these things having multiple findings like that, can -- you're left with this situation where you say, "Well, okay, what's important?" And so it's -- the problem for the reader is that it can be confusing.

DR. MILLER: Yeah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We understand that, we totally understand that. And, you know, I think part of the issue is how long do you want this document to be. I mean if we put in a discussion of why we picked every single number for the meta-analysis, we'd add another ten pages.

DR. MILLER: We've already cut a lot of details out actually, at your request.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So anyway, if we could just keep moving, I think some of the questions will get answered as we go along and then we can go back. I don't have that many slides.

PANEL MEMBER GLANTZ: I do think -- I just want to say one thing -- I'm sorry, Melanie. But I think this is for the panel. I mean some of the stuff that's coming up now was in the document before and deleted. And so I

think at the end of this meeting the panel is going to have to give them, OEHHA, some guidance. And, that is, I think -- everything should be written as well as it could and as clearly as it could and all of that. But I mean do you want everyone of these little things explained in excruciating detail? In which case the document's going to get longer. Or do you want document shorter?

CHAIRPERSON FROINES: No, no. I think --

PANEL MEMBER GLANTZ: I mean the questions --

CHAIRPERSON FROINES: -- I think the points that Paul's been making all day is we want the results within a context that makes sense about establishing it's important and it's the conclusions that go with it.

PANEL MEMBER GLANTZ: No, I'm not disagreeing with that. But I mean I've just been listening to this conversation, thinking about some of the meta-analysis work we've done on heart disease, which is not in this document, has nothing directly to do with the document. And one of the problems you have, whether you're talking about a formal meta-analysis or just a review of the literature, is no two studies are ever done quite the same way, and the endpoints they use are a little different, their measures of exposure is a little different. And so you're left with the question -- and they usually report the same things seven different ways, which I think is

actually a good thing to give the reader -- I'm talking about a paper -- you know, the clearest view of the data.

But in doing the analysis that OEHHA's doing in the meta-analysis, you end up having to pick one of these numbers, or sometimes combine a couple of them to get something that's comparable to the rest of what you did. And I think the thing that we need to give them some guidance on is how much detail should they be putting into the document on that, because that all ends up all these footnotes in the tables.

And, I'm sorry, I don't want --

CHAIRPERSON FROINES: Stan, the point I think that's been going on all morning is to the degree that you establish rules for dealing with the data and then follow them, then the panel can follow them.

PANEL MEMBER GLANTZ: No, I'm not disagreeing with that. I'm just saying we need to just -- well, I'll just shut up because I'm not being clear.

CHAIRPERSON FROINES: Well, let's go ahead, because we're repeating ourselves.

PANEL MEMBER GLANTZ: Go on, Melanie. I'm sorry.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Second bullet. Until Hanaoka, the Hanaoka paper, none of the cohort studies had assessed exposure that included childhood exposure, residential adult exposure and

occupational exposures, such that this created a problem with misclassification. In other words you ended up with people who maybe their husband didn't smoke, but they were exposed at work eight hours a day. And those people would be considered nonexposed and put into the referent group. Therein is the bottom line of why a cohort study is only as good as the exposure assessment.

And that's the only point we wanted to make.

PANEL MEMBER BYUS: Same with childhood, they didn't consider their childhood --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Most of them did not. And you can understand. I mean they're asking -- for example, if they're asking at the recruitment, "Do you live with a smoker or are you married to a smoker?" they weren't looking backwards in time at earlier exposures. And in most cases -- there's a few exceptions -- they also didn't ask about exposures at work.

CHAIRPERSON FROINES: We're doing a study, cohorts in genetic epidemiology study in China of lung cancer. And this issue of confounding exposures is just immense, because there is so much air pollution, there's so much indoor cooking, there's so much occupational exposure, that you just have so many other exposures going on that it's a very difficult problem.

And so the advantage of cohort studies often is that they are large, and so one has to balance the limitations of exposure assessment with the differences in size. And so I think it's more -- there's more to it than that one sentence implies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Most definitely. But, you know, I'm just -- I'm giving a very brief overview of some of the points.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: In fact this next slide when weighting studies -- and I'm just talking about -- I'm not talking about what Stan was talking about earlier, weighting them in a meta-analysis, but overall --

PANEL MEMBER HAMMOND: What are you evaluating?

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- when you're thinking about -- when you're evaluating studies, you need to balance between minimizing the recall bias, which is a good feature of cohort studies, and also size, and minimizing exposure misclassification, which in the case of ETS is less of a problem with the case-control studies.

And the issue of reporting bias related to retrospective case-control studies is somewhat mitigated in that the potential link of even active smoking, much

less ETS, to breast cancer is not something that's commonly known to the people you are asking the questions of. So to me that it's -- people make a big deal out of it, and I'm not so sure it's that important.

CHAIRPERSON FROINES: What about publication bias?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We can come to that. I have another slide about that.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Then at the last meeting panel members rightly said that "You guys are not letting us know what studies you weighted more heavily when you were thinking about whether there was an association or not." So -- and we pointed out this morning -- on page 7-132 we went through and said, "Okay, what characteristics of a study do we consider important in terms of helping us decide whether there's an association or not?" And for exposure assessment, if it includes residential, occupational, other non-residential, childhood and preferably multiple points in time, that study is given more weight in our minds than studies that don't do that.

If a study attempts to eliminate ETS-exposed people in the referent group, that study is given more weight. And you can't do number 2 unless you do number 1.

So that's part of the issue with the entire database on ETS.

If a study evaluates what we consider potentially susceptible exposure windows, which in the case of tobacco smoke is pre-pregnancy and peripubertal for breast cancer, then that study is given -- we think has done a better job of assessing exposure in terms of important windows. And then a prospective design is better as long as it has the above characteristics or at least some of the above characteristics. So that's -- we spelled that out a little better in our "Discussion" section than we had certainly before.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: We added a few tables of the studies that we thought had done a better job on -- just delineating the six that we thought had done a better job based on those criteria and what their findings were. This first table is breast cancer risk with passive smoking. This is for all women, not stratified pre or postmenopausal. On page 7-141, that knows the relative risks range from 1.1 up to about 2.5.

PANEL MEMBER GLANTZ: When these are the -- by most influential, you mean with the best exposure assessment, is that right?

OEHHA SUPERVISING TOXICOLOGIST MARTY: By the

characteristics that we said --

PANEL MEMBER GLANTZ: By those four criteria.

OEHHA SUPERVISING TOXICOLOGIST MARTY: By those four criteria, exactly.

And then the next table, which is right next to it, right underneath it on 7-141, is the same studies in what they said about -- or what they calculated for risk estimates for premenopausal women.

PANEL MEMBER BLANC: So, Melanie, is it just -- it's coincidental then that all of the studies that you felt were most -- were the highest quality based on the criteria you just outlined also provided stratified data by menopausal status; it just worked out that way? Because that wasn't one of your criteria for a good quality study; is that correct? Just want to confirm that.

DR. MILLER: I wouldn't say that it was coincidental. I would say these are studies that had more careful design and were a little clearer about what some of the issues were and collected more exposure information, in which case they had data that they were able to stratify. I think that's -- I don't know if, Ken you --

DR. JOHNSON: Yeah, I think the more carefully reported studies tend to provide both of those. But you

also need to note that two of the studies were only on premenopausal women. Smith and Kropp were both premenopausal.

PANEL MEMBER BLANC: And then the second question is -- I assume that for none of these studies did you need to recalculate the relative risk based on data in Wells' letters or the other secondary -- these are all depublished -- these are the relative risks as they appear in the published studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm not sure about Smith.

DR. MILLER: Smith is recalculated.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think that's true for all of them, except Smith I think we ended up recalculating.

DR. JOHNSON: I think Smith they only reported less than 200 smoker years and more than 200 smoker years. See, there wasn't one sum --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, that's right.

PANEL MEMBER HAMMOND: I have a question about the Smith study --

PANEL MEMBER BLANC: Well, I would just say that's an example. It touches on the question that Stan raised about how much detail do you want, and John

raised coming at it from another direction.

But I guess my own personal cutoff would be that -- and I know these are just tables that you have -- that you're showing us. But they also appear in the text, don't they?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER BLANC: And can you point where they are in the text itself?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, the pre-'99 ones would be on --

PANEL MEMBER BLANC: Are they broken up into different --

OEHHA SUPERVISING TOXICOLOGIST MARTY: You mean the description of the studies?

PANEL MEMBER BLANC: No, just the -- does this sort of table appear?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, this table, yes -- I'm sorry -- 7-141.

CHAIRPERSON FROINES: It's 7-141.

PANEL MEMBER BLANC: Okay. So 7.1.4.1E. So it's after where we are, right?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, It's actually in the -- where --

PANEL MEMBER BLANC: Yeah, I see it. It's page 7.1.4.1, okay.

So I would say that when I looked at a table like this as a reviewer, I'm going to presume that these are the relative risks as published in the papers. And I would really taken aback if I went to the paper and couldn't find this.

So there is a place, especially since you're selecting these out of so many studies for being the most influential to you. I think at a minimum that is a level of detail that I have to see. There needs to be a footnote or explanation there.

Now, the --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Those numbers are also in earlier tables and footnoted with where we did some calculating to come up with a number. So, for example, in Table 7.4.1B, which is several pages before that, for Smith, estimated overall passive smoking risk calculated by summarizing the unadjusted lifetime exposure categories, which is 1 to 200 cigarette years and greater than 200 cigarette years. So I think that is the only one.

PANEL MEMBER BLANC: Okay. But you can see what I'm getting at?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

DR. MILLER: These were something we just threw together for this revision here.

PANEL MEMBER BLANC: Yeah.

DR. MILLER: But all of those numbers come out of the previous tables, which are footnoted as to where the number came from.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'll bring forward the footnotes.

PANEL MEMBER BLANC: And you may wish to have a limitations section where you summarize what may be potential study limitations or analysis limitations all in one place. And one of those limitations might be that for a number of these studies the pertinent risk estimates were calculated after the publication of the original study, although some of these calculations were themselves published as letters to the editor, or whatever it is you wish to say. But that is, again -- when you're dealing with something this contentious, I think you can't be too meticulous.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We do have a section on limitations we've studied. It was very long, so we shortened it in response to the previous comments. But we took the information on the individual studies that were in there and stuck it back with the individual studies. So the information is it still there.

DR. MILLER: One of the things which you can do, and we did, with the meta-analysis program is just run

through the whole set of studies, dropping individually one -- each one. And no individual study made any difference at all in the risk estimates or the -- I mean, you know, more than, you know, .02 or something like --

PANEL MEMBER BLANC: So that would stand to reason given the number of studies that you have.

DR. MILLER: Right. So you can cut one or two and it's going to give you the same results.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So the point is is the premenopausal risks are all stronger. And going back to the strength-of-evidence argument, when you're above 2 for a lot of these up to 3.6, then it gets harder and harder to explain it away by confounding.

PANEL MEMBER HAMMOND: Melanie, you said Smith was entirely premenopausal?

DR. JOHNSON: Yes.

PANEL MEMBER HAMMOND: Then why aren't the numbers the same in those two tables for Smith?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Good question.

PANEL MEMBER HAMMOND: Then the entire study plus the premenopausal should be the same.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, you know what it is? Because one is probably the less than 200. I don't know. It should be 2 --

DR. JOHNSON: They should be the same.

OEHHA SUPERVISING TOXICOLOGIST MARTY: They should be the same. I don't know why they're not the same.

PANEL MEMBER HAMMOND: Well, I mean it's not only for the relative risk point estimate is different, but that the lower confidence interval -- I mean Smith and the premenopausal is the only non-significant study, whereas overall it was significant. It seems very strange.

DR. JOHNSON: I think the number's wrong.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, the numbers are wrong.

PANEL MEMBER HAMMOND: The whole row is wrong?

OEHHA SUPERVISING TOXICOLOGIST MARTY: The Table 7.4.1 --

PANEL MEMBER HAMMOND: I mean 7.4.1F looks like there are fewer people in it so it's got a wider confidence interval.

DR. MILLER: I think I know -- without going back and going through this. The numbers that are in the overall and premeno -- the real tables -- I can't tell you how many hours we've spent going around about these different numbers and what are the right statistical methods to use. We adjusted -- this is the old number that we had in the previous version. We adjusted it

downward. And I can't -- it has to do with --

PANEL MEMBER HAMMOND: Which one --

DR. MILLER: -- with some of the issues around combining those numbers.

PANEL MEMBER HAMMOND: Which --

DR. MILLER: Okay. We have to have our statistician --

CHAIRPERSON FROINES: In Table 7.4.1C --

DR. MILLER: Where it says 2.4 --

CHAIRPERSON FROINES: It's 2.4 with a lower confidence interval of 1.1.

DR. MILLER: Yeah. And --

PANEL MEMBER HAMMOND: And then it's 2.53 and then it's 2.63.

DR. MILLER: Yeah, but the --

PANEL MEMBER GLANTZ: I think --

DR. MILLER: The tables that this came from have been adjusted, and these numbers didn't get adjusted. I'm sorry.

PANEL MEMBER HAMMOND: Let's just put -- let's just say this is an illustration of why this can be confusing.

PANEL MEMBER HAMMOND: Yeah. Well, it's multiple iterations and --

PANEL MEMBER HAMMOND: It's true. But you know

what? It's not transparent anymore. If you can't explain it in a few sentences, it's a problem.

PANEL MEMBER HAMMOND: Yeah. But that's what happened.

PANEL MEMBER HAMMOND: It goes back to the -- you know, in terms of just -- unfortunately, you know, you can't say, "Trust us," you know. We have to go beyond that.

PANEL MEMBER GLANTZ: Yeah. And having done lots of documents that go through multiple iterations and numbers get changed one place or another, I think one thing that you might want to have is sort of almost an audit trail, because a lot of these subsequent tables are summaries of things from other tables. And you might just at the risk of making it -- it being hypocritical, then you might want to just have -- when you have these summary tables, have a footnote that says where each number came from if they're from the earlier tables, just to make sure they're all consistent internally.

CHAIRPERSON FROINES: Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, these numbers all came before we readjusted the numbers. So they're close, but they're not exactly the same. But they're -- you know, the point is that they --

PANEL MEMBER HAMMOND: The LCI isn't close.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm sorry. Say again.

PANEL MEMBER HAMMOND: The LCI is not close. The lower confidence interval number --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Confidence interval?

PANEL MEMBER HAMMOND: From .73 to 1.19, those are not close.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Smith, this is just wrong.

