

MEETING
STATE OF CALIFORNIA
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL

SOUTH SAN FRANCISCO CONFERENCE CENTER
255 SOUTH AIRPORT BOULEVARD
BADEN ROOMS A&B
SOUTH SAN FRANCISCO, CALIFORNIA

MONDAY, MARCH 14, 2005
10:00 A.M.

JAMES F. PETERS, CSR, RPR
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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 Epidemiologist, Public Health
Agency of Canada

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1 PROCEEDINGS

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

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

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

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

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

25 So, Gary.

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

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

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

21 CHAIRPERSON FROINES: Paul.

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

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

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

22 PANEL MEMBER GLANTZ: What is consultancy?

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

1 specific suggestions later on on how that could be
2 addressed.

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

10 CHAIRPERSON FROINES: Craig.

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

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

2 CHAIRPERSON FROINES: Of what?

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

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

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

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

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

13 CHAIRPERSON FROINES: Roger?

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

16 CHAIRPERSON FROINES: Stan and Kathy --

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

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

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

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

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

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

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

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

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

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

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

25 PANEL MEMBER GLANTZ: What's the substantive

1 issue here? I don't understand.

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

4 PANEL MEMBER GLANTZ: Okay.

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

8 PANEL MEMBER GLANTZ: Well, what are they?

9 CHAIRPERSON FROINES: Stan, quiet.

10 PANEL MEMBER GLANTZ: Okay.

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

15 PANEL MEMBER GLANTZ: Okay.

16 CHAIRPERSON FROINES: Okay?

17 PANEL MEMBER GLANTZ: I --

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

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

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

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

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

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

7 CHAIRPERSON FROINES: Sure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 CHAIRPERSON FROINES: Kathy.

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

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

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

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

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

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

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

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

1 they were."

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

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

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

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

6 CHAIRPERSON FROINES: Those tend to be internal
7 reviews.

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

10 These are internal reviewers.

11 PANEL MEMBER HAMMOND: Okay.

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

18 CHAIRPERSON FROINES: Who?

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

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

1 PANEL MEMBER HAMMOND: Okay.

2 CHAIRPERSON FROINES: And so the role of Johnson
3 is?

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

9 CHAIRPERSON FROINES: Stan.

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

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

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

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

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

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

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

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

1 OEHHA document were so clear there wasn't even a problem.

2 We just stated them and they were dealt with.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 be comfortable.

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

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

14 CHAIRPERSON FROINES: Gary.

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

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

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

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

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

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

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

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

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

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

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

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

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

13 For example, there -- in the Surgeon General's
14 2004 report there is a criticism of one of the studies
15 that OEHHA has taken as one of their six main studies.
16 And the IARC -- the Surgeon General's report talks about
17 confounding and explanation of the confounding. And so
18 they actually suggest that that study's positive nature
19 may not be as positive as OEHHA would have said. And
20 that's the kind of thing, it seems to me, that we have to
21 have OEHHA address as a methodologic issue that Paul's
22 raising.

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

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

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

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

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

19 Joe.

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

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

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

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

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

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

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

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

25 PANEL MEMBER HAMMOND: John?

1 CHAIRPERSON FROINES: Yeah.

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

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

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

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

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

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

16 CHAIRPERSON FROINES: Yeah, we're going there.

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

20 Are there any other comments from the panel?

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

1 So it's --

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

12 CHAIRPERSON FROINES: Good.

13 PANEL MEMBER BLANC: It was me.

14 I agree.

15 PANEL MEMBER HAMMOND: I thought it was.

16 Thank you. It was Paul, by the way.

17 (Laughter.)

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

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

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

1 started.

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

6 Melanie.

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

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

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

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

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

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

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: Section
24 1-4 starts on page 1-9, at least in my copy. I hope it's
25 the same in everybody's.

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

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

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

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

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

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

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

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

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

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

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

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

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

6 That is our --

7 PANEL MEMBER GLANTZ: I just --

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

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

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

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

25 PANEL MEMBER FRIEDMAN: Yeah, I agree, that

1 "influential" is not the correct --

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

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

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

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

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

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

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

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

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: On page
22 7-132 under Section 7414. And we are discussing
23 essentially the study characteristics that we think are
24 important for looking at effects of ETS. And this was
25 with regard to the breast cancer issue, because there are

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

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

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

16 PANEL MEMBER FRIEDMAN: So --

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

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

25 PANEL MEMBER FRIEDMAN: Okay.

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

3 PANEL MEMBER GLANTZ: You really like tables.

4 CHAIRPERSON FROINES: Well, I think that --

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: There is a
6 table.

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

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

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: If you're

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

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

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

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

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

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

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

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

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

24 And if I say anything wrong, stop me.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 certain studies or not.

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

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

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

25 CHAIRPERSON FROINES: Can I make just one comment

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

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

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

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

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

1 there.

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

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

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

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

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Actually
21 there is a table.

22 PANEL MEMBER GLANTZ: Let's let them answer.

23 CHAIRPERSON FROINES: Where?

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

25 First of all --

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

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

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

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

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

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

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

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

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

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

21 PANEL MEMBER BLANC: Yeah.

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

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

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

4 OEHHA SUPERVISING TOXICOLOGIST MARTY:
5 Suggestive.

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

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

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

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

24 PANEL MEMBER GLANTZ: Suggestive.

25 PANEL MEMBER BLANC: -- suggestive, but in fact

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: No.

6 PANEL MEMBER BLANC: So to support causality.

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

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

16 I think that --

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

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

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

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

7 Now --

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

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

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

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

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

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

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

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

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

1 Is there a homogeneity or heterogeneity?

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

5 And what's your estimate of the -- of the coin
6 estimate of the effect size? Which is magnitude of the
7 effect, which is a different question than the level of --
8 to me when you say consistency, it means you do the study
9 27 times and you get the same number 27 times. That would
10 be your most highest level of consistency.

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

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

18 PANEL MEMBER FRIEDMAN: Thanks.

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

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

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

25 PANEL MEMBER FRIEDMAN: Right. But, I mean when

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

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

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

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

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

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

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

25 And also in terms of consistency of results, does

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

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

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

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

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

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

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

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

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

11 I think that strength of association -- and
12 there's no intrinsic scientific reason that all
13 associations have to have relative risks or odds ratios of
14 5 or more at all. Some things could in fact -- if we knew
15 absolute truth and God came down and told us the truth --
16 and the truth might be for some agents that there's a
17 10-percent increase risk or a 50-percent -- the reality is
18 it's easier to detect the large effect. But if you have a
19 large enough study, if you have controlled for factors
20 well enough, then one can detect small enough. Look at
21 air pollution where we're looking at a few percent, a
22 handful of percent. So I think it's a time we actually
23 step away from that as a criteria.

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

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

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

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

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

21 PANEL MEMBER GLANTZ: No, you have it backwards.

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

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

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

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

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

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

20 PANEL MEMBER FRIEDMAN: Well --

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

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

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

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

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

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

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

19 This is in relationship to a suggestive
20 association.

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

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

1 used one strong epidemiology study. Was it formaldehyde?

2 But I think, John, you made the comment that this
3 committee had used just one Epi study in the past.

4 CHAIRPERSON FROINES: I don't think so.

5 PANEL MEMBER BLANC: Not for this kind of thing.

6 I mean we may have used it in the --

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

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

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

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

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

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

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

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

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

6 CHAIRPERSON FROINES: That's different --

7 PANEL MEMBER GLANTZ: Well, I just worry --

8 CHAIRPERSON FROINES: -- considerably.

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

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

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

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

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

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

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

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, I do.

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

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

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

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

1 agree with you.

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

6 PANEL MEMBER BLANC: As you will see in Chapter
7 5 --

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

16 OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, I think --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 PANEL MEMBER BLANC: You mean active smoking --

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

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

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: -- Section
6 7-4 perchance?

7 PANEL MEMBER HAMMOND: Funny I should mention
8 that?

9 PANEL MEMBER GLANTZ: What'd you say?

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: Section
11 7-4 perchance?

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

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

17 CHAIRPERSON FROINES: What page?

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

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

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

1 CHAIRPERSON FROINES: Well, do you think --

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

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
4 so.

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

7 And just let me get this out.

8 CHAIRPERSON FROINES: Seven dash what?

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

11 So the first paragraph starts talking about this.

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

14 CHAIRPERSON FROINES: Kathy, I'm sorry --

15 PANEL MEMBER BLANC: Seven dash nine.

16 PANEL MEMBER HAMMOND: Page 7 dash 9.

17 PANEL MEMBER BLANC: Chapter 7 page 9.

18 CHAIRPERSON FROINES: I don't have it. I have it
19 7-109, 110, or what have you. I don't have a --

20 PANEL MEMBER HAMMOND: Go earlier in the
21 document.

22 CHAIRPERSON FROINES: Oh, very early in the --

23 PANEL MEMBER HAMMOND: Early in the document.

24 PANEL MEMBER GLANTZ: Chapter 7 page 9.

25 PANEL MEMBER HAMMOND: Yes. Our 7.0.1.2.

1 CHAIRPERSON FROINES: I got it.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 PANEL MEMBER HAMMOND: That needs to be
25 clarified --

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

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

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

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

1 an argument they make later in the thing and --

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

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

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

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

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

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

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: Buried in
11 Chapter 7.

12 PANEL MEMBER BLANC: What's that?

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

15 PANEL MEMBER BLANC: Deeply buried.

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

18 PANEL MEMBER HAMMOND: Yeah, I think if --

19 PANEL MEMBER GLANTZ: But it's in Section
20 7.4.6.3Q.

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

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

1 things that Paul and the rest of us are suggesting in
2 Chapter 1, then when you get to the -- and you do it very
3 clearly, first of all, it could be laid out conceptually
4 without it being like, "Oh, this would be a nice
5 criteria" -- it may look to people like, "This might work
6 for me in this particular setting," and rather lay it out
7 as a -- on principle kind of issue. And then when you
8 need it in a chapter, you say, "As we said in Chapter
9 1.3.Q1W," you know, this and that.

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

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

22 (Laughter.)

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

1 are not only the --

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

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

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

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

21 PANEL MEMBER GLANTZ: Precision of what?

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, it

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

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

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

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

1 be better than the Surgeon General's report.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 PANEL MEMBER BLANC: Not that close.

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

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

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

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

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

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

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

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

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

16 PANEL MEMBER BLANC: Can we work backwards?

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

19 CHAIRPERSON FROINES: Jim.

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

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

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

25 PANEL MEMBER GLANTZ: Three o'clock.

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

3 PANEL MEMBER LANDOLPH: Sure.

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

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

8 PANEL MEMBER BYUS: How much later?

9 MR. BEHRMANN: There's flights every hour?

10 CHAIRPERSON FROINES: To Riverside?

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

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

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

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

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

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

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

8 CHAIRPERSON FROINES: So --

9 PANEL MEMBER GLANTZ: Well, could I?

10 CHAIRPERSON FROINES: Go ahead.

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

17 PANEL MEMBER BLANC: Sure, sure.

18 CHAIRPERSON FROINES: Well --

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

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

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

1 been -- there are two sets of issues here.

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

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

14 You know, we can all get together --

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

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

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

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

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

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

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

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

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

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

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

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

19 PANEL MEMBER BLANC: But in the meantime, if it's
20 possible, to do 3 instead of 4, that would help because --
21 I mean if you have to leave by -- you want us to leave at
22 4, we'll --

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

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

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

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

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

10 (Thereupon a lunch break was taken.)

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

15 (Thereupon an overhead presentation was

16 Presented as follows.)

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

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

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

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

22 CHAIRPERSON FROINES: Melanie?

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

25 CHAIRPERSON FROINES: Can I stop you for a

1 second.

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

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

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

20 CHAIRPERSON FROINES: No.

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: Which is
22 just published.

23 Well, we can get into more detail on that.

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

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

2 DR. MILLER: Who?

3 CHAIRPERSON FROINES: Hanaoka.

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: Hanaoka?

5 No.

6 CHAIRPERSON FROINES: Relative risk is 1.1.

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's

8 overall. And he does two things. He looks at overall and

9 he looks at premenopausal.

10 CHAIRPERSON FROINES: Yeah. I thought this was

11 overall.

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: It's

13 significantly elevated risk for premenopausal women.

14 There was one early, early cohort study that had an

15 elevated risk overall.

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

17 study.

18 Okay. So that's one that we're including that is

19 before 1999.

20 I think we can get more into that. But I would

21 like to --

22 CHAIRPERSON FROINES: It's a null study.

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: -- to give

24 the whole presentation.

25 --o0o--

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

9 DR. MILLER: It's overall.

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: It was
11 also overall?