CHAIRPERSON FROINES: Well, I think this is illustrative of a problem. But I think we've -- can we go on?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: Can I ask another question that's relate to this?

When I looked at this 7 -- Melanie, 7.41C table, the one we were just talking about, there are a number of cohort studies from 2000 on: Wartonburg, Shrubsole, Gammon, Hanaoka, and Reynolds. So there are 1, 2, 3, 4 cohort studies since 2000.

And there is this rhetoric that has pervaded these discussions -- there's the rhetoric that's pervaded these discussions that the newer findings are showing more positive results. And, in fact, since there are four 2004

studies in this table, four cohort studies in 2004, and of those four many of them are null values, what -- well, the problem is is I look at this table that you put up before on premenopausal and then I look at these five cohort studies that are null value, and they disappeared from the earth, and it's very difficult, for me anyway, to say to myself these studies are so bad that they are eliminated from consideration and they have null value, so that it seems like there's some selection issue going on.

OEHHA SUPERVISING TOXICOLOGIST MARTY: They're not eliminated from consideration. They're in the meta-analysis.

CHAIRPERSON FROINES: They're not in your ultimate six. Oh, they're in the meta-analysis. Okay.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

CHAIRPERSON FROINES: But I still think the meta-analysis is not -- one doesn't use the meta-analysis to define causality, in my view.

And that within this, the question is: Now does this not -- how does one look at these studies in terms of the quality of the studies of not being considered in terms of the ultimate determination?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We actually -- first of all, Gammon and Shrubsold are case-control studies, not cohort. Hanaoka's a cohort.

Reynold's a cohort. Egan's a cohort. Wartonburg's a cohort. Nishino's a cohort. And these were -- we wrote about them, we considered them, we put them in the meta-analysis for both premenopausal as well as overall. We did not discount those studies. The only point about --

CHAIRPERSON FROINES: Well, the fact that something gets in a meta-analysis -- I'm more skeptical about meta-analysis than you are, clearly. So that my view is that studies should be considered on their own merits in many ways and that -- so to me at some level they do disappear.

PANEL MEMBER GLANTZ: Well, wait a minute though. You can't -- I think there's some real -- I mean I think that if the Surgeon General had applied the arguments you're making now, they never would have said passive smoking causes lung cancer. And I think that -- the purpose of a meta-analysis is to get an overall estimate of the effect size and to try to get a more precise confidence interval for that effect size, or association magnitude if Gary wants to call it that.

And a meta-analysis is not truth. But the whole idea is that if you have many studies which are -- which don't have the power to get small confidence intervals, it's a way of bringing the data together to get an overall

estimate of the magnitude of the estimated risk. And that's all it is.

And, you know, I think one always wants to look at the studies individually too. But by saying we're only going to look at individual studies, you're throwing away a huge amount of information there. And if we did that for lung cancer or heart disease, you would say, "We don't have enough evidence to conclude there's a relationship there." I mean most -- to this day, the great majority of the studies of passive smoking and lung cancer looked at individually do not reach statistical significance. And so saying -- and to me, while many of these lung cancer -- of the breast cancer studies, like many of the lung cancer studies, don't individually reach statistical significance. The great bulk of them show elevated point estimates. And if in fact there was no affect, I would expect there to be about as many point estimates below 1 as above 1, you know. And so -- I mean that to me was like the most quick and dirty meta-analysis as to just see how many of the -- how many of the point estimates are above 1 and how many are below 1 and just figure out the probability of that happening.

So I think that you're advocating a way of looking at this which is really not -- I mean it's not the way people have looked at these kind of data ever since a

long time ago. I mean you have to look at the evidence all together. And, you know, there are some studies -- some of the breast cancer studies show risk point estimates below 1. And I think there's a couple of the lung cancer ones that do too. But the great bulk of them show point estimates above 1. So I mean you're -- I think you're sort of setting a straw man up on meta-analysis. I mean nobody ever said it's like if you do a meta-analysis and get a significant elevation in risk, that proves causality. That is I think a strong supporting evidence of causality. But you have to look at that together with, you know, the toxicology with the other things -- you know, the other things you know about mechanisms.

So, anyway, I'm sorry. I just think that -- I mean to listen to you, it's like arguments I haven't heard on this issue since about 1980. You know, it would throw out the 1986 Surgeon General's report on passive smoke.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think too -- getting back to the six studies. What we're doing is responding to a request at the last panel meeting, which we may have actually misinterpreted, but we did make this mention of studies that we thought had done the best job of exposure assessment. And that's all we're pointing out. They do have estimates of risk that are considerably higher than some of the other studies, and I don't think

that is accidental. I think it's because they did a better job of assessing exposure.

PANEL MEMBER BLANC: But I think that we're -- a potential problem in nuance comes into play in the meta-analyses, is that -- it depends on what you're -- you know, what you're using the meta-analysis for. And I think that there's a little bit -- there may be a little bit too much effort invested in the document in the issue of the underestimation of -- the imprecision and estimation of exposure in the cohort studies particularly. Although I suppose some of the case-controls have suffered from the same limitation.

DR. MILLER: Most of them.

PANEL MEMBER BLANC: Since ultimately you're only using that argument as a kind of nuance of -- you're using a meta-analysis to support why that -- because it gives a nuance in support for the argument that that hypothesized weakness may, in fact, be a true weakness. Because, in fact, when you divide the studies up that way, the ones that fall into the two groups seem to be more alike than different. And because when you divide them up that way, and point estimate of the relative risk is higher than the ones that you believe are more precise. But, in fact, it doesn't get -- you're core -- to support your core argument, you would use the Meta-analysis that includes

all of the studies. And so by having, you know, six different relative risk summary estimates -- five, I'm sorry -- at the bottom of the table, it kind of subtlety implies that you're putting more weight on this issue than maybe you really are ultimately.

So I'm sort of defending what you've done. But I think that there's some implication of everything -- it's as if everything revolves around the hypothesis of underestimation of dose or imprecision of exposure measurement in some of these studies compared to others. And whereas your argument ultimately is stronger than that, isn't it?

DR. MILLER: Yes.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. I mean we -- a lot of the study that actually didn't do that great a job on exposure assessment have elevated risks.

PANEL MEMBER BLANC: But it comes out sounding as if everything stands or falls on --

PANEL MEMBER HAMMOND: But this is not -- I mean, you know, this isn't like just a hypothesis. I mean this is something that we kind of understand, we already know.

PANEL MEMBER BLANC: Well, it's somewhat controversial literature. I mean --

PANEL MEMBER HAMMOND: Well, you know, I think that some of these studies, one has to actually look at

the studies and look at the -- the quality of the exposure assessment for some of these study would kind of appall you. And some of these studies, especially the cohort studies, were not intended to be studies of the relationship between breast cancer and ETS. I think this is an important point. They kind of -- there's one little question out there, and they kind of just crossed that amongst a bunch of other things. Then there are other studies where this was a primary hypothesis of the study and they actually devoted some energy to that, you know, by asking questions to that exposure assessment.

And I think that -- you know, we can see -- I could show you some data that show you that you get some very different information if you ask one question: Does your husband smoke? You know, and that's all you've got for exposure assessment, you get a very -- you know, you're not likely to get as good a result as if you take five minutes and ask a series of questions, or even if you ask five questions. And I think many of these studies, we don't realize how bad they are in the exposure assessment, unless you look at those papers, which I've had the pleasure of doing.

DR. JOHNSON: There's a classic example of the problem of misclassification bias in the Rothman and Greenland's book on modern epidemiology, sort of the Bible

of modern epidemiology. And in it they look at what would happen in terms of misclass -- and they have both four pages in the book that are excellent and very important. But they used the example of: If half -- if they were doing a study and half the people misrepresented whether they drank alcohol or not. And they work out a -- and it's in a cohort. They work out an example where the change -- if the underlying real relative risk was 5, with that misclassification of exposure it would reduce the relative risk you observed to 1.5 from 5, by reducing the risk by 90 percent essentially. And that's critical here.

PANEL MEMBER GLANTZ: I guess the question is the following. And this gets -- I mean I think -- you know, Paul is making the point that what you did, in a way trying to respond to the panel and strengthen the argument, he's saying could create an impression that could actually weaken the argument or the convincibility of the argument. And I guess the question is, is the -- I mean, again, as I've said before, I think the fact that when you do the meta-analysis with all of the studies, including ones that are very heavily biased toward the null because of this exposure misclassification problem, and you still get a statistically significant elevation in risk, that to me is a strong statement -- or strong evidence in support of their being a relationship.

And at one level, if all you're trying to do is say is there a relationship, then I think the best thing to do is just do a simple meta-analysis, throw all the studies in, say -- make the argument that a bunch of them are bias toward the null and even though that's the case, you still find a statistically significant elevation in your point estimate of the risk. So that's one thing you could do.

The problem with that is that if people then take that point estimate and run with it and say, "This is the estimate of the risk," you're probably understating what the true risk is because -- and a better way to do it, which is one of the other things you did, was to try to find the studies that you think had the best exposure assessment and are good in other ways. And you -- and then take and get a pooled estimate of the risk for that and say, "Well, that is based on looking at what we think are the good studies, closer to what the real risk is." But then -- which I think is what you did. But then that kind of opens you up to the thing you're saying, like, well, this confusing and you have multiple numbers and blah, blah, blah. And I mean -- so I mean what do people think is -- what should they do, what is the most sensible thing to do?

PANEL MEMBER FRIEDMAN: It seems to me that you

have established criteria by which you picked the studies that you thought were better studies. And I'm just curious, Paul, are you saying that the way they presented it makes it look like they picked them on the basis of the higher risks? Is that -- it sounds like that's what your concern is.

PANEL MEMBER BLANC: Well, the bulk of the table even though the relative risk that Stan is referring to, for example along 7.4.1B, the first one, is the one that's pooled from all studies, which is sort of the critical one. But I do think it does get a little bit lost. And then in the text, with so much text devoted to this issue of the good studies versus the bad, it starts to have that flavor. I think that a couple of the --

PANEL MEMBER FRIEDMAN: What flavor?

PANEL MEMBER BLANC: The flavor of cherry picking of this --

PANEL MEMBER FRIEDMAN: So that's what --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Cherry flavored. Sorry.

PANEL MEMBER BLANC: What?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Cherry flavored.

PANEL MEMBER HAMMOND: But isn't that your --

CHAIRPERSON FROINES: Can I say one thing?

PANEL MEMBER HAMMOND: Well, your suggestion, Paul --

CHAIRPERSON FROINES: Wait, Kathy. I want to say something as the Chair.

I think that there's nobody here who is talking about there being cherry picking.

PANEL MEMBER BLANC: I'm talking about the impression --

CHAIRPERSON FROINES: I want this for the record, because this -- we've had news media paying attention to this issue. And I want to take language out of the record -- or out of the consideration for the purposes of this meeting. There is no cherry picking going on by OEHHA, nor is that implied by this panel.

And I want that to be very clear.

PANEL MEMBER BLANC: I would fully agree with that. I was talking about impression and not substance.

PANEL MEMBER HAMMOND: But, Paul, I'm just going to ask -- and I agree totally with what John just said. Would -- I think part of this might get back to your original thing from this morning where you were suggesting that if in Chapter 1, one makes very clear these are the criteria -- this is what we mean by good studies and why they're important, and that's where you can have the discussion about misclassification of exposure and why

that makes a better study, and then you can set those criteria up in Chapter 1, rather than there appearing to be -- just appearing at the moment that you're looking at the results. So you set that --

DR. JOHNSON: Convenient --

PANEL MEMBER HAMMOND: Yeah, looks convenient. So, you know, it is something, it actually is and I know it is something that we know a priori before we ever open up the first Epi study. We know that. And if it's in the report that way, that is in Chapter 1, then you refer back to that and say, "Using these criteria for a good study, now this is what we get."

PANEL MEMBER BLANC: And I think that --

PANEL MEMBER HAMMOND: And I think -- I mean I think that's going back to what you wanted in the first place.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We actually did put additional information about exposure issues into Chapter 1 between that time and this time. But it clearly needs to be shortened and --

PANEL MEMBER HAMMOND: I think you're right about -- it may be succinct and to the point.

PANEL MEMBER BLANC: And then I think that for the -- because even though, you know, OEHHA's opinion is that the ascendancy cohort studies may be overrated,

since, you know, out there in -- there is that feeling. And I think you've sort of made an attempt by giving the stratified cohort study relative risk for the meta-analysis among the cohort studies with ETS sources missed. But I think what would be more interesting would be just all the cohort studies, with their pimples and all, what is the estimated relative risk and of all the case-control studies, you know, with all their flaws or good qualities, what is the -- and from a similar point of view because the issue of -- is there a trend over time of what's being published, I think that it would be very interesting to divide it roughly in half, you know, 2000 and thereafter what's the pooled estimate, and before 2000 what's the pooled estimate.

DR. JOHNSON: In my paper I actually do have I think what you're asking for, for summary risks for all cohort studies, all case-control studies.

For the cohort studies, I've listed as with important past exposure missing, but that's all of them. And an overall odds ratio of 1 -- or a relative risk of 1.06. And for all the case-controls -- I didn't provide for all the case-control studies. But a good case-control study's 1.9, poor case-control -- case-control study's missing -- or potentially missing for an exposure of 1.16.

PANEL MEMBER BLANC: Yeah, but you have here --

you have here -- OEHHA here as 1.11 for case-control studies with ETS missed. What I'm saying, it would be nice to see so your numbers may differ unless I just misheard you. But -- and I think -- I don't think that needs to be in the table. It could be in the text, for example, or something. But I think it would -- I think it would be an interesting way of addressing whether there seems to be a trend over time and whether or not there seems to be a systematic difference between case-control studies and cohort studies. I think it would neutralize potential criticism in terms of that de facto your weighting mechanism -- not weighting for the meta-analysis, but your data quality assessment even though it's based -- it's based on exposure assessment, it de facto ends up being a discounting of cohort studies, which in other settings tends to, for better or for worse, get thought of more highly. And so I just would inoculate the analysis against that.

And I think that part -- you know, another thing that I can see as a potential issue -- and I'll come back to this and if you'll turn to Chapter 1, is the issue of how you incorporate consultancy. Because I think that there are points of view that have been expressed in scientific debate over secondhand smoke and breast cancer. And I understand it, Dr. Johnson, you have a well

articulated point of view that has emphasized this issue of dose estimation in various studies, through letters and editorials and papers, not just the meta-analysis that's pending. And, therefore, to have you be the major architect or one of the major architects of this chapter makes it somewhat vulnerable to critique that what this is is a subchapter, is just a more in-depth articulation of a point -- of a point of view rather than a neutral review of a governmental agency. And I'm not saying that that's in substance --

DR. JOHNSON: I only provided the meta-analysis --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We wrote that chapter. He has looked at it and given us kind of --

PANEL MEMBER BLANC: But do you get my point about impression versus --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

So I think that the issue of how the agency, you know, employs -- not employs literally but how it puts to use outside input is -- it's a very complex issue. But I think there needs to be something at the beginning and I'll come back to that later. But this is one concrete example.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER GLANTZ: Well, I just wanted to

try -- I don't want to talk -- I want to go back to the earlier point though about the cohort versus case-control versus -- because I'm going to be trying to work with Melanie and her people to try to incorporate all this stuff as the lead person or a lead person.

My understanding of what you're suggesting in this Table 7.4.1C --

PANEL MEMBER BLANC: 1B and 1C.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER BLANC: Because they're parallel.

PANEL MEMBER GLANTZ: Okay.

-- is that there would basically be two pooled estimates, two meta-analyses report. One would be all studies and then the other one would be the high quality studies as defined using the criteria outlined in Chapter 1. And it would just be those two things in the table, for simplicity. But then in the text there would be a paragraph, or however long it took, adjusting this issue of cohort versus case-control studies. And what you're suggesting there is to include the pooled estimates, the meta-analysis estimates for the cohort and case-control studies in the text though, but to try to keep the table simpler. Is that what you'r saying?

PANEL MEMBER BLANC: I would --

PANEL MEMBER GLANTZ: I mean I'm just trying -- I

just want to make sure I understand.

PANEL MEMBER BLANC: I'd say what I would suggest is close to that, but I would actually say that for all the reasons I said before the pooled estimate of the -- you know, considered a better study if I didn't put in the table -- I'd put that in the text as well. I would just be neutral in the table and just put the one pooled estimate, because that's the one --

CHAIRPERSON FROINES: For case-control and cohort.

PANEL MEMBER HAMMOND: I guess I disagree with that. Because I think one often sets what are the better studies. And I think it's appropriate. And I think tables are where people look to find things. So if one has laid out the criteria clearly for what will be better studies, I think it's okay then and it's appropriate and actually is desirable to include the results of all the studies and then contrast that with what you get if you have those that meet the threshold, but however you set that threshold.

CHAIRPERSON FROINES: But I think you want us to look at the whole picture as well.

PANEL MEMBER HAMMOND: Oh, yeah, the whole picture. No, John, the whole picture would be there, but then you'd also set --

CHAIRPERSON FROINES: From a strategic standpoint let's assume that we are in Washington DC and I'm Jonathan Samet and this is somebody else and somebody else, and they have raised questions about selection bias and about all the issues, null studies and so on and so forth, and the list that I sent to Melanie are the issues -- the kinds of issues that are being raised.

And so the question is: What do you do to make sure that when people are looking at this document, those kinds of questions are being answered?

PANEL MEMBER HAMMOND: No, I totally agree --

DR. JOHNSON: Could I answer that? Because I --

PANEL MEMBER HAMMOND: Please, I want to answer that.

You know, when I -- I think we want back to the U.S. EPA report and the lung cancer, which really is very reminiscent of all those discussions on lung cancer and passive smoking. And if I remember correctly -- I don't have the report here, I'd like to look it up -- I think that we actually -- you know, what they ended up doing was reporting all studies and then the studies that were considered high quality studies. I think that that's -- isn't that the way it's normally done when you're making selections based on quality studies?

CHAIRPERSON FROINES: But I think you have to

also show the case-control cohort.

PANEL MEMBER HAMMOND: Well, they did do that. And that's what Jee is complaining. They got all of that here.

PANEL MEMBER BLANC: You know, I don't feel so strong about this. But let me just throw out an example, I mean, about whether it should be in the text only or in the text and the table. But let me just point out that were you -- I don't know what the numbers are going to come out to be. But if when you stratify by time and by type of study you find that the confidence intervals for cohort studies do not exclude the null effect and the confidence intervals for studies at 2000 and thereafter do not exclude the null effect, and those appear buried in the text, and the one that shows a really strong, you know, relative risk based on the, you know, preferred studies is in the table, you are going to again come into the situation of the potential for someone misinterpreting what you're doing.

Now, so I think your -- not a judgment. I'm just trying to tell you where I think the pitfalls are in misinterpretation of --

PANEL MEMBER GLANTZ: But I think one thing, if you look at this slide though, I don't think anybody -- maybe I misread the report again. I don't think anybody's

saying that the new studies are all showing higher point estimates than the old studies. And if you look at that graph, they're pretty -- you know, they're pretty much -- that they're across time, and the things bounce around. The thing that happens though is that you're getting more data as you accumulate more studies. And the more recent studies are the ones that have -- well, actually what -- see, when I think about new studies, I'm comparing it to stuff done in the seventies and the eighties, the early eighties, before people were really thinking carefully about the ETS -- the ETS-exposed people in the denominator of the risk. And so I mean I think the new versus old issue is did they account for -- or were they careful about who's in the control group, not risks over time.

But, again, I'm still very confused about what you're looking for in the table. And, that is -- I mean I agree with Kathy. I think there should be two things. You should have all the studies, and then no one can accuse you of selection bias because you've included them all, even the ones you think are biased toward the null. And then with some pre-established criteria, which you think are the best studies. And I think in the interests of not hacking and slicing and dicing, I think those are the two things one ought to focus on.

One question is asking: Is there taking a

super-conservative analysis elevation -- evidence of an elevated risk? Where the question is a yes-no question. That's the all studies.

And then second question is: Well, what's your best estimate of what that risk is? And for that I would use the best studies. And that's something this panel has done in the past is, you know, taken sometimes just one study.

CHAIRPERSON FROINES: I don't think there's any disagreement with that, Stan.

PANEL MEMBER BLANC: Pardon me?

CHAIRPERSON FROINES: Unless -- I don't see Paul or Gary disagreeing. But I think that you also need the case control versus cohort.

PANEL MEMBER HAMMOND: In the table or --

CHAIRPERSON FROINES: Sure.

PANEL MEMBER BLANC: In the text.

PANEL MEMBER HAMMOND: -- or in the text?

CHAIRPERSON FROINES: I would rather see things in tables.

PANEL MEMBER HAMMOND: Well, that's in the table now. I mean that's the thing --

PANEL MEMBER BLANC: No, it's not. It's only the bad case-control and the bad --

PANEL MEMBER HAMMOND: Oh, I see.

OEHHA SUPERVISING TOXICOLOGIST MARTY: None of the cohort studies ended up being studies that we thought had the best exposure assessment. Hanaoka had the best one of the cohort studies. And because it was a prospective design, we considered that it was one of the better studies. But you'll note in our meta-analysis that we didn't designate Hanaoka with a closed circle because they still were missing a lot of information they could have had gotten.

CHAIRPERSON FROINES: I just think if at this table was Michael Thun and Jonathan Samet, these kinds of questions that I'm raising now would be being asked by them. And I think that one has to be sensitive to the that population of persons who are -- who have this point of view.

PANEL MEMBER FRIEDMAN: You know, I think that this raises a question about our having a workshop. This is so important, so contentious. And, you know, I think it's at least as important as diesel exhaust. And I think -- although I don't want to slow --

PANEL MEMBER GLANTZ: Well, we did -- there was a workshop.

PANEL MEMBER FRIEDMAN: On ETS and breast cancer that we sponsored?

PANEL MEMBER GLANTZ: Yeah, it was on the whole

report.

PANEL MEMBER HAMMOND: When was that?

PANEL MEMBER GLANTZ: It was months ago. I don't -- a long time ago. Because I drove up to Sacramento for it. They even had people able to call in and it was web cast.

PANEL MEMBER FRIEDMAN: I wasn't aware of it.

PANEL MEMBER BLANC: Yeah, you've forgotten. It happened.

PANEL MEMBER GLANTZ: Yeah. You've forgotten it was so long ago.

PANEL MEMBER BLANC: It was a long time go.

PANEL MEMBER FRIEDMAN: Breast cancer was considered?

PANEL MEMBER HAMMOND: But not on breast cancer.

CHAIRPERSON FROINES: Well, Stan, would it be -- I don't want to prolong this process overly long. But if one brought the people who were working on the IARC report -- who had worked on IARC and people who had worked on the Surgeon General's and this panel and OEHHA, would that be -- plus other outsiders, would that be useful? I don't know the answer to that.

PANEL MEMBER GLANTZ: I actually don't think so, because we know -- I mean I think the issues -- I mean these are very good friends of mine. I know them. I've

talked to them about all this. The issues that they would bring to the table are at the table. I mean they're the things we've been talking about, they're the things that John raised in the E-mail, that he said to Melanie. I mean --

OEHHA SUPERVISING TOXICOLOGIST MARTY: And we also got comments.

PANEL MEMBER GLANTZ: And, plus, if you go back and read Michael Tune's comment, because Michael did submit a public comment, he raised all these issues in that comment.

CHAIRPERSON FROINES: Well, I talked to him for an hour, and he has actually more than --

PANEL MEMBER GLANTZ: Well, but, you know, I mean --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I make a comment about the Surgeon General's report, since it keeps bouncing around?

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: I have a slide on -- we took a look at the Surgeon General's 2004 report. Now, this is a report on active smoking. Okay, so they didn't focus on passive smoking, but they had a little section on it. And they basically dismiss any detailed consideration of the studies because they are

saying they don't see an effect of active smoking; therefore, there shouldn't be an effect of passive smoking.

If you look at the papers they cite in that document, they cite Morabia. That is the only passive smoking they cite -- passive smoking study they cite. And they try to dismiss some of the findings as the result of confounding, some of which was addressed in that study. And they didn't really do much more than a few sentences on that study.

This contrasts with the OEHHA analysis of four studies on ETS and breast cancer in the '97 document and an additional 15 in the current document. So bear in mind, they did not really address the issue of passive smoking. They just -- they did no analysis. There's nothing in that report of substance, in my opinion.

PANEL MEMBER HAMMOND: In fact, what they said in the report -- in the 2004 Surgeon General's report on active smoking, they said there's no effective active smoking. And despite the fact that the study of passive smoking shows an effect, we don't believe it because there's not active smoking. But they actually -- they actually concede that the study shows an effective passive smoking, it goes so far to say.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, they

do.

CHAIRPERSON FROINES: I think we're missing the -- I think we're making a mistake here by the over-reliance on -- I think the Surgeon General's report is important because it deals well -- pretty well with biological issues, which is what I raised I think in my E-mail. And, secondly, their Chapter 1 deals with causality and decision making in a very nice way as well.

So that, in fact, what I thought was important about the Surgeon General's report was not the actual review, because it was so limited with respect to passive smoking, but the issues of -- that Paul raised in your Chapter 1 and the issues which we have yet to get to on the toxicology and biological mechanisms. And so -- but I also know the players who are part of the passive smoking report that's coming down the road. And one has to take into consideration the point of view that was expressed in that report, that one, and think about it in terms of the future. And so that's what --

PANEL MEMBER GLANTZ: Yeah, but --

CHAIRPERSON FROINES: Stan, please.

That's what I mean about looking at it strategically.

Second, there is the IARC report, which evaluates a lot of literature, which we don't have and never have

seen, but is something that needs to be taken seriously as well. I talked to a guy from IARC this morning about it. And there is clearly not a race to adopt a different point of view than they adopted. So that's out on the road.

So that there are issues that have been raised. And I think that what we need to do is in this document try and deal with those kinds of questions that are being raised in this document so we -- you blunt the questions.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I would agree with that.

CHAIRPERSON FROINES: There is a constituency out there that's not necessarily the same as the people -- three of you at that table. And I think one -- and we reflect some of that here. So I think we just need to be sensitive to it in terms of what we -- how we try and make this report look as -- how we make the report as strong as possible in that sense.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think it was Dr. Byus brought up at the last meeting: Are there any papers that have -- on passive smoke and breast cancer that have dose response information?

PANEL MEMBER BYUS: That's what I -- this is -- I would like to move on to some dose response discussion. Because I do find that -- I do find the data you presented

very persuasive in that regard. And I have one additional question which I'd like to ask about dose response as it compares active dose response -- my question is -- and I'll tell you what my question is.

When you look at the active smoking literature, if you're down -- if you go way down on the low end of the dose response, essentially one or two cigarettes a day versus no cigarettes, if they do that, way down on the low end, should you not be able to see an increase, essentially? Or is it -- that's kind of my question. And I know -- I can see when you're going way up on the high end, that if it plateaus out, you don't see an effect. But way down at the low end do you see something?

And then of course I would like to hear more discussion of the passive smoking dose response information, which I view is probably the most persuasive data for the passive smoking case, if the data is real. This gets -- because very few -- however you choose it, if you choose studies that have dose response data, period, if that's your inclusion, and if they are in fact -- I mean and they all show an effect, then you don't really need to know anything more as far as I'm concerned. That's why I want to hear this again.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Well, let me start first with the table that's up there.

--o0o--

OEHHA SUPERVISING TOXICOLOGIST MARTY: So we found -- there's seven studies that looked at some way to measure dose response. And this gets back to the problem with the crudeness of estimating exposure especially for ETS. The Hanaoka study, which was the Japanese cohort just published looking at premenopausal women, found some evidence of dose response looking at how often were the women exposed, one to three days per month or more than that. So it's split out that way. Get a P test -- a P for trend test of 002.

Shrubsole, et al., which is a case-control study looking at the premenopausal data they had on occupational exposure in terms of minutes per day, they also get a significant trend test, going 1 to 59. They broke it out into quartiles, up to their highest quartile being statistically significant.

Kropp and Change, looking at lifetime ETS exposure in hours per day times years, splitting it out in two, 1 to 50 and greater than 50, they also see dose response trend that's significant.

On Johnson, et al., 2000, looking at lifetime residential and occupational exposure in smoker years -- and this is in premenopausal women -- also get a significant trend test, breaking it out by smoker years.

Jee, et al., which was the Korean cohort we talked about earlier, based on the husband's smoking status, looking at ex-smoker risks to women of -- married to ex-smokers versus current smokers versus smokers who they've been married to for greater than 30 years. And they see an elevation in risk, a gradation in risk.

And then Hirayama. And this one is actually in women 50 to 59 years old whose husbands smoked 1 to 19 cigarettes per day versus greater than 20 cigarettes per day. And they see evidence of a dose response.

PANEL MEMBER GLANTZ: So, Melanie, is that all the studies that were done that looked at dose response?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No. These are the ones -- no. And some studies looked at dose response and did not see it.