12 Okay. So that was also overall.

13 CHAIRPERSON FROINES: What was the third one?

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

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

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

20 PANEL MEMBER BLANC: Yes, yes, 1999.

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

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

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

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

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

14 OEHHHA SUPERVISING TOXICOLOGIST MARTY: No, that's
15 okay.

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

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

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

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

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

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

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

1 CHAIRPERSON FROINES: Just one question, Melanie.

2 And the three cohort studies that you refer to that you
3 say show elevated risk, according to what I'm looking at,
4 none of them are statistically significant. So that you
5 would classify them as -- show elevated risk. Well, they
6 don't -- there are no studies, it seems to me.

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

9 CHAIRPERSON FROINES: Table 7.4.1B.

10 PANEL MEMBER HAMMOND: What page?

11 CHAIRPERSON FROINES: 7-127.

12 PANEL MEMBER HAMMOND: All on the same page.

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

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

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

20 CHAIRPERSON FROINES: Okay.

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

1 1.73, 90 percent confidence interval, 1.12 to 2.6, for
2 Japanese never smoking women whose husbands smoke more
3 than 20 cigarettes per day.

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

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

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

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

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

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

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

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

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, I do.

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

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

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

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

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

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

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

16 DR. MILLER: No.

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

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

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

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

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

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

25 PANEL MEMBER BLANC: No, I know about the

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

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

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

15 DR. JOHNSON: I assume so.

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

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

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

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

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

1 point seven.

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

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

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

14 PANEL MEMBER BLANC: You had to provide --

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

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

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

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

9 DR. MILLER: Yeah.

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

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

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

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

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

8 CHAIRPERSON FROINES: No, no. I think --

9 PANEL MEMBER GLANTZ: I mean the questions --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 --oOo--

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

15 PANEL MEMBER HAMMOND: What are you evaluating?

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

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

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

5 CHAIRPERSON FROINES: What about publication
6 bias?

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

9 --o0o--

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

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

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

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

13 --o0o--

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: By the

1 characteristics that we said --

2 PANEL MEMBER GLANTZ: By those four criteria.

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

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

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

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

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

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

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

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

12 DR. MILLER: Smith is recalculated.

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

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

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

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

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

1 raised coming at it from another direction.

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

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

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

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

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

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

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

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

19 CHAIRPERSON FROINES: It's 7-141.

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

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

24 PANEL MEMBER BLANC: Yeah, I see it. It's page
25 7.1.4.1, okay.

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

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

11 Now, the --

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

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

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

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

1 PANEL MEMBER BLANC: Yeah.

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

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

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

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

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

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

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

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

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

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

16 DR. JOHNSON: Yes.

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

19 OEHHA SUPERVISING TOXICOLOGIST MARTY: Good
20 question.

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

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

1 DR. JOHNSON: They should be the same.

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

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

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

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

13 PANEL MEMBER HAMMOND: The whole row is wrong?

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: The Table
15 7.4.1 --

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

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

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

2 PANEL MEMBER HAMMOND: Which one --

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

5 PANEL MEMBER HAMMOND: Which --

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

8 CHAIRPERSON FROINES: In Table 7.4.1C --

9 DR. MILLER: Where it says 2.4 --

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

12 DR. MILLER: Yeah. And --

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

15 DR. MILLER: Yeah, but the --

16 PANEL MEMBER GLANTZ: I think --

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

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

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

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

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

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

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

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

20 CHAIRPERSON FROINES: Melanie.

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

25 PANEL MEMBER HAMMOND: The LCI isn't close.

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm sorry.

2 Say again.

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Confidence
6 interval?

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

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

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

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

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

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

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

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

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

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

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 DR. MILLER: Most of them.

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

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

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

13 DR. MILLER: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

25 PANEL MEMBER FRIEDMAN: It seems to me that you

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

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

15 PANEL MEMBER FRIEDMAN: What flavor?

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

18 PANEL MEMBER FRIEDMAN: So that's what --

19 OEHHA SUPERVISING TOXICOLOGIST MARTY: Cherry
20 flavored. Sorry.

21 PANEL MEMBER BLANC: What?

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Cherry
23 flavored.

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

25 CHAIRPERSON FROINES: Can I say one thing?

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

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

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

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

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

15 And I want that to be very clear.

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

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

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

5 DR. JOHNSON: Convenient --

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

13 PANEL MEMBER BLANC: And I think that --

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

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

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

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

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

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

18 For the cohort studies, I've listed as with
19 important past exposure missing, but that's all of them.
20 And an overall odds ratio of 1 -- or a relative risk of
21 1.06. And for all the case-controls -- I didn't provide
22 for all the case-control studies. But a good case-control
23 study's 1.9, poor case-control -- case-control study's
24 missing -- or potentially missing for an exposure of 1.16.

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

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

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

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

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

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

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

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

25 PANEL MEMBER GLANTZ: Well, I just wanted to

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

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

8 PANEL MEMBER BLANC: 1B and 1C.

9 PANEL MEMBER GLANTZ: Okay.

10 PANEL MEMBER BLANC: Because they're parallel.

11 PANEL MEMBER GLANTZ: Okay.

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

24 PANEL MEMBER BLANC: I would --

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

1 just want to make sure I understand.

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

9 CHAIRPERSON FROINES: For case-control and
10 cohort.

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

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

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

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

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

11 PANEL MEMBER HAMMOND: No, I totally agree --

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

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

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

25 CHAIRPERSON FROINES: But I think you have to

1 also show the case-control cohort.

2 PANEL MEMBER HAMMOND: Well, they did do that.

3 And that's what Jee is complaining. They got all of that
4 here.

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

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

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

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

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

25 One question is asking: Is there taking a

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

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

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

11 PANEL MEMBER BLANC: Pardon me?

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

15 PANEL MEMBER HAMMOND: In the table or --

16 CHAIRPERSON FROINES: Sure.

17 PANEL MEMBER BLANC: In the text.

18 PANEL MEMBER HAMMOND: -- or in the text?

19 CHAIRPERSON FROINES: I would rather see things
20 in tables.

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

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

25 PANEL MEMBER HAMMOND: Oh, I see.

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

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

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

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

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

25 PANEL MEMBER GLANTZ: Yeah, it was on the whole

1 report.

2 PANEL MEMBER HAMMOND: When was that?

3 PANEL MEMBER GLANTZ: It was months ago. I

4 don't -- a long time ago. Because I drove up to

5 Sacramento for it. They even had people able to call in

6 and it was web cast.

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

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

9 happened.

10 PANEL MEMBER GLANTZ: Yeah. You've forgotten it

11 was so long ago.

12 PANEL MEMBER BLANC: It was a long time go.

13 PANEL MEMBER FRIEDMAN: Breast cancer was

14 considered?

15 PANEL MEMBER HAMMOND: But not on breast cancer.

16 CHAIRPERSON FROINES: Well, Stan, would it be --

17 I don't want to prolong this process overly long. But if

18 one brought the people who were working on the IARC

19 report -- who had worked on IARC and people who had worked

20 on the Surgeon General's and this panel and OEHHA, would

21 that be -- plus other outsiders, would that be useful? I

22 don't know the answer to that.

23 PANEL MEMBER GLANTZ: I actually don't think so,

24 because we know -- I mean I think the issues -- I mean

25 these are very good friends of mine. I know them. I've

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

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: And we
7 also got comments.

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

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

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

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

19 --o0o--

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

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

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

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, they

1 do.

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

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

20 PANEL MEMBER GLANTZ: Yeah, but --

21 CHAIRPERSON FROINES: Stan, please.

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

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

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

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

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: I would
10 agree with that.

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

18 --oOo--

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

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

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

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

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

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

1 --o0o--

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 PANEL MEMBER BYUS: That's what I mean.

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

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

18 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

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

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

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

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

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

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

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

16 CHAIRPERSON FROINES: Melanie?

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

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

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

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

3 DR. JOHNSON: Or they report it several different
4 ways. Like Smith reports several different split --
5 stratifications. And they vary.

6 PANEL MEMBER FRIEDMAN: But if they looked at it
7 and didn't see it, you know, I think that would be
8 irresponsible not to report --

9 PANEL MEMBER BLANC: Well, you say it is in a
10 table -- it's in an existing table.

11 DR. MILLER: It's a different -- there's a dose
12 response --

13 Which table is that --

14 OEHHHA SUPERVISING TOXICOLOGIST MARTY: 7.4.1 --
15 is that an "I" --

16 PANEL MEMBER GLANTZ: What page?

17 OEHHHA SUPERVISING TOXICOLOGIST MARTY: I think
18 it's an "I". Yes, it's an "I". 7.4.1I on page 7-151.

19 CHAIRPERSON FROINES: Melanie, question.

20 Of these studies on the board, three of them are
21 in your top -- your list of six and three aren't.

22 OEHHHA SUPERVISING TOXICOLOGIST MARTY: Right.

23 CHAIRPERSON FROINES: Is there a reason why the
24 three who aren't aren't?

25 (Laughter.)

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, they
2 didn't meet the criteria that we had set out for having
3 residential, occupational, non-residential and/or
4 childhood in multiple time points.

5 PANEL MEMBER FRIEDMAN: So --

6 CHAIRPERSON FROINES: Then that's clearly stated
7 somewhere?

8 PANEL MEMBER FRIEDMAN: This table 7.4.1M lists a
9 bunch of studies that looked at dose response and none of
10 them found it.

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: 7.4.1I is
12 where we had -- I'm sorry -- 7.4.1, it's J.

13 PANEL MEMBER BLANC: J has the does response,
14 right?

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: J has the
16 dose response. Sorry.

17 PANEL MEMBER FRIEDMAN: But doesn't 7.4.1M also
18 have it? It says cohort studies with dose response. And
19 they don't show them.

20 DR. MILLER: Yeah, like I said, that's the cohort
21 portion.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, that's
23 the cohort portion. There's the cohort study -- we split
24 them out case-control and cohort. That's why there's two.

25 PANEL MEMBER GLANTZ: So I guess the short answer

1 to Craig's question is that if you look at all of the
2 studies, there were six that found a dose response
3 relationship and there were -- when you said -- and then
4 your question is: Have any of the studies found dose
5 response? The answer is "Yes, six did." And then there
6 were some other -- there's some number they'd have to add
7 up that we know looked for and then didn't find a dose
8 response, right? Is that a fair --

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.
10 That's right.

11 PANEL MEMBER BLANC: In terms of the theoretical
12 construct of the exposure under-estimation but not
13 complete misclassification of the cohort studies, is there
14 an inherent reason why the point estimates in those
15 studies would systematically fail to show an association
16 as well, in your view?

17 DR. JOHNSON: Absolutely.

18 PANEL MEMBER BLANC: And what is that?

19 DR. JOHNSON: Well, because when you misclassify,
20 you put people who are exposed in the referent group.

21 PANEL MEMBER BLANC: Well, I'm not talking about
22 that because that's not your argument with the cohort
23 studies. Your argument with the cohort studies is that
24 they don't estimate the full range of exposures, isn't --

25 DR. JOHNSON: No, no. But by not taking into

1 account the full range of exposures, you have some women
2 that you've put in the referent group because you think
3 they're not exposed because you never actually asked them
4 about their exposure.

5 PANEL MEMBER BLANC: -- about their work.

6 So it's not just the -- it's not just the
7 imprecision and --

8 DR. JOHNSON: Oh, no. Actually almost all of it
9 is not the imprecision. It's -- what you end up with
10 basically is it's likely -- for example, in the Wartenburg
11 study, the Big American CPS2's cohort, they found,
12 depending on which analysis, 50 or 60 percent of women
13 exposed. If you contrast that -- with basically just
14 looking at spousal exposure. If you contrast that with
15 the Fauthem study, where they did detailed -- a big lung
16 cancer study, they found something like 94 percent of
17 women had been exposed to tobacco smoke. If you even take
18 conservative assumptions on that, you may -- of those 50
19 percent of women that they say are not exposed, it may be
20 that 40 percent of those or 45 percent if you use the
21 Fauthem numbers, if it was exactly the same group
22 of women -- it isn't -- but, say, you just say 40 percent
23 of them. If 40 percent of them are misclassified, that
24 means that 80 percent of your referent group that they say
25 is unexposed actually is exposed.

1 PANEL MEMBER BLANC: Yeah, but let me follow up
2 on this question.

3 DR. JOHNSON: Sure.

4 PANEL MEMBER BLANC: Okay. That's --

5 DR. JOHNSON: I think that's the crux of the
6 argument.

7 PANEL MEMBER BLANC: That's the overall biasing
8 towards the null. Is there a systematic way that that
9 would bias such that if I separated out the women who
10 lived with husbands and had eight hours a day of exposure
11 to their husbands for 40 years, wouldn't still have a
12 point estimate that was higher relative to the
13 contaminated reference compared to the women who only
14 lived five years with --

15 PANEL MEMBER GLANTZ: Could I try to rephrase
16 your question?

17 I think what he's trying to ask, Ken, is -- and
18 if you have the exposure misclassification problem that
19 you've described, would that necessarily obscure the
20 presence of a dose response?

21 DR. JOHNSON: It would, because each of those
22 numbers would be attenuated. Rather than seeing risks of
23 1.5 to 2.53, you'll see risks of 1.1, 1.2, 1.3, 1.4, and
24 you won't be able to differentiate them and they won't be
25 statistically significant, because they'll be attenuated

1 dramatically.

2 In the letter I wrote about the Wartenburg study,
3 which was a -- the Journal of the National Cancer
4 Institute thought was important enough to publish, I
5 actually demonstrated what would happen to those numbers
6 and how it would be attenuated.

7 If the underlying risk was 2 and you had that
8 kind of misclassification, you would only see an overall
9 estimate of 1.15. So your dose response would be around
10 1.15 instead of around 2. You'd see 1.05, 1.15, 1.25
11 instead of 1.5, 2, 2.5.

12 PANEL MEMBER BLANC: But would that obscure a
13 test for trend?

14 DR. JOHNSON: Absolutely, because you just don't
15 have -- you don't have the separation and you don't have
16 the -- none of the estimates would be statistically
17 significant. They're too close to 1.

18 PANEL MEMBER BLANC: Oh, I'm thinking about --

19 PANEL MEMBER GLANTZ: No. So let me try to
20 rephrase his question.

21 PANEL MEMBER BLANC: The point estimates --

22 PANEL MEMBER GLANTZ: What you're saying -- I
23 mean it seems -- what you're saying -- or what he's saying
24 is, well, you might depress to point estimates. But would
25 the variance be depressed comparably so you'd still be

1 able to see the trend? Or is the variance going to stay
2 as high, so the smaller trend would be obscured? I mean
3 that's the question he's asking.

4 Does that -- does my rephrasing of it --

5 DR. JOHNSON: I'm not a statistician, so I can't
6 tell you for sure. But my sense is very strong that when
7 you get very close to 1, it's very hard to show anything
8 statistically significant. And there'll be overlap of all
9 those confidence intervals, far more likely than if the
10 numbers are spread and --

11 PANEL MEMBER BLANC: Well, but I'm asking about
12 the point estimates too. I'm sort of asking two
13 questions.

14 PANEL MEMBER GLANTZ: Well, but, you see, to see
15 the trend -- when you do a test for trend, you're looking
16 at the change against -- you're looking at the change with
17 does against the background random component.

18 PANEL MEMBER HAMMOND: You broaden everything.

19 PANEL MEMBER BLANC: No, I can see where --

20 PANEL MEMBER GLANTZ: And so I can see how what
21 he's saying there could obscure it.

22 PANEL MEMBER BLANC: I start to --

23 PANEL MEMBER HAMMOND: No, I think --

24 PANEL MEMBER BLANC: -- test for trend, but not
25 perhaps --

1 PANEL MEMBER HAMMOND: I think what it would --
2 is that you would have, since your exposure -- the actual
3 exposures, you know, are actually broader in both the
4 numerator and the denominator. See, the precision of your
5 estimates -- if you had a way to incorporate the
6 uncertainty of exposure into the precision of the
7 estimate, you'd find a very imprecise estimate. And
8 because of that, looking at ratios and trends would be
9 more difficult, they'd be more obscure. That uncertainty
10 would add to that.

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Andy has
12 something to add.

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT
14 CHIEF SALMON: Just a brief comment.

15 I think my -- my understanding of the question
16 about whether or not you could see the trend relates to
17 the fact that you would probably expect that the variance
18 in exposure from the occupational sources and other normal
19 spouse-related sources would likely be independent of the
20 variation in the exposure to spousal sources.

21 If that is so, then the contamination of the data
22 set with respect to spousal exposure criterion would not
23 affect the variance of the other part of the exposure,
24 which would therefore, as I think you were implying, mean
25 that the variation in all those dose groups would stay

1 high, and that would make it effectively impossible to see
2 trend.

3 Does that make sense?

4 PANEL MEMBER BLANC: Well, no, it's not entirely
5 convincing. I understand why it would be hard to see the
6 statistical significance of a test for trend. But there
7 should -- I'm trying to still figure out why we
8 wouldn't --

9 PANEL MEMBER HAMMOND: Well, I think if they're
10 depressed enough -- you know, if you could depress it down
11 to 1.1, you're not going to be able to -- you know,
12 overall you probably -- you know --

13 DR. JOHNSON: If you see 1.05, 1.1, 1.12, 1.16,
14 you think you've got a dose response, compared to you if
15 see 1.5, 2, 2.8, and 4.2?

16 PANEL MEMBER BLANC: Well, let me give you a
17 different example. If you saw an overall estimate of
18 1.05, which is not statistically significant, which is
19 kind of -- where a lot of these cohort studies are coming
20 out, and then I would expect to see that in the people
21 that -- you know, 10 husband years of exposure, you know,
22 it would actually falsely appear to be protective at .95.
23 And then with 20 years I'd see 1.1, and then with 30
24 years, as I started to get enough exposure, that relative
25 to the same baseline misclassification it's starting to

1 become strong enough -- it would be as if I had some
2 people in there who were active smokers, I would finally
3 start to see -- you know, I would see that. I mean I --

4 PANEL MEMBER FRIEDMAN: There's so much variation
5 other than --

6 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT
7 CHIEF SALMON: Yeah, because the variation is independent,
8 you've got a high level of variation regardless of what's
9 happening in the little bits of the variation that might
10 be showing a trend.

11 PANEL MEMBER FRIEDMAN: We'd be overwhelmed by
12 the noise of all these other --

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT UNIT
14 CHIEF SALMON: Exactly. The point is the noise stays
15 wide.

16 PANEL MEMBER HAMMOND: You know, I've been
17 looking at the IARC report that we've been talking about.
18 And I would like to put into the record and have you refer
19 to Table 2 -- compare Tables 2.2 and 2.5. And I want to
20 quickly say something about this that relates to this
21 overall impression we have of all the data.

22 This is the lung cancer among -- passive smoking
23 evaluation of lung cancer. And in Table 2.2, it's looking
24 at the epidemiologic studies based on spousal smoking.
25 And there are 40 case-control studies and 6 cohort

1 studies.

2 Not one of the 6 cohort studies is statistically
3 significant. It's null, the cohort studies, to date now.

4 The only significance comes in the case-control
5 studies for lung cancer. If you turn to Table 2.5, this
6 is looking at the risk for lung cancer in nonsmokers
7 exposed to passive smoke in the workplace. All right?
8 And in the workplace these are all case-control because
9 nobody in a cohort study does that analysis. This is the
10 reason the cohort studies have poor -- you know, why we
11 say they have poor exposure assessment. You don't have
12 that data, so it's only case-control.

13 And, again, one can see in the workplace alone,
14 with no home exposure, statistically significant increased
15 risk shows up in the case-control study. So where you
16 have the opportunity to do a good exposure assessment, you
17 can see it in a case-control study.

18 But this -- where we have -- most of us have just
19 said, you know, we accept that lung cancer, even there the
20 cohort studies don't show it. If you hung your hat only
21 on cohort, you would have to say that passive smoking does
22 not cause lung cancer. So I just think that that's an
23 important perspective with which -- filter with which we
24 should look at -- we shouldn't expect breast cancer to be
25 clearer than that, the lung cancer.

1 PANEL MEMBER FRIEDMAN: Some of the --

2 PANEL MEMBER BYUS: My last -- I'm sorry. I was
3 just listening to you, trying to --

4 PANEL MEMBER GLANTZ: Sorry. I know --

5 PANEL MEMBER BYUS: That's okay. No, that's
6 great.

7 PANEL MEMBER HAMMOND: Does it make any sense?

8 PANEL MEMBER BYUS: And so now I have a somewhat
9 answer to my other question. But I still -- might
10 rephrase my other question.

11 So if smoking is related to cancer, however you
12 get the smoke into you, and it must then plateau in some
13 sort of -- and/or go down some form of non-linear or
14 long-range dose response and plateaus. And I would like
15 to get back to the estrogen question here in the biology
16 at some point here, John, because I think this is the
17 wrong way to phrase it -- that you've phrased it by
18 calling it anti-estrogenic. I think that's incorrect.

19 So what would it mean? So this would mean? In
20 sort of active smoking would this be like one cigarette a
21 day or -- what sort of comparable -- I know this is --
22 maybe that from my -- you know, I'm a pharmacologist. I
23 just want you -- I mean I know this -- you know what I'm
24 trying to say? I'm just trying to put it in exposure
25 reference, if at all possible.

1 So if you never were exposed to passive smoke,
2 sort of like an Einstein-type mind experiment -- maybe not
3 Einstein, but you see what I mean.

4 So if you were never exposed to passive smoke and
5 then you went -- and if we were going to design an
6 epidemiology experiment prospectively -- which they won't
7 less us do -- and we would say, "Okay, we're going to put
8 people into different smoking categories," how much --
9 where are we going to set our dose response up for active
10 smoking? Is it going to be a one cigarette a week, a
11 month, a half a day or one a day? Roughly, what will our
12 dose response range be where we would see it with active
13 smoking? That's what I want to know.

14 PANEL MEMBER HAMMOND: All right. The problem
15 that I've tried to write about on this is that the
16 emissions of various chemicals are different in mainstream
17 and sidestream in the same setting.

18 PANEL MEMBER BYUS: Humor me for a minute.
19 Assume that they're roughly in some comparability.

20 PANEL MEMBER HAMMOND: So what's your question?
21 Your question's --

22 PANEL MEMBER BYUS: I want to know --

23 CHAIRPERSON FROINES: I don't understand --

24 PANEL MEMBER BYUS: -- what would you expect to
25 see the dose response in smoking actively with cigarettes?

1 CHAIRPERSON FROINES: But I still am -- before
2 she does that, I still think this active versus passive
3 smoking is -- I mean smokers are passive smokers.

4 PANEL MEMBER HAMMOND: Right. I mean -- first of
5 all, even if you look at -- we see a different answer to
6 your question if you look at lung cancer and if you look
7 at heart disease, just to pick two disease. In two
8 diseases -- and part -- and of course I would defer to
9 Stan to really explain this.

10 But in heart disease we have some sense of a
11 mechanism which gives some justification for the fact that
12 you see what appears to be a very steep curve early on the
13 dose response and then a tapering, and in an almost
14 asymptotic. Maybe that's too strong. But definitely a
15 two -- almost like two curves.

16 Whereas in lung cancer, we see something very
17 different. We see what looks much more linear.

18 Now, so the question is -- we could talk about
19 the mechanisms behind that and there's speculations around
20 that and people have observed those effects on people
21 exposed.

22 So what is the mechanism for breast cancer?

23 PANEL MEMBER BYUS: We don't know that.

24 PANEL MEMBER HAMMOND: I know. And the thing is,
25 but you'd have to make some hypothesis for that, wouldn't

1 you, to be able to even come up with this. And given that
2 active smoking is not showing breast cancer, at least not
3 very clearly --

4 PANEL MEMBER BYUS: Well, they're saying so
5 because they're subtracting -- because of the referent
6 group.

7 PANEL MEMBER HAMMOND: So then you get into --
8 you're almost looking into the crossing of two curves,
9 aren't you? You've got a -- the active smoking kind of
10 cuts your risks to some degree and --

11 PANEL MEMBER BYUS: It has --

12 PANEL MEMBER HAMMOND: -- it has to go up and
13 down and --

14 PANEL MEMBER BYUS: Active smoking must cause it
15 to some degree. Otherwise you'd see something.

16 PANEL MEMBER HAMMOND: It must be an up and down
17 kind of thing. And where would you hypothesize that those
18 things are happening? That's a hard question.

19 PANEL MEMBER BYUS: I don't know. I'm just --
20 it's just -- can you answer me? Do you know what I'm
21 getting at?

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: I know
23 what you're getting at.

24 PANEL MEMBER BYUS: It's the major -- one of the
25 major problems here.

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: It's hard
2 to look at the data and say, okay --

3 PANEL MEMBER GLANTZ: Can you tell us what he's
4 getting at, just so we all know.

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, he's
6 getting at: Why don't you see higher breast cancer risks
7 with active smoking than passive smoking? And the
8 bottom -- when people break out the dose response data for
9 active smoking, they're usually looking at 1 to 10, you
10 know, 11 to 20 cigs per day, more than 20 cigs per day;
11 and where do you start to see an effect?