PANEL MEMBER GLANTZ: And how many of those were there?

DR. MILLER: I'd have to go back and count.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'd have to go back and look them up.

So this was just in response to the question: Did anybody see dose response? And, yes --

DR. JOHNSON: Morabia and Smith did not see dose response. But both of them have odds ratios -- overall odds ratios of 2.5.

PANEL MEMBER BLANC: So I think that -- no, I don't want to put words in your mouth. But when you say, "Do you see a dose response?" it doesn't mean "What are the studies that saw a dose response?" It's when studies examined a dose response, how many saw it and how many didn't. I mean just bear that in mind.

PANEL MEMBER BYUS: That's what I mean.

PANEL MEMBER BLANC: I think this is a very small point, is I think it's -- I'm not sure what the inference is in Jee of -- I don't know how I interpret dose response from those three categories, and it's slightly different. Category 1, row 1 and row 2, are mutually exclusive. You were either an ex or you're a current, right? But they --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER BLANC: -- they said -- they provided the relative risk for the greater than 30 years and not for the less than 30 years?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER BLANC: They just didn't provide it at all?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It was current smokers and then current smokers where the wife was married to the smoker more than 30 years.

PANEL MEMBER BLANC: But you have already estimated from some other source what the overall -- what

the average risk was or something. So I guess you could put that -- I mean it's just hard to -- in the dose response context it's really hard to interpret what this means exactly. And so I think you could present those data differently. But I think you're obliged in the dose response argument to provide the studies that looked at a dose response and didn't see it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's in the table. We have a whole table --

PANEL MEMBER BLANC: Okay. So this is just for us?

OEHHA SUPERVISING TOXICOLOGIST MARTY: This is just answering the question: Did anyone see any evidence of dose response? That's all this is.

PANEL MEMBER BLANC: Okay, okay, I've got you.

CHAIRPERSON FROINES: Melanie?

PANEL MEMBER FRIEDMAN: How many didn't see it?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'd have to go back and look.

DR. JOHNSON: It's a bit difficult, because if they report it, they probably report it because they see it. So if they don't report anything -- well, it's hit and miss. If they don't report it, maybe because they don't see it, they don't have enough data, they don't have the right kind of data.

PANEL MEMBER FRIEDMAN: But if they looked at it --

DR. JOHNSON: Or they report it several different ways. Like Smith reports several different split -- stratifications. And they vary.

PANEL MEMBER FRIEDMAN: But if they looked at it and didn't see it, you know, I think that would be irresponsible not to report --

PANEL MEMBER BLANC: Well, you say it is in a table -- it's in an existing table.

DR. MILLER: It's a different -- there's a dose response --

Which table is that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: 7.4.1 -- is that an "I" --

PANEL MEMBER GLANTZ: What page?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think it's an "I". Yes, it's an "I". 7.4.1I on page 7-151.

CHAIRPERSON FROINES: Melanie, question.

Of these studies on the board, three of them are in your top -- your list of six and three aren't.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: Is there a reason why the three who aren't aren't?

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, they didn't meet the criteria that we had set out for having residential, occupational, non-residential and/or childhood in multiple time points.

PANEL MEMBER FRIEDMAN: So --

CHAIRPERSON FROINES: Then that's clearly stated somewhere?

PANEL MEMBER FRIEDMAN: This table 7.4.1M lists a bunch of studies that looked at dose response and none of them found it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: 7.4.1I is where we had -- I'm sorry -- 7.4.1, it's J.

PANEL MEMBER BLANC: J has the does response, right?

OEHHA SUPERVISING TOXICOLOGIST MARTY: J has the dose response. Sorry.

PANEL MEMBER FRIEDMAN: But doesn't 7.4.1M also have it? It says cohort studies with dose response. And they don't show them.

DR. MILLER: Yeah, like I said, that's the cohort portion.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, that's the cohort portion. There's the cohort study -- we split them out case-control and cohort. That's why there's two.

PANEL MEMBER GLANTZ: So I guess the short answer

to Craig's question is that if you look at all of the studies, there were six that found a dose response relationship and there were -- when you said -- and then your question is: Have any of the studies found dose response? The answer is "Yes, six did." And then there were some other -- there's some number they'd have to add up that we know looked for and then didn't find a dose response, right? Is that a fair --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right. That's right.

PANEL MEMBER BLANC: In terms of the theoretical construct of the exposure under-estimation but not complete misclassification of the cohort studies, is there an inherent reason why the point estimates in those studies would systematically fail to show an association as well, in your view?

DR. JOHNSON: Absolutely.

PANEL MEMBER BLANC: And what is that?

DR. JOHNSON: Well, because when you misclassify, you put people who are exposed in the referent group.

PANEL MEMBER BLANC: Well, I'm not talking about that because that's not your argument with the cohort studies. Your argument with the cohort studies is that they don't estimate the full range of exposures, isn't --

DR. JOHNSON: No, no. But by not taking into

account the full range of exposures, you have some women that you've put in the referent group because you think they're not exposed because you never actually asked them about their exposure.

PANEL MEMBER BLANC: -- about their work.

So it's not just the -- it's not just the imprecision and --

DR. JOHNSON: Oh, no. Actually almost all of it is not the imprecision. It's -- what you end up with basically is it's likely -- for example, in the Wartenburg study, the Big American CPS2's cohort, they found, depending on which analysis, 50 or 60 percent of women exposed. If you contrast that -- with basically just looking at spousal exposure. If you contrast that with the Fauthem study, where they did detailed -- a big lung cancer study, they found something like 94 percent of women had been exposed to tobacco smoke. If you even take conservative assumptions on that, you may -- of those 50 percent of women that they say are not exposed, it may be that 40 percent of those or 45 percent if you use the Fauthem numbers, if it was exactly the same group of women -- it isn't -- but, say, you just say 40 percent of them. If 40 percent of them are misclassified, that means that 80 percent of your referent group that they say is unexposed actually is exposed.

PANEL MEMBER BLANC: Yeah, but let me follow up on this question.

DR. JOHNSON: Sure.

PANEL MEMBER BLANC: Okay. That's --

DR. JOHNSON: I think that's the crux of the argument.

PANEL MEMBER BLANC: That's the overall biasing towards the null. Is there a systematic way that that would bias such that if I separated out the women who lived with husbands and had eight hours a day of exposure to their husbands for 40 years, wouldn't still have a point estimate that was higher relative to the contaminated reference compared to the women who only lived five years with --

PANEL MEMBER GLANTZ: Could I try to rephrase your question?

I think what he's trying to ask, Ken, is -- and if you have the exposure misclassification problem that you've described, would that necessarily obscure the presence of a dose response?

DR. JOHNSON: It would, because each of those numbers would be attenuated. Rather than seeing risks of 1.5 to 2.53, you'll see risks of 1.1, 1.2, 1.3, 1.4, and you won't be able to differentiate them and they won't be statistically significant, because they'll be attenuated

dramatically.

In the letter I wrote about the Wartenburg study, which was a -- the Journal of the National Cancer Institute thought was important enough to publish, I actually demonstrated what would happen to those numbers and how it would be attenuated.

If the underlying risk was 2 and you had that kind of misclassification, you would only see an overall estimate of 1.15. So your dose response would be around 1.15 instead of around 2. You'd see 1.05, 1.15, 1.25 instead of 1.5, 2, 2.5.

PANEL MEMBER BLANC: But would that obscure a test for trend?

DR. JOHNSON: Absolutely, because you just don't have -- you don't have the separation and you don't have the -- none of the estimates would be statistically significant. They're too close to 1.

PANEL MEMBER BLANC: Oh, I'm thinking about --

PANEL MEMBER GLANTZ: No. So let me try to rephrase his question.

PANEL MEMBER BLANC: The point estimates --

PANEL MEMBER GLANTZ: What you're saying -- I mean it seems -- what you're saying -- or what he's saying is, well, you might depress to point estimates. But would the variance be depressed comparably so you'd still be

able to see the trend? Or is the variance going to stay as high, so the smaller trend would be obscured? I mean that's the question he's asking.

Does that -- does my rephrasing of it --

DR. JOHNSON: I'm not a statistician, so I can't tell you for sure. But my sense is very strong that when you get very close to 1, it's very hard to show anything statistically significant. And there'll be overlap of all those confidence intervals, far more likely than if the numbers are spread and --

PANEL MEMBER BLANC: Well, but I'm asking about the point estimates too. I'm sort of asking two questions.

PANEL MEMBER GLANTZ: Well, but, you see, to see the trend -- when you do a test for trend, you're looking at the change against -- you're looking at the change with does against the background random component.

PANEL MEMBER HAMMOND: You broaden everything.

PANEL MEMBER BLANC: No, I can see where --

PANEL MEMBER GLANTZ: And so I can see how what he's saying there could obscure it.

PANEL MEMBER BLANC: I start to --

PANEL MEMBER HAMMOND: No, I think --

PANEL MEMBER BLANC: -- test for trend, but not perhaps --

PANEL MEMBER HAMMOND: I think what it would -- is that you would have, since your exposure -- the actual exposures, you know, are actually broader in both the numerator and the denominator. See, the precision of your estimates -- if you had a way to incorporate the uncertainty of exposure into the precision of the estimate, you'd find a very imprecise estimate. And because of that, looking at ratios and trends would be more difficult, they'd be more obscure. That uncertainty would add to that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Andy has something to add.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Just a brief comment.

I think my -- my understanding of the question about whether or not you could see the trend relates to the fact that you would probably expect that the variance in exposure from the occupational sources and other normal spouse-related sources would likely be independent of the variation in the exposure to spousal sources.

If that is so, then the contamination of the data set with respect to spousal exposure criterion would not affect the variance of the other part of the exposure, which would therefore, as I think you were implying, mean that the variation in all those dose groups would stay

high, and that would make it effectively impossible to see trend.

Does that make sense?

PANEL MEMBER BLANC: Well, no, it's not entirely convincing. I understand why it would be hard to see the statistical significance of a test for trend. But there should -- I'm trying to still figure out why we wouldn't --

PANEL MEMBER HAMMOND: Well, I think if they're depressed enough -- you know, if you could depress it down to 1.1, you're not going to be able to -- you know, overall you probably -- you know --

DR. JOHNSON: If you see 1.05, 1.1, 1.12, 1.16, you think you've got a dose response, compared to you if see 1.5, 2, 2.8, and 4.2?

PANEL MEMBER BLANC: Well, let me give you a different example. If you saw an overall estimate of 1.05, which is not statistically significant, which is kind of -- where a lot of these cohort studies are coming out, and then I would expect to see that in the people that -- you know, 10 husband years of exposure, you know, it would actually falsely appear to be protective at .95. And then with 20 years I'd see 1.1, and then with 30 years, as I started to get enough exposure, that relative to the same baseline misclassification it's starting to

become strong enough -- it would be as if I had some people in there who were active smokers, I would finally start to see -- you know, I would see that. I mean I --

PANEL MEMBER FRIEDMAN: There's so much variation other than --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, because the variation is independent, you've got a high level of variation regardless of what's happening in the little bits of the variation that might be showing a trend.

PANEL MEMBER FRIEDMAN: We'd be overwhelmed by the noise of all these other --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Exactly. The point is the noise stays wide.

PANEL MEMBER HAMMOND: You know, I've been looking at the IARC report that we've been talking about. And I would like to put into the record and have you refer to Table 2 -- compare Tables 2.2 and 2.5. And I want to quickly say something about this that relates to this overall impression we have of all the data.

This is the lung cancer among -- passive smoking evaluation of lung cancer. And in Table 2.2, it's looking at the epidemiologic studies based on spousal smoking. And there are 40 case-control studies and 6 cohort

studies.

Not one of the 6 cohort studies is statistically significant. It's null, the cohort studies, to date now.

The only significance comes in the case-control studies for lung cancer. If you turn to Table 2.5, this is looking at the risk for lung cancer in nonsmokers exposed to passive smoke in the workplace. All right? And in the workplace these are all case-control because nobody in a cohort study does that analysis. This is the reason the cohort studies have poor -- you know, why we say they have poor exposure assessment. You don't have that data, so it's only case-control.

And, again, one can see in the workplace alone, with no home exposure, statistically significant increased risk shows up in the case-control study. So where you have the opportunity to do a good exposure assessment, you can see it in a case-control study.

But this -- where we have -- most of us have just said, you know, we accept that lung cancer, even there the cohort studies don't show it. If you hung your hat only on cohort, you would have to say that passive smoking does not cause lung cancer. So I just think that that's an important perspective with which -- filter with which we should look at -- we shouldn't expect breast cancer to be clearer than that, the lung cancer.

PANEL MEMBER FRIEDMAN: Some of the --

PANEL MEMBER BYUS: My last -- I'm sorry. I was just listening to you, trying to --

PANEL MEMBER GLANTZ: Sorry. I know --

PANEL MEMBER BYUS: That's okay. No, that's great.

PANEL MEMBER HAMMOND: Does it make any sense?

PANEL MEMBER BYUS: And so now I have a somewhat answer to my other question. But I still -- might rephrase my other question.

So if smoking is related to cancer, however you get the smoke into you, and it must then plateau in some sort of -- and/or go down some form of non-linear or long-range dose response and plateaus. And I would like to get back to the estrogen question here in the biology at some point here, John, because I think this is the wrong way to phrase it -- that you've phrased it by calling it anti-estrogenic. I think that's incorrect.

So what would it mean? So this would mean? In sort of active smoking would this be like one cigarette a day or -- what sort of comparable -- I know this is -- maybe that from my -- you know, I'm a pharmacologist. I just want you -- I mean I know this -- you know what I'm trying to say? I'm just trying to put it in exposure reference, if at all possible.

So if you never were exposed to passive smoke, sort of like an Einstein-type mind experiment -- maybe not Einstein, but you see what I mean.

So if you were never exposed to passive smoke and then you went -- and if we were going to design an epidemiology experiment prospectively -- which they won't less us do -- and we would say, "Okay, we're going to put people into different smoking categories," how much -- where are we going to set our dose response up for active smoking? Is it going to be a one cigarette a week, a month, a half a day or one a day? Roughly, what will our dose response range be where we would see it with active smoking? That's what I want to know.

PANEL MEMBER HAMMOND: All right. The problem that I've tried to write about on this is that the emissions of various chemicals are different in mainstream and sidestream in the same setting.

PANEL MEMBER BYUS: Humor me for a minute. Assume that they're roughly in some comparability.

PANEL MEMBER HAMMOND: So what's your question? Your question's --

PANEL MEMBER BYUS: I want to know --

CHAIRPERSON FROINES: I don't understand --

PANEL MEMBER BYUS: -- what would you expect to see the dose response in smoking actively with cigarettes?

CHAIRPERSON FROINES: But I still am -- before she does that, I still think this active versus passive smoking is -- I mean smokers are passive smokers.

PANEL MEMBER HAMMOND: Right. I mean -- first of all, even if you look at -- we see a different answer to your question if you look at lung cancer and if you look at heart disease, just to pick two disease. In two diseases -- and part -- and of course I would defer to Stan to really explain this.

But in heart disease we have some sense of a mechanism which gives some justification for the fact that you see what appears to be a very steep curve early on the dose response and then a tapering, and in an almost ascentotic. Maybe that's too strong. But definitely a two -- almost like two curves.

Whereas in lung cancer, we see something very different. We see what looks much more linear.

Now, so the question is -- we could talk about the mechanisms behind that and there's speculations around that and people have observed those effects on people exposed.

So what is the mechanism for breast cancer?

PANEL MEMBER BYUS: We don't know that.

PANEL MEMBER HAMMOND: I know. And the thing is, but you'd have to make some hypothesis for that, wouldn't

you, to be able to even come up with this. And given that active smoking is not showing breast cancer, at least not very clearly --

PANEL MEMBER BYUS: Well, they're saying so because they're subtracting -- because of the referent group.

PANEL MEMBER HAMMOND: So then you get into -- you're almost looking into the crossing of two curves, aren't you? You've got a -- the active smoking kind of cuts your risks to some degree and --

PANEL MEMBER BYUS: It has --

PANEL MEMBER HAMMOND: -- it has to go up and down and --

PANEL MEMBER BYUS: Active smoking must cause it to some degree. Otherwise you'd see something.

PANEL MEMBER HAMMOND: It must be an up and down kind of thing. And where would you hypothesize that those things are happening? That's a hard question.

PANEL MEMBER BYUS: I don't know. I'm just -- it's just -- can you answer me? Do you know what I'm getting at?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I know what you're getting at.

PANEL MEMBER BYUS: It's the major -- one of the major problems here.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's hard to look at the data and say, okay --

PANEL MEMBER GLANTZ: Can you tell us what he's getting at, just so we all know.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, he's getting at: Why don't you see higher breast cancer risks with active smoking than passive smoking? And the bottom -- when people break out the dose response data for active smoking, they're usually looking at 1 to 10, you know, 11 to 20 cigs per day, more than 20 cigs per day; and where do you start to see an effect?

PANEL MEMBER BYUS: And I agree. You're not going to see it there. I do agree with you. So I'm not -- I'm just trying to get a feeling for where would you have to -- way down at the low end, is that roughly what we're looking at?

OEHHA SUPERVISING TOXICOLOGIST MARTY: You mean in terms of the dose of carcinogen?

PANEL MEMBER BYUS: Yes.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Comparing active smokers to passive smokers?

PANEL MEMBER BYUS: That's correct.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think that is a great big question mark. And here's a few reasons. We don't know for breast cancer which of the

carcinogens are causing the effect. There's many carcinogens. There's likely going to be interactions, synergisms, antagonisms, even with the non-carcinogenic components. Active smokers have induced detoxification enzymes. That could be playing a role.

And I know you don't like the anti-estrogen argument. But I think it's an important argument. And, you know, it didn't come -- we didn't make it up. It's in the literature in a lot of different places how active smokers definitely have, you know, lower age at menopause, more -- so on, these effects that are considered to be anti-estrogenic.

PANEL MEMBER BYUS: They don't have lower circulating levels of estrogen however.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, they don't. But they have different profiles of the estrogen metabolites.

PANEL MEMBER BYUS: Estrogen hormonal levels are the same, which I found out since the last time I was here.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It depends on the study. And --

PANEL MEMBER BYUS: Urinary levels are up, but the circulating serum levels are about the same in the best studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Total. But if you look at the activity of them, metabolites, you get a different profile.

PANEL MEMBER FRIEDMAN: Is there data on passive smoking in estrogen?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't think that there are. But --

PANEL MEMBER FRIEDMAN: So we don't know that passive smoking doesn't produce the same effect?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, the studies that looked at active smokers also looked at -- they compared people who smoked with nonsmokers. So in the nonsmoker pile are the passive smokers.

DR. JOHNSON: Also all those active smokers are passive smoking. So --

PANEL MEMBER GLANTZ: I just want to -- I think, you know, getting back to -- if I were to pretend to be Michael Thun, whose name was taken in vain recently, or Jonathan Samet, this -- I mean this is the key argument right here, you know. This thing of why are the risks -- I mean I think when you look at the meta-analysis, the risks for active smoking are higher than passive smoking but they're not much higher.

And I think that -- and in fact they even said -- it's even in the Surgeon General's list of 2004. I mean

that's the fundamental argument that is made for people who don't want to say that passive smoking increases the risk of lung -- or breast cancer. It's, why are the risks so similar? So I think if that -- it would be nice to more fully ventilate that argument, because that really -- that is the central argument, more so than case-control versus cohort, more so than confounding or publication bias or -- it's, why are the risks so similar? So what's the answer?

CHAIRPERSON FROINES: Yeah, but I think, Stan -- I'm not sure -- I would love to see a whole section on that and get into the biological, chemical mechanism very much. That's my area, so I would like that.

But I'm not sure that we want to do that in this report.

PANEL MEMBER GLANTZ: Well, but let's at least discuss it and see, because Craig --

CHAIRPERSON FROINES: But let me just say that -- I mean I think the issues around this are so complex biologically. I mean on the one hand, just to take a simple example, the induction of P 450 enzymes also enhances the bioactivation of PAH's that might lead to carcinogenic effects in the breast.

So you've got thing -- what you have is a situation where things are going up and other things are

going down. And so we don't know yet what's really going on. And I think anything that we get into in this report will be speculation, and I'm not sure it's useful. I think -- I would love to have a workshop on the biological mechanism of breast cancer and look at it in some detail. But I'm not sure we want to turn this report into that document.

PANEL MEMBER GLANTZ: Well, that may be true. But I think it would be highly enlightened -- or not -- I think it's worth taking the issues Craig has brought up now and at least hearing what OEHHA has to say and what Craig thinks about it and what you have to think about it. Because that is -- if you talk to the people who are skeptical about the conclusion in the report, that is the primary reason that they are skeptical, is that the risks which are seen -- I mean you've talked to them. I've spent lots and lots and lots of time talking to these guys. And, you know, that is -- I mean it's explicit in the Surgeon General's report. I mean it says here -- Kathy underlined it.

PANEL MEMBER HAMMOND: No, I didn't --

PANEL MEMBER GLANTZ: Okay, okay, okay. Well, they say the studies of passive smoking in breast cancer contrast somewhat with the findings of the far larger number of active smoking that are consistent with showing

no effects. So even the Surgeon General's report which we've been quoting recognizes that there's an elevation in risk reported in the passive smoking studies. But then they say, "But we didn't find it in active smoking, and so how could it be true?" So that -- and in fact if you look back and read them carefully, a lot of them did find an elevation in risk in active smoking. It was just not very large compared to what people thought it should be.

And so I think at least it's worth talking -- I mean even -- I think even a discussion of the kind of -- and this is getting out of my area of expertise. But I think a sane, articulate discussion even of the conflicting mechan -- you know, conflicting biological forces that are present and sort of laying that out clearly would actually help the discussion by simply maybe explaining why -- you know, what could be going on that's creating this sort of surprising result.

CHAIRPERSON FROINES: Well, in the journal Chemical Research and Toxicology there are papers every month about the metabolisms of estrogens and other hormones. And there are lots of biological mechanisms that people -- and chemical mechanisms that people talk about. There are quinone formation in terms of estrogen oxidation and so on and so forth. So there's an entire literature on that. And I think that that's a fascinating

topic. I'm just not sure it's the topic for this time.

PANEL MEMBER BLANC: Well, you know, I think I have a possible way out of this difference of opinion.

PANEL MEMBER BYUS: Another table? No.

(Laughter.)

PANEL MEMBER BLANC: There are really two separate arguments that are made. One is a sort of dichotomous argument, which is that if active smoking isn't related to breast cancer at all, how can passive smoking be related to breast cancer? And the second argument is, okay, well, active smoking is related to breast cancer, but why is the magnitude of risk so close, which is the argument that you made.

PANEL MEMBER GLANTZ: Well, both of those arguments.

PANEL MEMBER BLANC: Both of those arguments are made. And I think that the goal of the appendix that you've added and the attention that you've given to smoking -- active smoking is really -- I think where you should and have appropriately given some attention is to the first part of that argument, which is: In fact an argument can be made that there is relationship between active smoking and cancer and that there's a little bit of lag in analysis of those studies and that we'll probably -- you know, even though it's beyond the scope of

this document, that that's really, given the current state of our database, not strictly speaking correct.

On the other hand, I think it would make sense to recognize that, however you take it, the estimates of risk are fairly close. And there could be many explanations for that, which are, you know, really beyond the scope of this document. You know, you could -- you know, you can refer people out -- I think you do. But I think where -- I don't think you quite as explicitly as you could divide the argument into the two arguments. You sort of lump them together.

And I think separating them out and say, okay, here's Appendix A that addresses to our view unequivocally that the first argument really is not -- probably is not what the argument is. And, you know, the second argument is a very interesting one and is related to a lot of biology.

The only other way I think that would support your -- tend to support the secondhand smoke analysis is to the extent that the active smoking literature gives you some specific data on premenopausal versus postmenopausal, you would expect the direction of association to be similar. That is to say that when you look -- start looking in that stratum the pattern is less equivocal. And I think that would be very -- and that would --

CHAIRPERSON FROINES: Melanie, that was the question -- the last point that Paul made is the question I wanted to ask you, because I don't know the literature.

Do you know if there have been any studies that have looked at pre versus postmenopausal and active versus nonsmoking? Because I would predict based on the biology and physiology that premenopausal women would be at greater risk of breast cancer as active smokers. Although there's an -- obviously there's an age issue about when people develop cancer. So that it's not simple.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, there are actually a number of studies of active smoking that looked at that. The one that was published a couple weeks ago, Hanaoka, active smoking was positive, and statistically so, for breast cancer only in premenopausal women and not post.

CHAIRPERSON FROINES: That's interesting.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Band, et al., 2002. Do you remember? I'm pretty sure --

PANEL MEMBER BLANC: Do you have the study from the nurses' health study? Because you didn't cite it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Egan? Yeah, we have Egan.

PANEL MEMBER BLANC: What about Wael K. Al-Delaimy?

CHAIRPERSON FROINES: Who?

PANEL MEMBER BLANC: Wael K. Al-Delaimy.

PANEL MEMBER BYUS: It's easy for you to say.

(Laughter.)

CHAIRPERSON FROINES: See, I think that the biological issues associated with premenopausal women in active smoking are very interesting questions.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And, you know, there are -- there definitely is evidence that active smoking causes breast cancer and particularly in premenopausal women. So that it's --

CHAIRPERSON FROINES: Especially given the time-age versus risk where you have this hump in what, 35 or 40? So that something's going on.

PANEL MEMBER GLANTZ: Hump in what?

CHAIRPERSON FROINES: In the time --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, with the breast cancer rate.

CHAIRPERSON FROINES: -- time rate.

OEHHA SUPERVISING TOXICOLOGIST MARTY: There were also actives -- there was just another published study, Graham, et al., '05, that looked at girls starting smoking as teenagers. They are at elevated risk. And if I'm not mistaken --

PANEL MEMBER HAMMOND: -- the younger they start,

the higher the risk.

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- the younger they start, the higher the risk.

Egan also had --

DR. MILLER: Egan if you started smoking 16 or younger, that was where they thought --

OEHHA SUPERVISING TOXICOLOGIST MARTY:

-- elevated risk. But that's --

CHAIRPERSON FROINES: It's interesting --

PANEL MEMBER BYUS: My concern is that document here have the estrogen effect. And I -- the Surgeon General's report -- and I said this to you last time and gave you this paper, and the people I've talked to subsequently -- reference -- and I'll just read this to you: "The estrogenic hormone dependence of breast cancer is not well defined." And that is really true. It's not to sort of hang your hat, as it were, on estrogen, as opposed to any of the number of myriad other causes or myriad of potential effects I think is my concern; and, in particular, the fact that the basal hormone -- I mean not to say it's not -- it's just not compared to, say, endometrial cancer, some of the other cancers. And that also gets back to this fact that the estrogen levels are -- the circulating levels of estrogens as well as all the other hormones that they -- reproductive hormones that

have been measured in smokers versus nonsmokers in this fairly carefully done study, they're pretty much the same. It's circulating levels.

Now, this -- again, I grant you that there's metabolites data, there's very complex -- all the different oxidative metabolites, different activities, pre versus postmenopausal, overweight -- all the rest of it. But I think you don't necessarily want to hang your hat on that as the explanation.

DR. MILLER: You know, I --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't think that we actually are trying to hang our hat on any explanation, because it's very complicated.

PANEL MEMBER BYUS: Quite honestly, I think that what the data points to is that there's something significant in the etiology of breast cancer that we don't understand what it is. Its doesn't --

CHAIRPERSON FROINES: I think there are two different -- you're actually confusing a little bit -- just a little bit two different issues, one of which is: Is estrogen somehow related to breast cancer? I think the answer there is yes. Is active versus passive smoking -- are the differences really the estrogen? And there I think the answer is: It doesn't look like it, but we don't know.

PANEL MEMBER BYUS: Well, I'm telling you people are making -- I showed this paper last time. I gave you this paper. People are making the argument that estrogen is not necessarily directly related to breast cancer. You can make the argument. I mean there's multiple ways you can make it.

CHAIRPERSON FROINES: Hormones.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think there's thousands of studies that make the opposite argument, literally.

PANEL MEMBER BYUS: Well --

OEHHA SUPERVISING TOXICOLOGIST MARTY: And treatment is -- hormonal treatment is based on menopausal status. If you're a premenopausal there's no point in giving aromatase inhibitors, because your ovaries are pumping out estrogen. And the aromatase inhibitors work in postmenopausal women to decrease the production of estrogen in the fat cells.

So clearly from a clinical perspective, there's a huge, huge clinical trials looking at endocrine therapy. And they're still using it because it works at least partially; not fully, but partially.

So I think that it's -- we can't say that estrogen is not related to breast cancer progression. It may be unrelated to initiation or maybe -- or even the

earlier stages of carcinogenesis. But it's certainly related to promotion.