12 PANEL MEMBER BYUS: And I agree. You're not
13 going to see it there. I do agree with you. So I'm
14 not -- I'm just trying to get a feeling for where would
15 you have to -- way down at the low end, is that roughly
16 what we're looking at?

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: You mean
18 in terms of the dose of carcinogen?

19 PANEL MEMBER BYUS: Yes.

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Comparing
21 active smokers to passive smokers?

22 PANEL MEMBER BYUS: That's correct.

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
24 that is a great big question mark. And here's a few
25 reasons. We don't know for breast cancer which of the

1 carcinogens are causing the effect. There's many
2 carcinogens. There's likely going to be interactions,
3 synergisms, antagonisms, even with the non-carcinogenic
4 components. Active smokers have induced detoxification
5 enzymes. That could be playing a role.

6 And I know you don't like the anti-estrogen
7 argument. But I think it's an important argument. And,
8 you know, it didn't come -- we didn't make it up. It's in
9 the literature in a lot of different places how active
10 smokers definitely have, you know, lower age at menopause,
11 more -- so on, these effects that are considered to be
12 anti-estrogenic.

13 PANEL MEMBER BYUS: They don't have lower
14 circulating levels of estrogen however.

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, they
16 don't. But they have different profiles of the estrogen
17 metabolites.

18 PANEL MEMBER BYUS: Estrogen hormonal levels are
19 the same, which I found out since the last time I was
20 here.

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: It depends
22 on the study. And --

23 PANEL MEMBER BYUS: Urinary levels are up, but
24 the circulating serum levels are about the same in the
25 best studies.

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Total.

2 But if you look at the activity of them, metabolites, you
3 get a different profile.

4 PANEL MEMBER FRIEDMAN: Is there data on passive
5 smoking in estrogen?

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't
7 think that there are. But --

8 PANEL MEMBER FRIEDMAN: So we don't know that
9 passive smoking doesn't produce the same effect?

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, the
11 studies that looked at active smokers also looked at --
12 they compared people who smoked with nonsmokers. So in
13 the nonsmoker pile are the passive smokers.

14 DR. JOHNSON: Also all those active smokers are
15 passive smoking. So --

16 PANEL MEMBER GLANTZ: I just want to -- I think,
17 you know, getting back to -- if I were to pretend to be
18 Michael Thun, whose name was taken in vain recently, or
19 Jonathan Samet, this -- I mean this is the key argument
20 right here, you know. This thing of why are the risks --
21 I mean I think when you look at the meta-analysis, the
22 risks for active smoking are higher than passive smoking
23 but they're not much higher.

24 And I think that -- and in fact they even said --
25 it's even in the Surgeon General's list of 2004. I mean

1 that's the fundamental argument that is made for people
2 who don't want to say that passive smoking increases the
3 risk of lung -- or breast cancer. It's, why are the risks
4 so similar? So I think if that -- it would be nice to
5 more fully ventilate that argument, because that really --
6 that is the central argument, more so than case-control
7 versus cohort, more so than confounding or publication
8 bias or -- it's, why are the risks so similar? So what's
9 the answer?

10 CHAIRPERSON FROINES: Yeah, but I think, Stan --
11 I'm not sure -- I would love to see a whole section on
12 that and get into the biological, chemical mechanism very
13 much. That's my area, so I would like that.

14 But I'm not sure that we want to do that in this
15 report.

16 PANEL MEMBER GLANTZ: Well, but let's at least
17 discuss it and see, because Craig --

18 CHAIRPERSON FROINES: But let me just say that --
19 I mean I think the issues around this are so complex
20 biologically. I mean on the one hand, just to take a
21 simple example, the induction of P 450 enzymes also
22 enhances the bioactivation of PAH's that might lead to
23 carcinogenic effects in the breast.

24 So you've got thing -- what you have is a
25 situation where things are going up and other things are

1 going down. And so we don't know yet what's really going
2 on. And I think anything that we get into in this report
3 will be speculation, and I'm not sure it's useful. I
4 think -- I would love to have a workshop on the biological
5 mechanism of breast cancer and look at it in some detail.
6 But I'm not sure we want to turn this report into that
7 document.

8 PANEL MEMBER GLANTZ: Well, that may be true.
9 But I think it would be highly enlightened -- or not -- I
10 think it's worth taking the issues Craig has brought up
11 now and at least hearing what OEHHA has to say and what
12 Craig thinks about it and what you have to think about it.
13 Because that is -- if you talk to the people who are
14 skeptical about the conclusion in the report, that is the
15 primary reason that they are skeptical, is that the risks
16 which are seen -- I mean you've talked to them. I've
17 spent lots and lots and lots of time talking to these
18 guys. And, you know, that is -- I mean it's explicit in
19 the Surgeon General's report. I mean it says here --
20 Kathy underlined it.

21 PANEL MEMBER HAMMOND: No, I didn't --

22 PANEL MEMBER GLANTZ: Okay, okay, okay. Well,
23 they say the studies of passive smoking in breast cancer
24 contrast somewhat with the findings of the far larger
25 number of active smoking that are consistent with showing

1 no effects. So even the Surgeon General's report which
2 we've been quoting recognizes that there's an elevation in
3 risk reported in the passive smoking studies. But then
4 they say, "But we didn't find it in active smoking, and so
5 how could it be true?" So that -- and in fact if you look
6 back and read them carefully, a lot of them did find an
7 elevation in risk in active smoking. It was just not very
8 large compared to what people thought it should be.

9 And so I think at least it's worth talking -- I
10 mean even -- I think even a discussion of the kind of --
11 and this is getting out of my area of expertise. But I
12 think a sane, articulate discussion even of the
13 conflicting mechan -- you know, conflicting biological
14 forces that are present and sort of laying that out
15 clearly would actually help the discussion by simply maybe
16 explaining why -- you know, what could be going on that's
17 creating this sort of surprising result.

18 CHAIRPERSON FROINES: Well, in the journal
19 Chemical Research and Toxicology there are papers every
20 month about the metabolisms of estrogens and other
21 hormones. And there are lots of biological mechanisms
22 that people -- and chemical mechanisms that people talk
23 about. There are quinone formation in terms of estrogen
24 oxidation and so on and so forth. So there's an entire
25 literature on that. And I think that that's a fascinating

1 topic. I'm just not sure it's the topic for this time.

2 PANEL MEMBER BLANC: Well, you know, I think I
3 have a possible way out of this difference of opinion.

4 PANEL MEMBER BYUS: Another table? No.

5 (Laughter.)

6 PANEL MEMBER BLANC: There are really two
7 separate arguments that are made. One is a sort of
8 dichotomous argument, which is that if active smoking
9 isn't related to breast cancer at all, how can passive
10 smoking be related to breast cancer? And the second
11 argument is, okay, well, active smoking is related to
12 breast cancer, but why is the magnitude of risk so close,
13 which is the argument that you made.

14 PANEL MEMBER GLANTZ: Well, both of those
15 arguments.

16 PANEL MEMBER BLANC: Both of those arguments are
17 made. And I think that the goal of the appendix that
18 you've added and the attention that you've given to
19 smoking -- active smoking is really -- I think where you
20 should and have appropriately given some attention is to
21 the first part of that argument, which is: In fact an
22 argument can be made that there is relationship between
23 active smoking and cancer and that there's a little bit of
24 lag in analysis of those studies and that we'll
25 probably -- you know, even though it's beyond the scope of

1 this document, that that's really, given the current state
2 of our database, not strictly speaking correct.

3 On the other hand, I think it would make sense to
4 recognize that, however you take it, the estimates of risk
5 are fairly close. And there could be many explanations
6 for that, which are, you know, really beyond the scope of
7 this document. You know, you could -- you know, you can
8 refer people out -- I think you do. But I think where --
9 I don't think you quite as explicitly as you could divide
10 the argument into the two arguments. You sort of lump
11 them together.

12 And I think separating them out and say, okay,
13 here's Appendix A that addresses to our view unequivocally
14 that the first argument really is not -- probably is not
15 what the argument is. And, you know, the second argument
16 is a very interesting one and is related to a lot of
17 biology.

18 The only other way I think that would support
19 your -- tend to support the secondhand smoke analysis is
20 to the extent that the active smoking literature gives you
21 some specific data on premenopausal versus postmenopausal,
22 you would expect the direction of association to be
23 similar. That is to say that when you look -- start
24 looking in that stratum the pattern is less equivocal.
25 And I think that would be very -- and that would --

1 CHAIRPERSON FROINES: Melanie, that was the
2 question -- the last point that Paul made is the question
3 I wanted to ask you, because I don't know the literature.

4 Do you know if there have been any studies that
5 have looked at pre versus postmenopausal and active versus
6 nonsmoking? Because I would predict based on the biology
7 and physiology that premenopausal women would be at
8 greater risk of breast cancer as active smokers. Although
9 there's an -- obviously there's an age issue about when
10 people develop cancer. So that it's not simple.

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah,
12 there are actually a number of studies of active smoking
13 that looked at that. The one that was published a couple
14 weeks ago, Hanaoka, active smoking was positive, and
15 statistically so, for breast cancer only in premenopausal
16 women and not post.

17 CHAIRPERSON FROINES: That's interesting.

18 OEHHA SUPERVISING TOXICOLOGIST MARTY: Band, et
19 al., 2002. Do you remember? I'm pretty sure --

20 PANEL MEMBER BLANC: Do you have the study from
21 the nurses' health study? Because you didn't cite it.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Egan?
23 Yeah, we have Egan.

24 PANEL MEMBER BLANC: What about Wael K.
25 Al-Delaimy?

1 CHAIRPERSON FROINES: Who?

2 PANEL MEMBER BLANC: Wael K. Al-Delaimy.

3 PANEL MEMBER BYUS: It's easy for you to say.

4 (Laughter.)

5 CHAIRPERSON FROINES: See, I think that the
6 biological issues associated with premenopausal women in
7 active smoking are very interesting questions.

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: And, you
9 know, there are -- there definitely is evidence that
10 active smoking causes breast cancer and particularly in
11 premenopausal women. So that it's --

12 CHAIRPERSON FROINES: Especially given the
13 time-age versus risk where you have this hump in what, 35
14 or 40? So that something's going on.

15 PANEL MEMBER GLANTZ: Hump in what?

16 CHAIRPERSON FROINES: In the time --

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, with
18 the breast cancer rate.

19 CHAIRPERSON FROINES: -- time rate.

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: There were
21 also actives -- there was just another published study,
22 Graham, et al., '05, that looked at girls starting smoking
23 as teenagers. They are at elevated risk. And if I'm not
24 mistaken --

25 PANEL MEMBER HAMMOND: -- the younger they start,

1 the higher the risk.

2 OEHHA SUPERVISING TOXICOLOGIST MARTY: -- the
3 younger they start, the higher the risk.

4 Egan also had --

5 DR. MILLER: Egan if you started smoking 16 or
6 younger, that was where they thought --

7 OEHHA SUPERVISING TOXICOLOGIST MARTY:

8 -- elevated risk. But that's --

9 CHAIRPERSON FROINES: It's interesting --

10 PANEL MEMBER BYUS: My concern is that document
11 here have the estrogen effect. And I -- the Surgeon
12 General's report -- and I said this to you last time and
13 gave you this paper, and the people I've talked to
14 subsequently -- reference -- and I'll just read this to
15 you: "The estrogenic hormone dependence of breast cancer
16 is not well defined." And that is really true. It's not
17 to sort of hang your hat, as it were, on estrogen, as
18 opposed to any of the number of myriad other causes or
19 myriad of potential effects I think is my concern; and, in
20 particular, the fact that the basal hormone -- I mean
21 not to say it's not -- it's just not compared to, say,
22 endometrial cancer, some of the other cancers. And that
23 also gets back to this fact that the estrogen levels
24 are -- the circulating levels of estrogens as well as all
25 the other hormones that they -- reproductive hormones that

1 have been measured in smokers versus nonsmokers in this
2 fairly carefully done study, they're pretty much the same.
3 It's circulating levels.

4 Now, this -- again, I grant you that there's
5 metabolites data, there's very complex -- all the
6 different oxidative metabolites, different activities, pre
7 versus postmenopausal, overweight -- all the rest of it.
8 But I think you don't necessarily want to hang your hat on
9 that as the explanation.

10 DR. MILLER: You know, I --

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't
12 think that we actually are trying to hang our hat on any
13 explanation, because it's very complicated.

14 PANEL MEMBER BYUS: Quite honestly, I think that
15 what the data points to is that there's something
16 significant in the etiology of breast cancer that we don't
17 understand what it is. Its doesn't --

18 CHAIRPERSON FROINES: I think there are two
19 different -- you're actually confusing a little bit --
20 just a little bit two different issues, one of which is:
21 Is estrogen somehow related to breast cancer? I think the
22 answer there is yes. Is active versus passive smoking --
23 are the differences really the estrogen? And there I
24 think the answer is: It doesn't look like it, but we
25 don't know.