PANEL MEMBER BYUS: What you're saying here is premenopausal effects.

I'm just saying the data looks -- from my opinion, there's something else. And, again, I'm not an expert. But there's other things other than estrogen that we are missing in the etiology. And when we understand it, maybe you can link it to smoking. But to me it does not look like it's estrogen. Just that's my opinion.

PANEL MEMBER LANDOLPH: I was listening to Craig's comment there and what Katherine said earlier. You know, they're really different reagents, the active smoking versus the passive smoking. One of the things you get is radical formation during the pyrolysis of cigarette products going directly into the lungs. By the time the passive smoke is inhaled by distal people, you've probably lost all those. They're probably very short lived.

So on an initiation basis you could make a very simple postulate too, that they are different reagents. And what you're comparing is the ratio of lung cancer to breast cancer and active versus passive smoking. And I can't say that estrogen's not involved. But I could say that the attacking reagents are different in those cases. So it's reasonable to expect the ratio of lung to breast

in both to be different. I don't -- initially I was a little bit worried about that argument. Now I'm not so worried about it. I think it's not unreasonable, and it shouldn't be used to obviate the findings in passive smoking and breast cancer. I think that obviation argument is wrong.

CHAIRPERSON FROINES: I'd say that there's another issue, Joe. I think there's a lot of commonality among the components of those particles. And I think that the ability of the carcinogens to come off the particles may be different between active and passive smoking. So your bioavailability may be different.

PANEL MEMBER BLANC: Can I just --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Mark's just going to point out what we actually said.

PANEL MEMBER BLANC: Can I just -- as I said there earlier, I need about a half an hour approximately for Chapter 1. It's approaching 3:30. I understand we're adjourning at 4. I'm not sure where we stand on your presentation on this.

Are you -- have you gone through all the slides --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think so. I think I've hit the points that I was going to hit.

PANEL MEMBER GLANTZ: Could we just hear -- you

know, we spent a very long time on Chapter 1. And I'd just like to finish a couple things here. I mean Mark was about to say something.

PANEL MEMBER BLANC: Well, I was just checking in on the time.

PANEL MEMBER GLANTZ: Okay. Well, we're getting near end. That's fine.

But what were you going to say, Mark?

DR. MILLER: Well, I just -- as far as the document goes, I mean I don't know that we could address this estrogen thing in any depth. You know, the Surgeon General, in fact, that was probably the best part of that discussion. But having a -- I feel responsible for this part of it, having been, you know, quite involved in the drafts of this. And what I tried to do, whether it was -- came across, was to simply say, you know, here's what the data is and here in the literature are some of the hypotheses that have been presented. And we're not hanging our hat on any of those or used those for anything other than to just present some of the information to a reader so that they could begin to think about it.

So that's the extent of what I was trying to say.

CHAIRPERSON FROINES: I think you can just refer in the document to that -- to the Surgeon General's report and it can stay as a reference. I don't think you need a

lot more. I don't think you needed all of a sudden go move everything and develop a new literature search. I would just reference it and leave it at that, frankly.

PANEL MEMBER GLANTZ: You mean reference -- to make what point?

CHAIRPERSON FROINES: I'm just saying -- he's talking about the biology issue. And I just said, "Why don't you add to the existing report a reference to the Surgeon General's discussion," which is clearly pretty well done, "and let it go at that."

PANEL MEMBER GLANTZ: You mean of the estrogen hypothesis?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

DR. MILLER: Just say there's a discussion -- a good discussion here and reference it. And as I remember, they come up with a kind of a "Well, it's not so clear."

CHAIRPERSON FROINES: Exactly.

PANEL MEMBER BYUS: That's all I'm getting -- it is not that clear. And there's any of a number of mechanisms --

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: A very small one.

Melanie, I liked your slide very much which discussed a little bit about the Surgeon General's report. And I think that's a nice transition, just from my point

of view. If you could capture that concisely and put it somewhere in your document, I think that would be a nice transition from that Surgeon General's document, which has received so much attention, to where you are now. And I think it's great.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

PANEL MEMBER GLANTZ: Can I just ask -- I just want to ask one point. Again, I'm just trying to figure -- based on this discussion, it seems -- I think there needs to be at least some mention of these issues. I don't think the report has to go on about them. I mean do you guys think it would be best placed in that appendix they wrote on active smoking rather than in the main body of the report?

CHAIRPERSON FROINES: The biology part?

PANEL MEMBER GLANTZ: Yeah. I mean just do people have an opinion about that? Because, you know, the literature in this area, I mean the estrogen hypothesis is wide -- people talk about it a lot. But it's always presented as a hypothesis.

And then maybe this other stuff about -- which was in the response to public comments and also the report about perhaps differing natures of the smoke, oxidant loads, things like that. I mean would that be best to put in the appendix rather than in the -- where is it now?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's just in the main body where we're talking about our conclusions -- findings and conclusions. So it's not in the appendix, in part because the appendix is only talking about active smoking and the body of the document's talking about ETS.

PANEL MEMBER GLANTZ: Never mind.

PANEL MEMBER BLANC: It depends on what their approach is. If you like this idea about breaking off the argument about smoking, yes-no, and then smoking degree of risk --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We actually have done that. We did that. We took all of the text on the active smoking studies and put it in an appendix. But we have the conclusion --

PANEL MEMBER GLANTZ: Oh, no. He's making a different point, Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, the point is that we are saying in here that there is evidence that active smoking is associated with breast cancer. So that's argument one. And argument two we're saying, "We really don't know why that the risks look about the same, but they do."

PANEL MEMBER BLANC: Right. And what I would say is that the -- whereas I would -- I think it made sense to

partition part 1 to the appendix mostly, you know, where all the data, the details of why it's not "no" for smoking. But some of the arguments about why the magnitude of the association is close to the magnitude of the association on secondhand smoke probably shouldn't get relegated to the appendix, because it's probably a little --

PANEL MEMBER GLANTZ: Did you say "should" or "shouldn't"?

PANEL MEMBER BLANC: Should not. That part of it maybe should --

DR. MILLER: Being as that that's such --

OEHHA SUPERVISING TOXICOLOGIST MARTY: That made sense.

DR. MILLER: -- an important controversial item there.

PANEL MEMBER BYUS: That's your big issue as far as I am concerned.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

DR. MILLER: We wanted to try to address that as head-on as we could.

CHAIRPERSON FROINES: But the point is is it's still -- the conclusion of that section is we really don't know at this point.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER GLANTZ: So I guess with this, what you're saying, John, as the way to present this is to say we believe, assuming that we believe it, that in fact there are data demonstrating an elevated risk of active smoking. So the -- well, if active smoking doesn't increase the risk, how could passive smoking increase the risk is a falsely predicated statement. That I think is well supported by the data.

But then to say, "We really don't know why the risks are so similar. Here are a few theories that are out there. The observation is something one can report, but there's no widely accepted explanation. There are a few theories that some people think are plausible, but there's no direct empirical support for it."

CHAIRPERSON FROINES: That would be my view. And I also think that the -- we'll talk about this next time -- but the discussion on toxicology could be like Pandora's box and one could get into a huge discussion about toxicokinetics and animal models and all sorts of things. And it seems to me that we're not doing that in this report, which is emphasizing epidemiology. And so my only concern is to make a credible showing but not open Pandora's box basically.

PANEL MEMBER BYUS: It's biological -- I mean again back to these criteria. It is biological

plausibility. If it's biologically implausible, well, then you have to look for confounders back in these epidemiology things and without the lack of a dose response. But if it's biologically plausible, and that's what you're saying, and that's what -- there's a biological plausibility for the difference between animal -- I mean why the dose response doesn't keep going up.

CHAIRPERSON FROINES: I think that the --

PANEL MEMBER BYUS: It would be the same. That's all.

CHAIRPERSON FROINES: I think that the toxicology needs to be kept very tightly within the context of adding some measure of biological plausibility and not letting it go forward to saying that this reinforces our causal -- I don't want to take it beyond that, because one could -- one could get into lots of arguments about the toxicology that I don't think we want to get into. Because this report, we'll vote on it, it will stand on its own in terms of the epidemiology or it won't. But it's not going to stand on its own based on some estrogen theory or carcinogen theory.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER GLANTZ: Are you saying this -- I mean there wasn't a huge amount of discussion of the -- I

mean, again, this is the stuff you know a lot more than I do about. But there wasn't a huge amount of discussion about toxicological arguments in the report, I didn't think, other than saying there are these compounds which have been shown to be mammary carcinogens. And are you saying that there should be even less than there is now?

CHAIRPERSON FROINES: I'm saying it should -- unless -- I'm saying it could stay as it is. But I would also say from a toxicologic standpoint that it's frustratingly short. So that I'd like to get into all sorts of debates about those issues. But I think that in the spirit of what I think is happening is we're making a decision one way or the other based on epidemiology. And if you want to really use the toxicology, then you're going to have to get into it and you're going to double the size of this report.

PANEL MEMBER LANDOLPH: I agree with you. I think we should stay like it is. I think it's good enough for the --

PANEL MEMBER HAMMOND: And I don't think it would be more informative. I think it would not --

CHAIRPERSON FROINES: Well, it could be interesting though.

PANEL MEMBER HAMMOND: -- be more informative by the time you finished the first one.

Yeah, interesting.

CHAIRPERSON FROINES: Because she's not hanging her hat on either of those issues. She's using them -- some of the little sentences that are sort of thrown in here and there throughout the whole report about the toxicology should be taken out. And Gary mentioned that to me. Or there should be at least a reference to where you do find the discussions, so it's not just kind of these little sentences all over the place.

But that aside, I think that the point is made there's exposure to carcinogens. That doesn't prove cancer. And to get into whether the carcinogen exposure leads to cancer is a big issue, and that's what we don't want to take in because we're going to base it on Epi.

Is that fair?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

Can we go back to Chapter 1?

PANEL MEMBER BLANC: Only if you --

PANEL MEMBER GLANTZ: I want to just raise one other very quick issue, because I'm sort of thinking of that list of things. I mean do you guys want -- there are two issues that have been just very briefly mentioned here that I'd like to just get on the record of what you think; and, that is -- then I think we can get back to Chapter 1.

One is the issue of residual confounding, the

statement that the relative risks are not gigantic and so you always have to worry about residual confounding.

And then the other one is the publication bias question.

And, you know, I'd just like to quickly hear what you guys have to say about those. And then I think we will have through the course of the day discussed every one of your expressed concerns.

CHAIRPERSON FROINES: Can I ask you a question?

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: Can we -- 1, 2 -- do I count as a quorum? --

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: -- 3, 4, 5. If the three of you leave, we can continue. Paul -- no?

PANEL MEMBER LANDOLPH: I'll stay as long as you need.

CHAIRPERSON FROINES: That's six.

PANEL MEMBER GLANTZ: Well, we can continue having a discussion.

PANEL MEMBER BLANC: I really would rather not.

PANEL MEMBER GLANTZ: Okay. But what --

PANEL MEMBER BLANC: We've got enough time left. I'll be brief.

PANEL MEMBER GLANTZ: I don't think this will

take a long time.

So those are the -- I'd just like to ventilate those two questions.

PANEL MEMBER BYUS: I'll give you my view and position on confounding.

And, that is, I think there is a significant lack in our understanding of the etiology of breast cancer to say that we don't understand it. And because of that, because of this lack of understanding, there is something or a series of things that we don't understand, clearly distinct from many of the other cancers, that that means that there could be more confounding because we just don't know what it is that is going on there. It's not estrogen, in my opinion, not clearly estrogen. It's not clearly pre or postmenopausal. It's not obesity. There's lifestyle issues. We don't know what it is. And so because of that, in terms of the mechanism and risk factor association for it, it increases the likelihood of there being more confounding. That's all. I mean -- now, again, that's kind of -- maybe -- if you don't agree with me, that's okay. I mean it's just -- I guess maybe there is a -- but it's just in my mind, let me put it that way, in my mind.

DR. JOHNSON: Which I can't speak to.

PANEL MEMBER BYUS: You cannot speak about my

mind, can you?

(Laughter.)

PANEL MEMBER BLANC: Nor would he wish to.

(Laughter.)

PANEL MEMBER BYUS: Nor would you wish to.

I mean maybe that doesn't follow. But, anyway -- you don't have to respond to that. I don't think it needs a response.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We just had a couple of slides, one on publication bias and the passive smoking breast cancer studies.

The publication bias occurs when studies with positive results are more likely to be published than those with negative results.

And we -- it's kind of funny, because to me, when I look at the data, there's a lot of studies that, you know, don't knock your socks off, and so in terms of the risk estimates and overall are null. So I don't see how that applies personally anyway.

Thirteen of the 19 studies that we looked at suggest increased risk. Most of those were not necessarily significant at least overall. All five with the relatively complete exposure measures suggest increased risk -- statistically significant increased risk. And there would have to be a number of unpublished

studies with good exposure measures which were all negative for publication bias to be a reasonable explanation. And we just don't think that it's likely.

PANEL MEMBER FRIEDMAN: There's techniques for check -- there's this funnel plot that you can do. Have you tried that --

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, we have not done the funnel plots, in part because there's difficulties interpreting the funnel plots depending on how you -- what measure you use, sample size or one over the standard error, you know, in order to make the funnel plots.

And also -- well, Stan can go on much better than I.

PANEL MEMBER GLANTZ: I said to Melanie, "You need to do a funnel plot." And Melanie said, "We don't like funnel plots." So I woke up in the middle of the night and did it. But I couldn't remember exactly how to make them. And so I went on to pub med and searched for a funnel plot. And the first paper that came up was "Misleading Funnel Plot for Detecting of Bias in Meta-analysis." It's a very good paper. And there are four different ways to do funnel plots. And they took a hundred and some odd meta-analyses from the Cochran collaboration and showed how you get different results

depending which way you make the graph.

So I think that it was -- it kind of blew it away. And, in fact, the two books -- the two meta-analyses which I have say how to do it differently. So I -- after like -- I called Melanie back and said never mind.

There are however -- we did -- Lisa Barrow and I did a paper where we looked for publication bias and lung cancer in ETS, and there's just no evidence for it there.

And there's a paper --

PANEL MEMBER FRIEDMAN: Did you use a funnel plot?

PANEL MEMBER GLANTZ: Well, we did that, but we also looked at the results of reviews. And I can give it to you.

But I thought this was very -- when I was digging around, obsessing about this. This is in Diana Petitti's book. And this is quoting Begg and Berlin, who are two of the guys who invented this whole thing. And they said, "Begg and Berlin, however, speculate that historically a bias toward publication with no results may have characterized a study of asbestos in cancer. When there are adverse financial or regulatory consequences for positive result, a bias in favor of publication of negative or null results is a theoretical possibility."

So, you know, I think -- I mean when I did the funnel plots, it didn't look like there was a positive -- in fact the couple ways I tried it, it actually suggested a bias toward publication of negative studies.

So when you do it, there's also a bunch of different diagnostics you can compute. And having -- and they actually were pointing in the other direction. Although it's hard to believe that if somebody had a positive big study, they wouldn't publish it.

PANEL MEMBER HAMMOND: Well, I think that people who have public funding, you know -- if you invested in a cohort study or case-control study where this was a prime hypothesis, you know, if you didn't publish it, you wouldn't be getting any more money, you know. I mean there's a certain reality there.

Now, if it was a secondary or tertiary or quaternary hypothesis you tagged on and you just ran an analysis or something, that might or might not be an issue. But anything that has -- and that's where you don't have a very good -- it's not a very good study in the first place. It's not designed for that.

But if it were designed that, my guess, then you could probably -- if you could go and look at the funding that had, you know, been made for ETS and various outcomes, and I'll bet you'll find a paper for most of

those publicly funded things.

By contrast, one could imagine studies being done financed by private companies that might have an interest in this, who, if they found positive results, they would not be required to publish it. So one could speculate -- I mean I know that people talk about a lot. But whenever people try to look at -- I've also heard of people really doing a search of all the funded studies and to find they all been published. So that it's more something people talk about than necessarily actually happens, except for the kind of off-the-cuff analysis that's done on the side.

PANEL MEMBER GLANTZ: I think it's a bigger issue when you're talking about small clinical trials rather than Epi studies. But, anyway.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Then there was another concern about confounding in the passive smoke breast cancer studies. And this gets to be more of a concern when your risk estimate is relatively low.

The major known breast cancer risk factors were controlled for pretty well in most of the studies, reproductive history, agent menarche, and so on. And alcohol was accounted for in many of the studies. And they still showed an increased risk for passive smoking.

PANEL MEMBER BYUS: BMI you said as well.

OEHHA SUPERVISING TOXICOLOGIST MARTY: By mass

index is another.

So you'd have to hypothesize an unknown risk factor that's associated with both breast cancer and passive smoking that, you know, would differentially -- that would be able to account for the study.

PANEL MEMBER HAMMOND: And that has been undiscovered to date.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER HAMMOND: And, you know, some of my colleagues at NCI have commented, after years and years of trying to look for these confounders. In reality the only confounder that they found in occupational studies, despite all these people are concerned about it -- but consistently the big one is -- the only real one that's possibly smoking for lung cancer, because the relative risk is so large, that a small difference in smoking rates in your exposed and control groups or your case and your control groups would lead to it. And yet those differences aren't actually found when people go to look at smoking rates -- unless you really pick your groups wrong -- in the studies that have been done.

So that confounding is actually something that people worry about a lot more than has actually been, you know, found.

PANEL MEMBER FRIEDMAN: Well, there's not only

the question of whether all the appropriate variables were included in the analysis, but how well they were characterized. For example, if you say they control for alcohol, was it just drinkers versus not-drinkers, or did they say, you know, one to two drinks per day, three to five, et cetera, and for, you know, age versus --

DR. JOHNSON: It would be more likely to be more likely to be characterized controlled. And the case-control studies and the cohort studies would have been more likely to have asked more detailed questions.

PANEL MEMBER FRIEDMAN: But didn't -- I mean whether it was -- I don't know about likely. But did they do it?

DR. JOHNSON: Well, it varies by study. All the studies -- essentially all the studies controlled for alcohol but about two or three. And certainly all the ones that we considered a better -- had better exposure measures.

Yeah, but did they --

DR. MILLER: Some of them are grams per day kind of a thing.

PANEL MEMBER FRIEDMAN: -- did they with regard to -- they did do things like that.

And for reproductive variables, did they say just, you know, nulliparous versus --

DR. JOHNSON: They tend to have 4 or 5 of the better -- of most -- maybe 15 or more of the studies, case-control and cohort, will have controlled for between 7 and 12 different variables, 4 or 5 of them being reproductive -- or 5 or 6 of them being reproductive.

PANEL MEMBER FRIEDMAN: So you think they generally did a good job of controlling for these variables?

DR. JOHNSON: I think they -- I think they did a pretty good job. Plus there's another thing that goes -- there's two things that go into confounding. First of all, the confounder actually has to have an impact on the disease or it's not going to be a confounder.

PANEL MEMBER FRIEDMAN: Sure.

DR. JOHNSON: Secondly, that potential confounder has to have a relationship with passive smoking, and probably a fairly intimate one.

Now, Peggy Reynolds' analysis of the correlates of passive smoking suggest a few that there is correlation, some things around diet, SES, and whether you've had pap smears and such.

But I'll just read something quickly from the IARC monograph. And this is -- they're talking about dietary -- they're talking about confounding for passive smoking and lung cancer. And this is -- they just have

one short paragraph, and I'll only read part of it.

"Several potential confounders have been proposed that may partly or fully explain the increased risk of lung cancer associated with exposure to secondhand smoke from the spouse." Okay?

"None of these" -- and we're talking about a risk of 1.2. So a lot more -- real likelihood of it compared to a risk of approaching 2 that we're looking at for breast cancer. "None of these potential confounders has been established as having a causal link with lung cancer." Acknowledged.

Then they say: "Several of the observational studies have attempted to adjust for consumption of different dietary items that might be impacting on lung cancer. But when you control for those factors, it doesn't change the risk estimates," suggesting they aren't strong confounders. So they say -- they showed that the effect of dietary confounding was negligible.

And I think you'll find that for the breast cancer, when you look at crude estimates -- often they do age controlled estimates and then they do multi-factorial, all the potential confounders -- and you find almost no difference in the risk estimate. The risk estimate may differ by 5 or 10 percent maximum.

So for the existing things that we know about, it

seems very unlikely that any of those are serious confounders. For things we don't know about, well, there -- that's always --

PANEL MEMBER BLANC: Can I step in?

Wait a second. In all fairness to me, it's now a quarter of an hour.

PANEL MEMBER FRIEDMAN: Well, I just think that that kind of discussion should appear in the report, a good strong argument as to why you don't think confounding would explain it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We'll do it.

PANEL MEMBER BLANC: Well, if I could tie it into chapter 1, I think -- and I had mentioned earlier that I thought that in the same way that you felt it useful to talk about categorization, I think there should be a general discussion about confounding and saying that, as you go through all of these different issues, you do in your looking at study quality take into account whether co-factors which are known or suspected to be potentially related to both the outcome and the exposure have been taken into account; and, if so, appropriately. And estimates -- re-estimates done on that basis.

And, similarly, if you are going to take a decision about a publication bias, you're going to look at

it -- you're not going to look at it systematically as you go through, say that in -- you know, in your methods that in general we have not given particular attention to publication bias because there doesn't seem to be, you know, much evidence that this is a true issue. However, if we have come across a citation that has analyzed it in relationship to a specific outcome, we do cite the paper if appropriate, or something like that. And we haven't, you know, independently done our own analyses, such as funnel analysis or whatever it is. So it's clear we're not embarking on this and it's like we decided to do it for breast or decided not to do it for breast, but we did it for lung or some other site or did it for asthma.

So that's how I would tie this last discussion into Chapter 1, because all of these things I think are relevant.

So just briefly to go through some other things that I think would help. In Section 1.1 on page 1.2, when you talk about the organization of the report, I think it would helpful to say, not just the organization or the order of chapters, but explain to the reader why it is that each chapter is organized in a standard way and what it is that you do in a chapter. You start each chapter with a table that summarizes blah, blah, blah. And then we go through systematically various and/or organ effects

or disease processes or whatever it is you're doing, just to explain that and why they're organized internally within chapter organization.

Going to Section 1.2, which is the definition of ETS. This is actually also applicable to your executive summary. I think you're a little blasé about the potential symbolic importance people place on some of these synonyms of ETS. And I would have the statement clearly, "We are going to use the term 'ETS' almost exclusively throughout this document. There are other terms that have been used and they are" blah, blah, blah, blah, "but this is what we're going to use." It's sort of -- it's not stated explicitly. It's just sort of sideways, you know.

And I think that when you start talking about how you define ETS, then -- I mean I think it is useful -- for example, you get very explicit about you're not going to consider ETS exposure when a mother actively smokes -- the exposure to the fetus, even though in a way that is kind of -- from the fetus' point of view it's ETS. But from the point of view of this document, it's not. And I think that level of detail is okay.

I do think that the stuff about what is a -- what is a nonsmoker -- I mean it is true that an ex-smoker maybe in some studies is a nonsmoker. But, you know, it's

sort of a -- it's sort of a weird thing. I mean I think I would just say that that's not what you mean by it. The same way you mean that passive smoking is not an actively smoking mother whose fetus is passively. So you're not saying --

PANEL MEMBER HAMMOND: It says just the opposite. It says, "In general, ex-smokers are not excluded" -- are not excluded.

PANEL MEMBER BLANC: But nobody would consider an ex-smoker a nonsmoker. I mean you're an ex-smoker. I wouldn't --

PANEL MEMBER GLANTZ: No, that's not true. I mean I have a -- I was out --

PANEL MEMBER HAMMOND: It depends on the -- this is for a set of endpoints.

PANEL MEMBER BLANC: Right.

PANEL MEMBER GLANTZ: I mean some of the studies do consider ex-smokers to be nonsmokers.

PANEL MEMBER BLANC: And those were to be a very weak study in your point of view --

PANEL MEMBER GLANTZ: Well, not --

OEHHA SUPERVISING TOXICOLOGIST MARTY: It depends on the outcome that you're measuring.

PANEL MEMBER HAMMOND: Yeah.

PANEL MEMBER GLANTZ: Like for heart disease if

it's an ex-smoker -- a five years ex-smoker --

PANEL MEMBER BLANC: Okay. I got -- your point's well taken.

But you need to be a little bit more explicit on that.

When we get into the methodology section I think that I have covered parts of it, but other parts I haven't. And the very first section I think you should say something about how you chose or didn't choose to use the consultants. The consultancy doesn't appear in here.

I think that since you did take all the time to respond to a public comment period, part of the methodology is that there was a period of public comment and that you responded to those comments. I mean that's an important part of the methods.

And the issue of the literature review -- scientific literature review, because it can come up later in terms of what -- you know, what was your time cutoff and some things you went farther and some things you didn't. I think you should be perhaps a little bit more pedantic also there about up to what time you searched and -- for my own point of view I actually even like to know the key words you used or some of the key words. But maybe that's asking too -- for these -- not for the disease outcome side, because that would be really

exhausting. But, you know, you used secondhand smoke, you used ETS, you used involuntary smoking. Or you could just say you used all of the synonyms that we just cited before in our definition of ETS, if you want to save space.

And you don't say here explicitly when you -- but I know that you did this -- when you pulled a paper, if the references of the paper included citations which you hadn't otherwise found. You attract those down, didn't you? But you don't say that.

And what is a call-in -- a data call-in?

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's a bureaucratic term that ARB uses when they start a toxic air contaminant process. They have what they call a data call-in. So they say, "We are starting the process for identifying this compound as a TAC. So just send in whatever data you have." And it's a public data call-in.

DR. MILLER: We got three boxes of materials that were sent in.

PANEL MEMBER BLANC: You did?

PANEL MEMBER HAMMOND: So it's kind of a request for comments from the public?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's a request for: What data do you have on the health effects of ETS:

PANEL MEMBER BLANC: Then you had unpublished

studies that were sent in to you that way?

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

PANEL MEMBER BLANC: You had studies that you wouldn't have otherwise found the med line that you used?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, I don't --

PANEL MEMBER HAMMOND: But there was the opportunity to --

DR. MILLER: We've got all kinds of stuff.

PANEL MEMBER BLANC: And then, "While published peer-reviewed literature serves as the primary source of data, additional sources, for example, from abstracts of meeting presentations or doctoral dissertations, may be included, particularly if they provide information in an area where data are lacking."

Were there such areas here?

CHAIRPERSON FROINES: There was one abstract that was discussed.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: At least one, maybe two.

OEHHA SUPERVISING TOXICOLOGIST MARTY: There was one.

PANEL MEMBER BLANC: I mean --

OEHHA SUPERVISING TOXICOLOGIST MARTY: There may

have been some in the exposure side.

Do you remember a doctoral dissertation on the exposure side?

PANEL MEMBER BLANC: Because that's -- you know, I haven't seen it come up with something where I thought it was driving a conclusion in some odd way. But then --

PANEL MEMBER GLANTZ: Yeah, but, you know -- but, you know, I think that's good, because that sort of goes to the whole publication bias issue. And there's nothing wrong with citing at-meeting abstracts or doctoral dissertations.

PANEL MEMBER BLANC: If you do it systematically. But if you don't do it systematically and it's because you're getting fed certain ones in certain ways, then it could be a problem. That's why I'm bringing it up. It's very hard systematically to review abstracts. So you have to be careful. And one of the things that you do use, as it turns out, that's not listed here, are letters to the editor, data -- the analyses that are embedded in letters to the editor which involve personal communications. And for certain of your outcomes those come into play more than for others. But it doesn't appear here in your methods. So I think it's going to come back and haunt you. Otherwise I would be explicit.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think

some of those letters to the editor we got as part of a data call-in.

PANEL MEMBER BLANC: Well, then say it. I mean -- you know. I don't think the letters to the editor related to breast cancer came from a data call-in, did they?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think Judson Wells either sent them at the data call-in or at some point in the public process.

PANEL MEMBER BLANC: All right. And then a more minor thing, but I think it's just another sample of where you sell yourself short in a way, you know, you were more rigorous than it might seem. So I was a little bit surprised, Kathy, that you didn't bring this up. But they have a tendency to talk about biomarkers, which would only refer to cotinine or cotinine-like metabolites, and not to talk at all about exposure assessed through airborne non-biomarker, things like nicotine or particulate.

PANEL MEMBER FRIEDMAN: Excuse me, Paul.