1 PANEL MEMBER BYUS: Well, I'm telling you people
2 are making -- I showed this paper last time. I gave you
3 this paper. People are making the argument that estrogen
4 is not necessarily directly related to breast cancer. You
5 can make the argument. I mean there's multiple ways you
6 can make it.

7 CHAIRPERSON FROINES: Hormones.

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
9 there's thousands of studies that make the opposite
10 argument, literally.

11 PANEL MEMBER BYUS: Well --

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: And
13 treatment is -- hormonal treatment is based on menopausal
14 status. If you're a premenopausal there's no point in
15 giving aromatase inhibitors, because your ovaries are
16 pumping out estrogen. And the aromatase inhibitors work
17 in postmenopausal women to decrease the production of
18 estrogen in the fat cells.

19 So clearly from a clinical perspective, there's a
20 huge, huge clinical trials looking at endocrine therapy.
21 And they're still using it because it works at least
22 partially; not fully, but partially.

23 So I think that it's -- we can't say that
24 estrogen is not related to breast cancer progression. It
25 may be unrelated to initiation or maybe -- or even the

1 earlier stages of carcinogenesis. But it's certainly
2 related to promotion.

3 PANEL MEMBER BYUS: What you're saying here is
4 premenopausal effects.

5 I'm just saying the data looks -- from my
6 opinion, there's something else. And, again, I'm not an
7 expert. But there's other things other than estrogen that
8 we are missing in the etiology. And when we understand
9 it, maybe you can link it to smoking. But to me it does
10 not look like it's estrogen. Just that's my opinion.

11 PANEL MEMBER LANDOLPH: I was listening to
12 Craig's comment there and what Katherine said earlier.
13 You know, they're really different reagents, the active
14 smoking versus the passive smoking. One of the things you
15 get is radical formation during the pyrolysis of cigarette
16 products going directly into the lungs. By the time the
17 passive smoke is inhaled by distal people, you've probably
18 lost all those. They're probably very short lived.

19 So on an initiation basis you could make a very
20 simple postulate too, that they are different reagents.
21 And what you're comparing is the ratio of lung cancer to
22 breast cancer and active versus passive smoking. And I
23 can't say that estrogen's not involved. But I could say
24 that the attacking reagents are different in those cases.
25 So it's reasonable to expect the ratio of lung to breast

1 in both to be different. I don't -- initially I was a
2 little bit worried about that argument. Now I'm not so
3 worried about it. I think it's not unreasonable, and it
4 shouldn't be used to obviate the findings in passive
5 smoking and breast cancer. I think that obviation
6 argument is wrong.

7 CHAIRPERSON FROINES: I'd say that there's
8 another issue, Joe. I think there's a lot of commonality
9 among the components of those particles. And I think that
10 the ability of the carcinogens to come off the particles
11 may be different between active and passive smoking. So
12 your bioavailability may be different.

13 PANEL MEMBER BLANC: Can I just --

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: Mark's
15 just going to point out what we actually said.

16 PANEL MEMBER BLANC: Can I just -- as I said
17 there earlier, I need about a half an hour approximately
18 for Chapter 1. It's approaching 3:30. I understand we're
19 adjourning at 4. I'm not sure where we stand on your
20 presentation on this.

21 Are you -- have you gone through all the
22 slides --

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
24 so. I think I've hit the points that I was going to hit.

25 PANEL MEMBER GLANTZ: Could we just hear -- you

1 know, we spent a very long time on Chapter 1. And I'd
2 just like to finish a couple things here. I mean Mark was
3 about to say something.

4 PANEL MEMBER BLANC: Well, I was just checking in
5 on the time.

6 PANEL MEMBER GLANTZ: Okay. Well, we're getting
7 near end. That's fine.

8 But what were you going to say, Mark?

9 DR. MILLER: Well, I just -- as far as the
10 document goes, I mean I don't know that we could address
11 this estrogen thing in any depth. You know, the Surgeon
12 General, in fact, that was probably the best part of that
13 discussion. But having a -- I feel responsible for this
14 part of it, having been, you know, quite involved in the
15 drafts of this. And what I tried to do, whether it was --
16 came across, was to simply say, you know, here's what the
17 data is and here in the literature are some of the
18 hypotheses that have been presented. And we're not
19 hanging our hat on any of those or used those for anything
20 other than to just present some of the information to a
21 reader so that they could begin to think about it.

22 So that's the extent of what I was trying to say.

23 CHAIRPERSON FROINES: I think you can just refer
24 in the document to that -- to the Surgeon General's report
25 and it can stay as a reference. I don't think you need a

1 lot more. I don't think you needed all of a sudden go
2 move everything and develop a new literature search. I
3 would just reference it and leave it at that, frankly.

4 PANEL MEMBER GLANTZ: You mean reference -- to
5 make what point?

6 CHAIRPERSON FROINES: I'm just saying -- he's
7 talking about the biology issue. And I just said, "Why
8 don't you add to the existing report a reference to the
9 Surgeon General's discussion," which is clearly pretty
10 well done, "and let it go at that."

11 PANEL MEMBER GLANTZ: You mean of the estrogen
12 hypothesis?

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

14 DR. MILLER: Just say there's a discussion -- a
15 good discussion here and reference it. And as I remember,
16 they come up with a kind of a "Well, it's not so clear."

17 CHAIRPERSON FROINES: Exactly.

18 PANEL MEMBER BYUS: That's all I'm getting -- it
19 is not that clear. And there's any of a number of
20 mechanisms --

21 CHAIRPERSON FROINES: Joe.

22 PANEL MEMBER LANDOLPH: A very small one.

23 Melanie, I liked your slide very much which
24 discussed a little bit about the Surgeon General's report.
25 And I think that's a nice transition, just from my point

1 of view. If you could capture that concisely and put it
2 somewhere in your document, I think that would be a nice
3 transition from that Surgeon General's document, which has
4 received so much attention, to where you are now. And I
5 think it's great.

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

7 PANEL MEMBER GLANTZ: Can I just ask -- I just
8 want to ask one point. Again, I'm just trying to
9 figure -- based on this discussion, it seems -- I think
10 there needs to be at least some mention of these issues.
11 I don't think the report has to go on about them. I mean
12 do you guys think it would be best placed in that appendix
13 they wrote on active smoking rather than in the main body
14 of the report?

15 CHAIRPERSON FROINES: The biology part?

16 PANEL MEMBER GLANTZ: Yeah. I mean just do
17 people have an opinion about that? Because, you know, the
18 literature in this area, I mean the estrogen hypothesis is
19 wide -- people talk about it a lot. But it's always
20 presented as a hypothesis.

21 And then maybe this other stuff about -- which
22 was in the response to public comments and also the report
23 about perhaps differing natures of the smoke, oxidant
24 loads, things like that. I mean would that be best to put
25 in the appendix rather than in the -- where is it now?

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: It's just
2 in the main body where we're talking about our
3 conclusions -- findings and conclusions. So it's not in
4 the appendix, in part because the appendix is only talking
5 about active smoking and the body of the document's
6 talking about ETS.

7 PANEL MEMBER GLANTZ: Never mind.

8 PANEL MEMBER BLANC: It depends on what their
9 approach is. If you like this idea about breaking off the
10 argument about smoking, yes-no, and then smoking degree of
11 risk --

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: We
13 actually have done that. We did that. We took all of the
14 text on the active smoking studies and put it in an
15 appendix. But we have the conclusion --

16 PANEL MEMBER GLANTZ: Oh, no. He's making a
17 different point, Melanie.

18 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, the
19 point is that we are saying in here that there is evidence
20 that active smoking is associated with breast cancer. So
21 that's argument one. And argument two we're saying, "We
22 really don't know why that the risks look about the same,
23 but they do."

24 PANEL MEMBER BLANC: Right. And what I would say
25 is that the -- whereas I would -- I think it made sense to

1 partition part 1 to the appendix mostly, you know, where
2 all the data, the details of why it's not "no" for
3 smoking. But some of the arguments about why the
4 magnitude of the association is close to the magnitude of
5 the association on secondhand smoke probably shouldn't get
6 relegated to the appendix, because it's probably a
7 little --

8 PANEL MEMBER GLANTZ: Did you say "should" or
9 "shouldn't"?

10 PANEL MEMBER BLANC: Should not. That part of it
11 maybe should --

12 DR. MILLER: Being as that that's such --

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: That made
14 sense.

15 DR. MILLER: -- an important controversial item
16 there.

17 PANEL MEMBER BYUS: That's your big issue as far
18 as I am concerned.

19 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

20 DR. MILLER: We wanted to try to address that as
21 head-on as we could.

22 CHAIRPERSON FROINES: But the point is is it's
23 still -- the conclusion of that section is we really don't
24 know at this point.

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

1 PANEL MEMBER GLANTZ: So I guess with this, what
2 you're saying, John, as the way to present this is to say
3 we believe, assuming that we believe it, that in fact
4 there are data demonstrating an elevated risk of active
5 smoking. So the -- well, if active smoking doesn't
6 increase the risk, how could passive smoking increase the
7 risk is a falsely predicated statement. That I think is
8 well supported by the data.

9 But then to say, "We really don't know why the
10 risks are so similar. Here are a few theories that are
11 out there. The observation is something one can report,
12 but there's no widely accepted explanation. There are a
13 few theories that some people think are plausible, but
14 there's no direct empirical support for it."

15 CHAIRPERSON FROINES: That would be my view. And
16 I also think that the -- we'll talk about this next
17 time -- but the discussion on toxicology could be like
18 Pandora's box and one could get into a huge discussion
19 about toxicokinetics and animal models and all sorts of
20 things. And it seems to me that we're not doing that in
21 this report, which is emphasizing epidemiology. And so my
22 only concern is to make a credible showing but not open
23 Pandora's box basically.

24 PANEL MEMBER BYUS: It's biological -- I mean
25 again back to these criteria. It is biological

1 plausibility. If it's biologically implausible, well,
2 then you have to look for confounders back in these
3 epidemiology things and without the lack of a dose
4 response. But if it's biologically plausible, and that's
5 what you're saying, and that's what -- there's a
6 biological plausibility for the difference between
7 animal -- I mean why the dose response doesn't keep going
8 up.

9 CHAIRPERSON FROINES: I think that the --

10 PANEL MEMBER BYUS: It would be the same. That's
11 all.

12 CHAIRPERSON FROINES: I think that the toxicology
13 needs to be kept very tightly within the context of adding
14 some measure of biological plausibility and not letting it
15 go forward to saying that this reinforces our causal -- I
16 don't want to take it beyond that, because one could --
17 one could get into lots of arguments about the toxicology
18 that I don't think we want to get into. Because this
19 report, we'll vote on it, it will stand on its own in
20 terms of the epidemiology or it won't. But it's not going
21 to stand on its own based on some estrogen theory or
22 carcinogen theory.

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

24 PANEL MEMBER GLANTZ: Are you saying this -- I
25 mean there wasn't a huge amount of discussion of the -- I

1 mean, again, this is the stuff you know a lot more than I
2 do about. But there wasn't a huge amount of discussion
3 about toxicological arguments in the report, I didn't
4 think, other than saying there are these compounds which
5 have been shown to be mammary carcinogens. And are you
6 saying that there should be even less than there is now?

7 CHAIRPERSON FROINES: I'm saying it should --
8 unless -- I'm saying it could stay as it is. But I would
9 also say from a toxicologic standpoint that it's
10 frustratingly short. So that I'd like to get into all
11 sorts of debates about those issues. But I think that in
12 the spirit of what I think is happening is we're making a
13 decision one way or the other based on epidemiology. And
14 if you want to really use the toxicology, then you're
15 going to have to get into it and you're going to double
16 the size of this report.

17 PANEL MEMBER LANDOLPH: I agree with you. I
18 think we should stay like it is. I think it's good enough
19 for the --

20 PANEL MEMBER HAMMOND: And I don't think it would
21 be more informative. I think it would not --

22 CHAIRPERSON FROINES: Well, it could be
23 interesting though.

24 PANEL MEMBER HAMMOND: -- be more informative by
25 the time you finished the first one.

1 Yeah, interesting.

2 CHAIRPERSON FROINES: Because she's not hanging
3 her hat on either of those issues. She's using them --
4 some of the little sentences that are sort of thrown in
5 here and there throughout the whole report about the
6 toxicology should be taken out. And Gary mentioned that
7 to me. Or there should be at least a reference to where
8 you do find the discussions, so it's not just kind of
9 these little sentences all over the place.