Some of these, in my opinion -- and maybe I'm wrong -- some of these border on minor comments. And I was wondering. You had some really general principles about your --

PANEL MEMBER BLANC: Well, I'm trying to use them as an example of I think that this is not adequate

methods. I guess I'm just -- maybe I'm beating a dead horse. And I'd be happy to give you my notes. But I think that you haven't looked at this as a methods section. And I feel the need to have it. And I'm just trying to point out. And I know that's -- I'm done pretty much.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Paul, I think the biomarkers was addressed more in Part A, the nicotine as a biomarker. Cotanene -- ways to measure airborne --

PANEL MEMBER HAMMOND: Airborne nicotine.

PANEL MEMBER BLANC: It's not a biomarker.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm sorry, not biomarker.

Airborne -- ways to assess exposure to ETS in airborne measurements was all addressed in Part A.

CHAIRPERSON FROINES: Well, the DNA addicts are biomarkers.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

PANEL MEMBER HAMMOND: Well, and very, very --

OEHHA SUPERVISING TOXICOLOGIST MARTY: And we have just a little bit of that.

PANEL MEMBER HAMMOND: Yeah, there's very few Epi studies -- there are very few Epi studies, especially for the retrospective, you know, cancer studies.

PANEL MEMBER BLANC: Yeah, for the respiratory more you cite Mark's work and -- Mark Eisner's. And it's not biomarker work.

PANEL MEMBER GLANTZ: So I don't quite understand the point you're trying to make. What do you want them to do?

PANEL MEMBER BLANC: I want them to be more rigorous in their --

PANEL MEMBER GLANTZ: But I mean specifically what do you want -- what do you want them --

PANEL MEMBER HAMMOND: When they talk about how to do exposure assessment to include airborne markers as well as biomarkers, right?

PANEL MEMBER BLANC: Well, they did it. All I'm saying is when you write it the way you write it, it's sloppy.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We will work with Paul on Chapter 1; which I think you just got volunteered to be a lead on Chapter 1 revisions.

PANEL MEMBER BLANC: That's it. I'm done.

And have you gone back through all your introductory tables and the beginnings of your chapters and make sure now that they're up to date with the numbers of studies in your various -- I notice that, for example --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We did that after the last SRP meeting. But it keeps changing. So we have to -- you know, before we send forward the next version, we'll do it again.

PANEL MEMBER BLANC: Because I notice like in the breast cancer there are less than you actually have.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

CHAIRPERSON FROINES: I'm assuming that you will take about two months to make these changes. Is that right?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'll try to do it. See, it would --

CHAIRPERSON FROINES: Well, you tell me.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have to give you guys time to review it.

CHAIRPERSON FROINES: Well, see, I -- that's one thing that I want to -- that's the reason I asked the question, is I'd like to be able to schedule a meeting so that -- this time was a little tight.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

CHAIRPERSON FROINES: And I think what happened was because of the U.S.A. Today story, people busted their tails this last weekend to really reread everything and get prepared.

But we hope that sort of incentive doesn't happen

again and that we can have some time to review it. I would say two or three weeks, four weeks, if you could, for the panel. Although I don't know whether most people read it towards the end anyway. But --

PANEL MEMBER GLANTZ: Everyone always reads everything toward the end.

CHAIRPERSON FROINES: So we should plan -- Jim and I'll plan the meeting in consultation with you so that there a good time -- like this is March -- March -- the rest of March, April, May. So that would mean June?

Does anybody have a major crisis?

PANEL MEMBER GLANTZ: Well --

CHAIRPERSON FROINES: July starts to get tricky.

PANEL MEMBER GLANTZ: Yeah. I have one sort of logistical thing. This report here was -- they did it in a red-line strikeout format, which I found very helpful. The question is for the next draft, should they accept the changes that were made to this draft and then produce one which shows the changes made between this draft and the next one, or should -- do you want all of this stuff?

PANEL MEMBER BLANC: No, that's fine, that's fine. It gets illegible that way.

PANEL MEMBER HAMMOND: Although I do like that way "delete" is done. I don't know how you -- that's nice.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's Office 2003 does that.

PANEL MEMBER HAMMOND: Just pulling it off like that is really nice.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, why don't --

PANEL MEMBER GLANTZ: Okay. But anyway, so the next -- that's it, and --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Why don't we try to have the document ready for an early June meeting, so that we can avoid the summertime problem.

CHAIRPERSON FROINES: We -- never mind.

PANEL MEMBER BLANC: I don't know about this.

DR. MILLER: It's pretty short.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Mark's saying it's too short.

PANEL MEMBER BLANC: I think September --

CHAIRPERSON FROINES: What did you just say, Melanie or Paul?

PANEL MEMBER BLANC: I said I thought September was more realistic.

PANEL MEMBER GLANTZ: Well, let's -- why don't you do this: We don't have to set the meeting right now. Why don't you let Melanie and her people go back, think about this a little bit, and decide how much work it's

going to take to address the issues that were brought up. I mean I think this is a good discussion.

I didn't hear anything said which would lead them to the conclusion that there was some fundamental blunder that's going to require throwing out major sections and starting all over again. It's a matter of addressing a lot of specific issues and how things are presented.

So I think it should be fairly evident within a week or so.

Melanie, I mean I was just saying, I think within a week or so you should have some sense of whether you can meet that schedule or not.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER GLANTZ: I would -- rather than trying to do it now, why don't you give them a chance to really look at the realities of how much work was generated.

CHAIRPERSON FROINES: There's no problem. We're flexible. I'm just -- my plea is that we have plenty of time to go over the document. And we have -- I hesitate to open my mouth and say this, but we have another chemical coming down the road that Roger's smiling about. And so we may have two meetings.

PANEL MEMBER HAMMOND: And the other thing that would be helpful, John -- I don't know if it's going to be

possible. But I guess we all thought we would just be done with this ETS in this meeting. And then it became very clear at the end that the focus was going to be on one chapter -- or two chapters really. And if we don't think we can finish it in the next meeting, it would very helpful -- because I feel overloaded and overwhelmed with all this data -- if we were to say that we're going to really particularly focus on some particular chapters rather than the whole thing.

PANEL MEMBER GLANTZ: Well, that's true.

Could I -- I mean "I" speaking as the lead. I mean, at the last meeting John said if people have specific criticisms, they should get them to the staff and to me. And I think a lot of -- this has been a fine discussion. But I think a lot of this stuff is stuff that, had people come and let the staff know about it beforehand, could have been dealt with. So what I would suggest is that if people have more things -- because the report has been pretty thoroughly discussed except for these couple of chapters, which, you know -- if you could get more specific criticisms to the staff, they can be dealt with, rather than waiting for --

CHAIRPERSON FROINES: Well, I think all that's fine to say. But I think it's --

PANEL MEMBER GLANTZ: No, he already did it.

CHAIRPERSON FROINES: I think it's a little more hopeful and -- because I think we have to have a discussion with the leadership of Cal EPA and ARB and OEHHA. And we're going to have to change the process for how we do business in the future. Because the problem is is people don't have the wherewithal, the time to do the level of work that's required to do as thorough an evaluation as we would like. And so a lot of issues have come up in the last week because of the external factors that got involved. And so it forced more rigorous preparation I think than would have occurred without that. And I think that we need to take seriously how we're going to handle both consultants within OEHHA and how we're going to handle our consultants and whether we have conferences and --

PANEL MEMBER BLANC: Actually you're bringing up a point, John, that I actually want to say it may affect the time line. I actually would like -- I would like to have a -- I would like you guys to solicit a round of additional consultation for those sections of the report for which there's been a step up of causality.

PANEL MEMBER GLANTZ: Well, you know, I just think -- I mean I don't think that's going to get you anything. I mean I think if -- I mean if there are people that you know -- I mean I've encouraged everybody I know

who's interested in this stuff, and including the people who've been critical, to read the report and submit public comments, you know. In fact -- and a couple of them did and some of them were critical. And I think the issues that are there are there. I think we know what the issues are. I don't -- and I think that there's a time when you have to either say, yes, we agree with this or, no, we don't. I don't think anything new would come out of that process.

I think if you go back and read Michael Tunes public comment, the issue -- the fundamental issues that we spent a lot of the day talking about are all raised there. And there are three or four other very strong comments, you know, that raised these issues. And I -- I mean I think that -- I mean I just think that's a waste of time. And, you know, on one hand you say people are overloaded with work and on the other hand you're making more work.

I mean you're free as a member -- this is a public document, you know. And if you want to encourage anyone you know who you think could provide useful input to you, show it to them. It's on the Internet. They can be free -- instead of all these phone calls that are going around. You know, get them to put their comments in writing. I mean, in fact, I have to say when the report

first came out I happened to talk to Michael Thun. And he may have put in the comment as a result of the conversation I had with him. Because he was very critical on the telephone.

And I said to him, "It's very nice that you're telling me this. There's a public process here" -- you know, which we have to remember, there is a process and it served this panel and the process well for a very long time. And I said, "If you're critical of this report," I said, "I'm taking" -- "I'm not making any personal judgments. But if you feel strongly about these criticisms, write them down and send them in," because by law the Cal EPA will have to deal with them. You know, they can't just throw them in the trash. And I think that has -- that process has happened. And I think, you know, if people want to solicit informal criticisms to help guide them as panel members, that's fine. But I just think that's a complete waste of time, absolute total waste of time.

PANEL MEMBER BLANC: But what do you think about the idea?

(Laughter.)

PANEL MEMBER GLANTZ: Well, other than that, I think it's great.

PANEL MEMBER BYUS: Your real opinion, Stan.

CHAIRPERSON FROINES: I think that -- I don't agree with Stan, although that seems to have been the pattern today. But the -- I think that we would benefit from some external peer review. I don't think it does any harm.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, this is George Alexeeff.

It's not clear what was being asked. And I had interpreted what Paul said to like elicit some -- to identify a couple experts and ask them for an opinion. What Stan I think interpreted and maybe another interpretation was to go out for another round of public comments.

PANEL MEMBER GLANTZ: Yes, that's how --

CHAIRPERSON FROINES: So what Paul meant was what you said, a couple of experts within a particular area.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Right.

PANEL MEMBER GLANTZ: I have no problem --

OEHHA DEPUTY DIRECTOR ALEXEEFF: But I think what has happened in the past and I think what would be maybe -- it might be worth it for the Air Board to talk with the Chair. But the idea would be that the Chair would be soliciting a couple different opinions from experts. I mean if we solicit it, it's a whole different ball game, because now we're going -- basically we'd be

going through an additional peer-review process for you and we'd have respond to the comments before we got to you, so we'd be talking at least another year before we get back to you on it.

PANEL MEMBER BLANC: I see.

OEHHA DEPUTY DIRECTOR ALEXEEFF: But if you're asking -- if you're feeling that you need some additional expertise, then that might be a slightly different process.

CHAIRPERSON FROINES: I think that the -- we talked about this at lunch. It's very clear that we all benefited dramatically by having Dale Hattis review the formaldehyde literature. He was the person who drove the ultimately decision on formaldehyde. And his expertise was really quite special in that regard. And I think that we really need to do that more to take the load off the panel, but also to get very highly qualified people. And we're talking about one or two people --

PANEL MEMBER BLANC: Well, I think what George is saying is just that the technical requester may end up being us and not them. And that's -- I don't have any objection to that. And what I would like to do is just have it be the sense of the committee to empower our Chair to help facilitate that working with the leads or whatever to get names. And the only thing I would say is that my

priority for that kind of input would be those parts of the document which have, you know, a step up in -- or a change. It could have been a step down, but I don't think there were any, because those --

PANEL MEMBER GLANTZ: I don't have any -- I mean I interpreted it exactly as George said, is another round of public comment.

PANEL MEMBER BLANC: No, no. That's not what I was asking for.

PANEL MEMBER GLANTZ: You know, I think if the Chair wants to -- if that's the appropriate mechanism -- to solicit some additional -- you know, someone to look at parts of this, I don't have a problem with that, with two caveats.

One is that I think that, you know, it would need -- given the length of time this has been dragging on and my skepticism that it will yield any new information, I would hope that it could be done in an expedited way that wouldn't delay the process.

And the other thing is I think the critique should be in writing, so that it can be responded to in writing. Because I -- you know, my experience in discussing this report with a lot of people is many of the ones -- not all, but many of the people who were critical hadn't read it; and several of the people that I

originally talked to about this when it first came out, just to let them know it was there, after they read it, their opinions changed.

So I think it's very important that whatever reviewers you want to bring in engage the nitty-gritty in the specifics of the document in the same way that we've been talking about, and not just simply come in with sort of sweeping statements.

CHAIRPERSON FROINES: Well, I think there's another issue that's strategic as well. And, that is, if we have a couple of reviewers -- I was talking to Beate Ritz, who's a very fine epidemiologist, about this. And her comments were very uninformed. And it seems to me that if you have a couple of people who actually have done a review, they then become the people who at meetings are saying that this report is credible and so on and so forth. In other words, they -- you start to create a nest of allies who actually see the report in a positive light. Whereas right now there is a very wide number of people who are critical, in part because of what you say, in part because of lack of information.

PANEL MEMBER GLANTZ: But also -- and I don't want to delay this. But it's not that wide. I mean the same people we've talked about before are the people who wrote the IARC report. And, you know, they're -- well, I

don't know. I mean I can suggest some people who have not -- who are very knowledgeable, who have not taken a public -- who've been following this and not taken a public position that would -- I think, if you can get them to do it, would be very credible as scientific reviewers. And, you know, I'll talk to you later about who that might be.

CHAIRPERSON FROINES: Yeah, I talked to Kurt Straif today, who's at IARC. And, you know, he reflected the IARC report. So there are people who just don't know. So the more you have some knowledge base out there, I think the stronger it gets.

PANEL MEMBER GLANTZ: No, I agree, I agree. And I think that the process of one of the things that this report has done is it has forced people to actually confront this newer evidence, and I think that's why some people's views have been changing.

CHAIRPERSON FROINES: I think Kathy and some -- whoever else she chooses to work with should write about -- I mean since she, you know, held her red book up and said, "Froines cohort studies don't show any results and" blah, blah, blah, that one should put that argument in the literature.

PANEL MEMBER GLANTZ: Well, the red book was the IARC report, not Chairman Froines, just for the record.

(Laughter.)

CHAIRPERSON FROINES: What?

PANEL MEMBER GLANTZ: The red book was the IARC report and not Chairman Froines red book, just for the record so we don't have any political ramifications.

CHAIRPERSON FROINES: My lips are sealed.

(Laughter.)

CHAIRPERSON FROINES: Motion to close the meeting?

PANEL MEMBER BLANC: I so move.

PANEL MEMBER GLANTZ: Second.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: Thanks, everybody.

(Thereupon the California Air Resources Board, Scientific Review Panel meeting adjourned at 4:15 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 21st day of March, 2005.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063