10 But that aside, I think that the point is made
11 there's exposure to carcinogens. That doesn't prove
12 cancer. And to get into whether the carcinogen exposure
13 leads to cancer is a big issue, and that's what we don't
14 want to take in because we're going to base it on Epi.

15 Is that fair?

16 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

17 Can we go back to Chapter 1?

18 PANEL MEMBER BLANC: Only if you --

19 PANEL MEMBER GLANTZ: I want to just raise one
20 other very quick issue, because I'm sort of thinking of
21 that list of things. I mean do you guys want -- there are
22 two issues that have been just very briefly mentioned here
23 that I'd like to just get on the record of what you think;
24 and, that is -- then I think we can get back to Chapter 1.

25 One is the issue of residual confounding, the

1 statement that the relative risks are not gigantic and so
2 you always have to worry about residual confounding.

3 And then the other one is the publication bias
4 question.

5 And, you know, I'd just like to quickly hear what
6 you guys have to say about those. And then I think we
7 will have through the course of the day discussed every
8 one of your expressed concerns.

9 CHAIRPERSON FROINES: Can I ask you a question?

10 PANEL MEMBER GLANTZ: Yeah.

11 CHAIRPERSON FROINES: Can we -- 1, 2 -- do I
12 count as a quorum? --

13 PANEL MEMBER GLANTZ: Yeah.

14 CHAIRPERSON FROINES: -- 3, 4, 5. If the three
15 of you leave, we can continue. Paul -- no?

16 PANEL MEMBER LANDOLPH: I'll stay as long as you
17 need.

18 CHAIRPERSON FROINES: That's six.

19 PANEL MEMBER GLANTZ: Well, we can continue
20 having a discussion.

21 PANEL MEMBER BLANC: I really would rather not.

22 PANEL MEMBER GLANTZ: Okay. But what --

23 PANEL MEMBER BLANC: We've got enough time left.
24 I'll be brief.

25 PANEL MEMBER GLANTZ: I don't think this will

1 take a long time.

2 So those are the -- I'd just like to ventilate
3 those two questions.

4 PANEL MEMBER BYUS: I'll give you my view and
5 position on confounding.

6 And, that is, I think there is a significant lack
7 in our understanding of the etiology of breast cancer to
8 say that we don't understand it. And because of that,
9 because of this lack of understanding, there is something
10 or a series of things that we don't understand, clearly
11 distinct from many of the other cancers, that that means
12 that there could be more confounding because we just don't
13 know what it is that is going on there. It's not
14 estrogen, in my opinion, not clearly estrogen. It's not
15 clearly pre or postmenopausal. It's not obesity. There's
16 lifestyle issues. We don't know what it is. And so
17 because of that, in terms of the mechanism and risk factor
18 association for it, it increases the likelihood of there
19 being more confounding. That's all. I mean -- now,
20 again, that's kind of -- maybe -- if you don't agree with
21 me, that's okay. I mean it's just -- I guess maybe there
22 is a -- but it's just in my mind, let me put it that way,
23 in my mind.

24 DR. JOHNSON: Which I can't speak to.

25 PANEL MEMBER BYUS: You cannot speak about my

1 mind, can you?

2 (Laughter.)

3 PANEL MEMBER BLANC: Nor would he wish to.

4 (Laughter.)

5 PANEL MEMBER BYUS: Nor would you wish to.

6 I mean maybe that doesn't follow. But, anyway --
7 you don't have to respond to that. I don't think it needs
8 a response.

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: We just
10 had a couple of slides, one on publication bias and the
11 passive smoking breast cancer studies.

12 The publication bias occurs when studies with
13 positive results are more likely to be published than
14 those with negative results.

15 And we -- it's kind of funny, because to me, when
16 I look at the data, there's a lot of studies that, you
17 know, don't knock your socks off, and so in terms of the
18 risk estimates and overall are null. So I don't see how
19 that applies personally anyway.

20 Thirteen of the 19 studies that we looked at
21 suggest increased risk. Most of those were not
22 necessarily significant at least overall. All five with
23 the relatively complete exposure measures suggest
24 increased risk -- statistically significant increased
25 risk. And there would have to be a number of unpublished

1 studies with good exposure measures which were all
2 negative for publication bias to be a reasonable
3 explanation. And we just don't think that it's likely.

4 PANEL MEMBER FRIEDMAN: There's techniques for
5 check -- there's this funnel plot that you can do. Have
6 you tried that --

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, we
8 have not done the funnel plots, in part because there's
9 difficulties interpreting the funnel plots depending on
10 how you -- what measure you use, sample size or one over
11 the standard error, you know, in order to make the funnel
12 plots.

13 And also -- well, Stan can go on much better than
14 I.

15 PANEL MEMBER GLANTZ: I said to Melanie, "You
16 need to do a funnel plot." And Melanie said, "We don't
17 like funnel plots." So I woke up in the middle of the
18 night and did it. But I couldn't remember exactly how to
19 make them. And so I went on to pub med and searched for a
20 funnel plot. And the first paper that came up was
21 "Misleading Funnel Plot for Detecting of Bias in
22 Meta-analysis." It's a very good paper. And there are
23 four different ways to do funnel plots. And they took a
24 hundred and some odd meta-analyses from the Cochran
25 collaboration and showed how you get different results

1 depending which way you make the graph.

2 So I think that it was -- it kind of blew it
3 away. And, in fact, the two books -- the two
4 meta-analyses which I have say how to do it differently.
5 So I -- after like -- I called Melanie back and said never
6 mind.

7 There are however -- we did -- Lisa Barrow and I
8 did a paper where we looked for publication bias and lung
9 cancer in ETS, and there's just no evidence for it there.

10 And there's a paper --

11 PANEL MEMBER FRIEDMAN: Did you use a funnel
12 plot?

13 PANEL MEMBER GLANTZ: Well, we did that, but we
14 also looked at the results of reviews. And I can give it
15 to you.

16 But I thought this was very -- when I was digging
17 around, obsessing about this. This is in Diana Petitti's
18 book. And this is quoting Begg and Berlin, who are two of
19 the guys who invented this whole thing. And they said,
20 "Begg and Berlin, however, speculate that historically a
21 bias toward publication with no results may have
22 characterized a study of asbestos in cancer. When there
23 are adverse financial or regulatory consequences for
24 positive result, a bias in favor of publication of
25 negative or null results is a theoretical possibility."

1 So, you know, I think -- I mean when I did the
2 funnel plots, it didn't look like there was a positive --
3 in fact the couple ways I tried it, it actually suggested
4 a bias toward publication of negative studies.

5 So when you do it, there's also a bunch of
6 different diagnostics you can compute. And having -- and
7 they actually were pointing in the other direction.
8 Although it's hard to believe that if somebody had a
9 positive big study, they wouldn't publish it.

10 PANEL MEMBER HAMMOND: Well, I think that people
11 who have public funding, you know -- if you invested in a
12 cohort study or case-control study where this was a prime
13 hypothesis, you know, if you didn't publish it, you
14 wouldn't be getting any more money, you know. I mean
15 there's a certain reality there.

16 Now, if it was a secondary or tertiary or
17 quaternary hypothesis you tagged on and you just ran an
18 analysis or something, that might or might not be an
19 issue. But anything that has -- and that's where you
20 don't have a very good -- it's not a very good study in
21 the first place. It's not designed for that.

22 But if it were designed that, my guess, then you
23 could probably -- if you could go and look at the funding
24 that had, you know, been made for ETS and various
25 outcomes, and I'll bet you'll find a paper for most of

1 those publicly funded things.

2 By contrast, one could imagine studies being done
3 financed by private companies that might have an interest
4 in this, who, if they found positive results, they would
5 not be required to publish it. So one could speculate --
6 I mean I know that people talk about a lot. But whenever
7 people try to look at -- I've also heard of people really
8 doing a search of all the funded studies and to find they
9 all been published. So that it's more something people
10 talk about than necessarily actually happens, except for
11 the kind of off-the-cuff analysis that's done on the side.

12 PANEL MEMBER GLANTZ: I think it's a bigger issue
13 when you're talking about small clinical trials rather
14 than Epi studies. But, anyway.

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Then there
16 was another concern about confounding in the passive smoke
17 breast cancer studies. And this gets to be more of a
18 concern when your risk estimate is relatively low.

19 The major known breast cancer risk factors were
20 controlled for pretty well in most of the studies,
21 reproductive history, agent menarche, and so on. And
22 alcohol was accounted for in many of the studies. And
23 they still showed an increased risk for passive smoking.

24 PANEL MEMBER BYUS: BMI you said as well.

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: By mass

1 index is another.

2 So you'd have to hypothesize an unknown risk
3 factor that's associated with both breast cancer and
4 passive smoking that, you know, would differentially --
5 that would be able to account for the study.

6 PANEL MEMBER HAMMOND: And that has been
7 undiscovered to date.

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

9 PANEL MEMBER HAMMOND: And, you know, some of my
10 colleagues at NCI have commented, after years and years of
11 trying to look for these confounders. In reality the only
12 confounder that they found in occupational studies,
13 despite all these people are concerned about it -- but
14 consistently the big one is -- the only real one that's
15 possibly smoking for lung cancer, because the relative
16 risk is so large, that a small difference in smoking rates
17 in your exposed and control groups or your case and your
18 control groups would lead to it. And yet those
19 differences aren't actually found when people go to look
20 at smoking rates -- unless you really pick your groups
21 wrong -- in the studies that have been done.

22 So that confounding is actually something that
23 people worry about a lot more than has actually been, you
24 know, found.

25 PANEL MEMBER FRIEDMAN: Well, there's not only

1 the question of whether all the appropriate variables were
2 included in the analysis, but how well they were
3 characterized. For example, if you say they control for
4 alcohol, was it just drinkers versus not-drinkers, or did
5 they say, you know, one to two drinks per day, three to
6 five, et cetera, and for, you know, age versus --

7 DR. JOHNSON: It would be more likely to be more
8 likely to be characterized controlled. And the
9 case-control studies and the cohort studies would have
10 been more likely to have asked more detailed questions.

11 PANEL MEMBER FRIEDMAN: But didn't -- I mean
12 whether it was -- I don't know about likely. But did they
13 do it?

14 DR. JOHNSON: Well, it varies by study. All the
15 studies -- essentially all the studies controlled for
16 alcohol but about two or three. And certainly all the
17 ones that we considered a better -- had better exposure
18 measures.

19 Yeah, but did they --

20 DR. MILLER: Some of them are grams per day kind
21 of a thing.

22 PANEL MEMBER FRIEDMAN: -- did they with regard
23 to -- they did do things like that.

24 And for reproductive variables, did they say
25 just, you know, nulliparous versus --

1 DR. JOHNSON: They tend to have 4 or 5 of the
2 better -- of most -- maybe 15 or more of the studies,
3 case-control and cohort, will have controlled for between
4 7 and 12 different variables, 4 or 5 of them being
5 reproductive -- or 5 or 6 of them being reproductive.

6 PANEL MEMBER FRIEDMAN: So you think they
7 generally did a good job of controlling for these
8 variables?

9 DR. JOHNSON: I think they -- I think they did a
10 pretty good job. Plus there's another thing that goes --
11 there's two things that go into confounding. First of
12 all, the confounder actually has to have an impact on the
13 disease or it's not going to be a confounder.

14 PANEL MEMBER FRIEDMAN: Sure.

15 DR. JOHNSON: Secondly, that potential confounder
16 has to have a relationship with passive smoking, and
17 probably a fairly intimate one.

18 Now, Peggy Reynolds' analysis of the correlates
19 of passive smoking suggest a few that there is
20 correlation, some things around diet, SES, and whether
21 you've had pap smears and such.

22 But I'll just read something quickly from the
23 IARC monograph. And this is -- they're talking about
24 dietary -- they're talking about confounding for passive
25 smoking and lung cancer. And this is -- they just have

1 one short paragraph, and I'll only read part of it.

2 "Several potential confounders have been proposed
3 that may partly or fully explain the increased risk of
4 lung cancer associated with exposure to secondhand smoke
5 from the spouse." Okay?

6 "None of these" -- and we're talking about a risk
7 of 1.2. So a lot more -- real likelihood of it compared
8 to a risk of approaching 2 that we're looking at for
9 breast cancer. "None of these potential confounders has
10 been established as having a causal link with lung
11 cancer." Acknowledged.

12 Then they say: "Several of the observational
13 studies have attempted to adjust for consumption of
14 different dietary items that might be impacting on lung
15 cancer. But when you control for those factors, it
16 doesn't change the risk estimates," suggesting they aren't
17 strong confounders. So they say -- they showed that the
18 effect of dietary confounding was negligible.

19 And I think you'll find that for the breast
20 cancer, when you look at crude estimates -- often they do
21 age controlled estimates and then they do multi-factorial,
22 all the potential confounders -- and you find almost no
23 difference in the risk estimate. The risk estimate may
24 differ by 5 or 10 percent maximum.

25 So for the existing things that we know about, it

1 seems very unlikely that any of those are serious
2 confounders. For things we don't know about, well,
3 there -- that's always --

4 PANEL MEMBER BLANC: Can I step in?

5 Wait a second. In all fairness to me, it's now a
6 quarter of an hour.

7 PANEL MEMBER FRIEDMAN: Well, I just think that
8 that kind of discussion should appear in the report, a
9 good strong argument as to why you don't think confounding
10 would explain it.

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.
12 We'll do it.

13 PANEL MEMBER BLANC: Well, if I could tie it into
14 chapter 1, I think -- and I had mentioned earlier that I
15 thought that in the same way that you felt it useful to
16 talk about categorization, I think there should be a
17 general discussion about confounding and saying that, as
18 you go through all of these different issues, you do in
19 your looking at study quality take into account whether
20 co-factors which are known or suspected to be potentially
21 related to both the outcome and the exposure have been
22 taken into account; and, if so, appropriately. And
23 estimates -- re-estimates done on that basis.

24 And, similarly, if you are going to take a
25 decision about a publication bias, you're going to look at

1 it -- you're not going to look at it systematically as you
2 go through, say that in -- you know, in your methods that
3 in general we have not given particular attention to
4 publication bias because there doesn't seem to be, you
5 know, much evidence that this is a true issue. However,
6 if we have come across a citation that has analyzed it in
7 relationship to a specific outcome, we do cite the paper
8 if appropriate, or something like that. And we haven't,
9 you know, independently done our own analyses, such as
10 funnel analysis or whatever it is. So it's clear we're
11 not embarking on this and it's like we decided to do it
12 for breast or decided not to do it for breast, but we did
13 it for lung or some other site or did it for asthma.

14 So that's how I would tie this last discussion
15 into Chapter 1, because all of these things I think are
16 relevant.

17 So just briefly to go through some other things
18 that I think would help. In Section 1.1 on page 1.2, when
19 you talk about the organization of the report, I think it
20 would helpful to say, not just the organization or the
21 order of chapters, but explain to the reader why it is
22 that each chapter is organized in a standard way and what
23 it is that you do in a chapter. You start each chapter
24 with a table that summarizes blah, blah, blah. And then
25 we go through systematically various and/or organ effects

1 or disease processes or whatever it is you're doing, just
2 to explain that and why they're organized internally
3 within chapter organization.

4 Going to Section 1.2, which is the definition of
5 ETS. This is actually also applicable to your executive
6 summary. I think you're a little blasé about the
7 potential symbolic importance people place on some of
8 these synonyms of ETS. And I would have the statement
9 clearly, "We are going to use the term 'ETS' almost
10 exclusively throughout this document. There are other
11 terms that have been used and they are" blah, blah, blah,
12 blah, "but this is what we're going to use." It's sort
13 of -- it's not stated explicitly. It's just sort of
14 sideways, you know.

15 And I think that when you start talking about how
16 you define ETS, then -- I mean I think it is useful -- for
17 example, you get very explicit about you're not going to
18 consider ETS exposure when a mother actively smokes -- the
19 exposure to the fetus, even though in a way that is
20 kind of -- from the fetus' point of view it's ETS. But
21 from the point of view of this document, it's not. And I
22 think that level of detail is okay.

23 I do think that the stuff about what is a -- what
24 is a nonsmoker -- I mean it is true that an ex-smoker
25 maybe in some studies is a nonsmoker. But, you know, it's

1 sort of a -- it's sort of a weird thing. I mean I think I
2 would just say that that's not what you mean by it. The
3 same way you mean that passive smoking is not an actively
4 smoking mother whose fetus is passively. So you're not
5 saying --

6 PANEL MEMBER HAMMOND: It says just the opposite.
7 It says, "In general, ex-smokers are not excluded" --
8 are not excluded.

9 PANEL MEMBER BLANC: But nobody would consider an
10 ex-smoker a nonsmoker. I mean you're an ex-smoker. I
11 wouldn't --

12 PANEL MEMBER GLANTZ: No, that's not true. I
13 mean I have a -- I was out --

14 PANEL MEMBER HAMMOND: It depends on the -- this
15 is for a set of endpoints.

16 PANEL MEMBER BLANC: Right.

17 PANEL MEMBER GLANTZ: I mean some of the studies
18 do consider ex-smokers to be nonsmokers.

19 PANEL MEMBER BLANC: And those were to be a very
20 weak study in your point of view --

21 PANEL MEMBER GLANTZ: Well, not --

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: It depends
23 on the outcome that you're measuring.

24 PANEL MEMBER HAMMOND: Yeah.

25 PANEL MEMBER GLANTZ: Like for heart disease if

1 it's an ex-smoker -- a five years ex-smoker --

2 PANEL MEMBER BLANC: Okay. I got -- your point's
3 well taken.

4 But you need to be a little bit more explicit on
5 that.

6 When we get into the methodology section I think
7 that I have covered parts of it, but other parts I
8 haven't. And the very first section I think you should
9 say something about how you chose or didn't choose to use
10 the consultants. The consultancy doesn't appear in here.

11 I think that since you did take all the time to
12 respond to a public comment period, part of the
13 methodology is that there was a period of public comment
14 and that you responded to those comments. I mean that's
15 an important part of the methods.

16 And the issue of the literature review --
17 scientific literature review, because it can come up later
18 in terms of what -- you know, what was your time cutoff
19 and some things you went farther and some things you
20 didn't. I think you should be perhaps a little bit more
21 pedantic also there about up to what time you searched
22 and -- for my own point of view I actually even like to
23 know the key words you used or some of the key words. But
24 maybe that's asking too -- for these -- not for the
25 disease outcome side, because that would be really

1 exhausting. But, you know, you used secondhand smoke, you
2 used ETS, you used involuntary smoking. Or you could just
3 say you used all of the synonyms that we just cited before
4 in our definition of ETS, if you want to save space.

5 And you don't say here explicitly when you -- but
6 I know that you did this -- when you pulled a paper, if
7 the references of the paper included citations which you
8 hadn't otherwise found. You attract those down, didn't
9 you? But you don't say that.

10 And what is a call-in -- a data call-in?

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's a
12 bureaucratic term that ARB uses when they start a toxic
13 air contaminant process. They have what they call a data
14 call-in. So they say, "We are starting the process for
15 identifying this compound as a TAC. So just send in
16 whatever data you have." And it's a public data call-in.

17 DR. MILLER: We got three boxes of materials that
18 were sent in.

19 PANEL MEMBER BLANC: You did?

20 PANEL MEMBER HAMMOND: So it's kind of a request
21 for comments from the public?

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: It's a
23 request for: What data do you have on the health effects
24 of ETS:

25 PANEL MEMBER BLANC: Then you had unpublished

1 studies that were sent in to you that way?

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

4 PANEL MEMBER BLANC: You had studies that you
5 wouldn't have otherwise found the med line that you used?

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, I
7 don't --

8 PANEL MEMBER HAMMOND: But there was the
9 opportunity to --

10 DR. MILLER: We've got all kinds of stuff.

11 PANEL MEMBER BLANC: And then, "While published
12 peer-reviewed literature serves as the primary source of
13 data, additional sources, for example, from abstracts of
14 meeting presentations or doctoral dissertations, may be
15 included, particularly if they provide information in an
16 area where data are lacking."

17 Were there such areas here?

18 CHAIRPERSON FROINES: There was one abstract that
19 was discussed.

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

21 CHAIRPERSON FROINES: At least one, maybe two.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: There was
23 one.

24 PANEL MEMBER BLANC: I mean --

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: There may

1 have been some in the exposure side.

2 Do you remember a doctoral dissertation on the
3 exposure side?

4 PANEL MEMBER BLANC: Because that's -- you know,
5 I haven't seen it come up with something where I thought
6 it was driving a conclusion in some odd way. But then --

7 PANEL MEMBER GLANTZ: Yeah, but, you know -- but,
8 you know, I think that's good, because that sort of goes
9 to the whole publication bias issue. And there's nothing
10 wrong with citing at-meeting abstracts or doctoral
11 dissertations.

12 PANEL MEMBER BLANC: If you do it systematically.
13 But if you don't do it systematically and it's because
14 you're getting fed certain ones in certain ways, then it
15 could be a problem. That's why I'm bringing it up. It's
16 very hard systematically to review abstracts. So you have
17 to be careful. And one of the things that you do use, as
18 it turns out, that's not listed here, are letters to the
19 editor, data -- the analyses that are embedded in letters
20 to the editor which involve personal communications. And
21 for certain of your outcomes those come into play more
22 than for others. But it doesn't appear here in your
23 methods. So I think it's going to come back and haunt
24 you. Otherwise I would be explicit.

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think

1 some of those letters to the editor we got as part of a
2 data call-in.

3 PANEL MEMBER BLANC: Well, then say it. I
4 mean -- you know. I don't think the letters to the editor
5 related to breast cancer came from a data call-in, did
6 they?

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
8 Judson Wells either sent them at the data call-in or at
9 some point in the public process.

10 PANEL MEMBER BLANC: All right. And then a more
11 minor thing, but I think it's just another sample of where
12 you sell yourself short in a way, you know, you were more
13 rigorous than it might seem. So I was a little bit
14 surprised, Kathy, that you didn't bring this up. But they
15 have a tendency to talk about biomarkers, which would only
16 refer to cotinine or cotinine-like metabolites, and not to
17 talk at all about exposure assessed through airborne
18 non-biomarker, things like nicotine or particulate.

19 PANEL MEMBER FRIEDMAN: Excuse me, Paul.
20 Some of these, in my opinion -- and maybe I'm
21 wrong -- some of these border on minor comments. And I
22 was wondering. You had some really general principles
23 about your --

24 PANEL MEMBER BLANC: Well, I'm trying to use them
25 as an example of I think that this is not adequate

1 methods. I guess I'm just -- maybe I'm beating a dead
2 horse. And I'd be happy to give you my notes. But I
3 think that you haven't looked at this as a methods
4 section. And I feel the need to have it. And I'm just
5 trying to point out. And I know that's -- I'm done pretty
6 much.

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: Paul, I
8 think the biomarkers was addressed more in Part A, the
9 nicotine as a biomarker. Cotanene -- ways to measure
10 airborne --

11 PANEL MEMBER HAMMOND: Airborne nicotine.

12 PANEL MEMBER BLANC: It's not a biomarker.

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: I'm sorry,
14 not biomarker.

15 Airborne -- ways to assess exposure to ETS in
16 airborne measurements was all addressed in Part A.

17 CHAIRPERSON FROINES: Well, the DNA addicts are
18 biomarkers.

19 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

20 PANEL MEMBER HAMMOND: Well, and very, very --

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: And we
22 have just a little bit of that.

23 PANEL MEMBER HAMMOND: Yeah, there's very few Epi
24 studies -- there are very few Epi studies, especially for
25 the retrospective, you know, cancer studies.

1 PANEL MEMBER BLANC: Yeah, for the respiratory
2 more you cite Mark's work and -- Mark Eisner's. And it's
3 not biomarker work.

4 PANEL MEMBER GLANTZ: So I don't quite understand
5 the point you're trying to make. What do you want them to
6 do?

7 PANEL MEMBER BLANC: I want them to be more
8 rigorous in their --

9 PANEL MEMBER GLANTZ: But I mean specifically
10 what do you want -- what do you want them --

11 PANEL MEMBER HAMMOND: When they talk about how
12 to do exposure assessment to include airborne markers as
13 well as biomarkers, right?

14 PANEL MEMBER BLANC: Well, they did it. All I'm
15 saying is when you write it the way you write it, it's
16 sloppy.

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: We will
18 work with Paul on Chapter 1; which I think you just got
19 volunteered to be a lead on Chapter 1 revisions.

20 PANEL MEMBER BLANC: That's it. I'm done.

21 And have you gone back through all your
22 introductory tables and the beginnings of your chapters
23 and make sure now that they're up to date with the numbers
24 of studies in your various -- I notice that, for
25 example --

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: We did
2 that after the last SRP meeting. But it keeps changing.
3 So we have to -- you know, before we send forward the next
4 version, we'll do it again.

5 PANEL MEMBER BLANC: Because I notice like in the
6 breast cancer there are less than you actually have.

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

8 CHAIRPERSON FROINES: I'm assuming that you will
9 take about two months to make these changes. Is that
10 right?

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: We'll try
12 to do it. See, it would --

13 CHAIRPERSON FROINES: Well, you tell me.

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: We have to
15 give you guys time to review it.

16 CHAIRPERSON FROINES: Well, see, I -- that's one
17 thing that I want to -- that's the reason I asked the
18 question, is I'd like to be able to schedule a meeting so
19 that -- this time was a little tight.

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

21 CHAIRPERSON FROINES: And I think what happened
22 was because of the U.S.A. Today story, people busted their
23 tails this last weekend to really reread everything and
24 get prepared.

25 But we hope that sort of incentive doesn't happen

1 again and that we can have some time to review it. I
2 would say two or three weeks, four weeks, if you could,
3 for the panel. Although I don't know whether most people
4 read it towards the end anyway. But --

5 PANEL MEMBER GLANTZ: Everyone always reads
6 everything toward the end.

7 CHAIRPERSON FROINES: So we should plan -- Jim
8 and I'll plan the meeting in consultation with you so that
9 there a good time -- like this is March -- March -- the
10 rest of March, April, May. So that would mean June?

11 Does anybody have a major crisis?

12 PANEL MEMBER GLANTZ: Well --

13 CHAIRPERSON FROINES: July starts to get tricky.

14 PANEL MEMBER GLANTZ: Yeah. I have one sort of
15 logistical thing. This report here was -- they did it in
16 a red-line strikeout format, which I found very helpful.
17 The question is for the next draft, should they accept the
18 changes that were made to this draft and then produce one
19 which shows the changes made between this draft and the
20 next one, or should -- do you want all of this stuff?

21 PANEL MEMBER BLANC: No, that's fine, that's
22 fine. It gets illegible that way.

23 PANEL MEMBER HAMMOND: Although I do like that
24 way "delete" is done. I don't know how you -- that's
25 nice.

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's
2 Office 2003 does that.

3 PANEL MEMBER HAMMOND: Just pulling it off like
4 that is really nice.

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, why
6 don't --

7 PANEL MEMBER GLANTZ: Okay. But anyway, so the
8 next -- that's it, and --

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: Why don't
10 we try to have the document ready for an early June
11 meeting, so that we can avoid the summertime problem.

12 CHAIRPERSON FROINES: We -- never mind.

13 PANEL MEMBER BLANC: I don't know about this.

14 DR. MILLER: It's pretty short.

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Mark's
16 saying it's too short.

17 PANEL MEMBER BLANC: I think September --

18 CHAIRPERSON FROINES: What did you just say,
19 Melanie or Paul?

20 PANEL MEMBER BLANC: I said I thought September
21 was more realistic.

22 PANEL MEMBER GLANTZ: Well, let's -- why don't
23 you do this: We don't have to set the meeting right now.
24 Why don't you let Melanie and her people go back, think
25 about this a little bit, and decide how much work it's

1 going to take to address the issues that were brought up.

2 I mean I think this is a good discussion.

3 I didn't hear anything said which would lead them
4 to the conclusion that there was some fundamental blunder
5 that's going to require throwing out major sections and
6 starting all over again. It's a matter of addressing a
7 lot of specific issues and how things are presented.

8 So I think it should be fairly evident within a
9 week or so.

10 Melanie, I mean I was just saying, I think within
11 a week or so you should have some sense of whether you can
12 meet that schedule or not.

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

14 PANEL MEMBER GLANTZ: I would -- rather than
15 trying to do it now, why don't you give them a chance to
16 really look at the realities of how much work was
17 generated.

18 CHAIRPERSON FROINES: There's no problem. We're
19 flexible. I'm just -- my plea is that we have plenty of
20 time to go over the document. And we have -- I hesitate
21 to open my mouth and say this, but we have another
22 chemical coming down the road that Roger's smiling about.
23 And so we may have two meetings.

24 PANEL MEMBER HAMMOND: And the other thing that
25 would be helpful, John -- I don't know if it's going to be

1 possible. But I guess we all thought we would just be
2 done with this ETS in this meeting. And then it became
3 very clear at the end that the focus was going to be on
4 one chapter -- or two chapters really. And if we don't
5 think we can finish it in the next meeting, it would very
6 helpful -- because I feel overloaded and overwhelmed with
7 all this data -- if we were to say that we're going to
8 really particularly focus on some particular chapters
9 rather than the whole thing.

10 PANEL MEMBER GLANTZ: Well, that's true.

11 Could I -- I mean "I" speaking as the lead. I
12 mean, at the last meeting John said if people have
13 specific criticisms, they should get them to the staff and
14 to me. And I think a lot of -- this has been a fine
15 discussion. But I think a lot of this stuff is stuff
16 that, had people come and let the staff know about it
17 beforehand, could have been dealt with. So what I would
18 suggest is that if people have more things -- because the
19 report has been pretty thoroughly discussed except for
20 these couple of chapters, which, you know -- if you could
21 get more specific criticisms to the staff, they can be
22 dealt with, rather than waiting for --

23 CHAIRPERSON FROINES: Well, I think all that's
24 fine to say. But I think it's --

25 PANEL MEMBER GLANTZ: No, he already did it.

1 CHAIRPERSON FROINES: I think it's a little more
2 hopeful and -- because I think we have to have a
3 discussion with the leadership of Cal EPA and ARB and
4 OEHHA. And we're going to have to change the process for
5 how we do business in the future. Because the problem is
6 is people don't have the wherewithal, the time to do the
7 level of work that's required to do as thorough an
8 evaluation as we would like. And so a lot of issues have
9 come up in the last week because of the external factors
10 that got involved. And so it forced more rigorous
11 preparation I think than would have occurred without that.
12 And I think that we need to take seriously how we're going
13 to handle both consultants within OEHHA and how we're
14 going to handle our consultants and whether we have
15 conferences and --

16 PANEL MEMBER BLANC: Actually you're bringing up
17 a point, John, that I actually want to say it may affect
18 the time line. I actually would like -- I would like to
19 have a -- I would like you guys to solicit a round of
20 additional consultation for those sections of the report
21 for which there's been a step up of causality.

22 PANEL MEMBER GLANTZ: Well, you know, I just
23 think -- I mean I don't think that's going to get you
24 anything. I mean I think if -- I mean if there are people
25 that you know -- I mean I've encouraged everybody I know

1 who's interested in this stuff, and including the people
2 who've been critical, to read the report and submit public
3 comments, you know. In fact -- and a couple of them did
4 and some of them were critical. And I think the issues
5 that are there are there. I think we know what the issues
6 are. I don't -- and I think that there's a time when you
7 have to either say, yes, we agree with this or, no, we
8 don't. I don't think anything new would come out of that
9 process.

10 I think if you go back and read Michael Tunes
11 public comment, the issue -- the fundamental issues that
12 we spent a lot of the day talking about are all raised
13 there. And there are three or four other very strong
14 comments, you know, that raised these issues. And I -- I
15 mean I think that -- I mean I just think that's a waste of
16 time. And, you know, on one hand you say people are
17 overloaded with work and on the other hand you're making
18 more work.

19 I mean you're free as a member -- this is a
20 public document, you know. And if you want to encourage
21 anyone you know who you think could provide useful input
22 to you, show it to them. It's on the Internet. They can
23 be free -- instead of all these phone calls that are going
24 around. You know, get them to put their comments in
25 writing. I mean, in fact, I have to say when the report

1 first came out I happened to talk to Michael Thun. And he
2 may have put in the comment as a result of the
3 conversation I had with him. Because he was very critical
4 on the telephone.

5 And I said to him, "It's very nice that you're
6 telling me this. There's a public process here" -- you
7 know, which we have to remember, there is a process and it
8 served this panel and the process well for a very long
9 time. And I said, "If you're critical of this report," I
10 said, "I'm taking" -- "I'm not making any personal
11 judgments. But if you feel strongly about these
12 criticisms, write them down and send them in," because by
13 law the Cal EPA will have to deal with them. You know,
14 they can't just throw them in the trash. And I think that
15 has -- that process has happened. And I think, you know,
16 if people want to solicit informal criticisms to help
17 guide them as panel members, that's fine. But I just
18 think that's a complete waste of time, absolute total
19 waste of time.

20 PANEL MEMBER BLANC: But what do you think about
21 the idea?

22 (Laughter.)

23 PANEL MEMBER GLANTZ: Well, other than that, I
24 think it's great.

25 PANEL MEMBER BYUS: Your real opinion, Stan.

1 CHAIRPERSON FROINES: I think that -- I don't
2 agree with Stan, although that seems to have been the
3 pattern today. But the -- I think that we would benefit
4 from some external peer review. I don't think it does any
5 harm.

6 OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, this is
7 George Alexeeff.

8 It's not clear what was being asked. And I had
9 interpreted what Paul said to like elicit some -- to
10 identify a couple experts and ask them for an opinion.
11 What Stan I think interpreted and maybe another
12 interpretation was to go out for another round of public
13 comments.

14 PANEL MEMBER GLANTZ: Yes, that's how --

15 CHAIRPERSON FROINES: So what Paul meant was what
16 you said, a couple of experts within a particular area.

17 OEHHA DEPUTY DIRECTOR ALEXEEFF: Right.

18 PANEL MEMBER GLANTZ: I have no problem --

19 OEHHA DEPUTY DIRECTOR ALEXEEFF: But I think what
20 has happened in the past and I think what would be
21 maybe -- it might be worth it for the Air Board to talk
22 with the Chair. But the idea would be that the Chair
23 would be soliciting a couple different opinions from
24 experts. I mean if we solicit it, it's a whole different
25 ball game, because now we're going -- basically we'd be

1 going through an additional peer-review process for you
2 and we'd have respond to the comments before we got to
3 you, so we'd be talking at least another year before we
4 get back to you on it.

5 PANEL MEMBER BLANC: I see.

6 OEHHA DEPUTY DIRECTOR ALEXEEFF: But if you're
7 asking -- if you're feeling that you need some additional
8 expertise, then that might be a slightly different
9 process.

10 CHAIRPERSON FROINES: I think that the -- we
11 talked about this at lunch. It's very clear that we all
12 benefited dramatically by having Dale Hattis review the
13 formaldehyde literature. He was the person who drove the
14 ultimately decision on formaldehyde. And his expertise
15 was really quite special in that regard. And I think that
16 we really need to do that more to take the load off the
17 panel, but also to get very highly qualified people. And
18 we're talking about one or two people --

19 PANEL MEMBER BLANC: Well, I think what George is
20 saying is just that the technical requester may end up
21 being us and not them. And that's -- I don't have any
22 objection to that. And what I would like to do is just
23 have it be the sense of the committee to empower our Chair
24 to help facilitate that working with the leads or whatever
25 to get names. And the only thing I would say is that my

1 priority for that kind of input would be those parts of
2 the document which have, you know, a step up in -- or a
3 change. It could have been a step down, but I don't think
4 there were any, because those --

5 PANEL MEMBER GLANTZ: I don't have any -- I mean
6 I interpreted it exactly as George said, is another round
7 of public comment.

8 PANEL MEMBER BLANC: No, no. That's not what I
9 was asking for.

10 PANEL MEMBER GLANTZ: You know, I think if the
11 Chair wants to -- if that's the appropriate mechanism --
12 to solicit some additional -- you know, someone to look at
13 parts of this, I don't have a problem with that, with two
14 caveats.

15 One is that I think that, you know, it would
16 need -- given the length of time this has been dragging on
17 and my skepticism that it will yield any new information,
18 I would hope that it could be done in an expedited way
19 that wouldn't delay the process.

20 And the other thing is I think the critique
21 should be in writing, so that it can be responded to in
22 writing. Because I -- you know, my experience in
23 discussing this report with a lot of people is many of the
24 ones -- not all, but many of the people who were critical
25 hadn't read it; and several of the people that I

1 originally talked to about this when it first came out,
2 just to let them know it was there, after they read it,
3 their opinions changed.

4 So I think it's very important that whatever
5 reviewers you want to bring in engage the nitty-gritty in
6 the specifics of the document in the same way that we've
7 been talking about, and not just simply come in with sort
8 of sweeping statements.

9 CHAIRPERSON FROINES: Well, I think there's
10 another issue that's strategic as well. And, that is, if
11 we have a couple of reviewers -- I was talking to Beate
12 Ritz, who's a very fine epidemiologist, about this. And
13 her comments were very uninformed. And it seems to me
14 that if you have a couple of people who actually have done
15 a review, they then become the people who at meetings are
16 saying that this report is credible and so on and so
17 forth. In other words, they -- you start to create a nest
18 of allies who actually see the report in a positive light.
19 Whereas right now there is a very wide number of people
20 who are critical, in part because of what you say, in part
21 because of lack of information.

22 PANEL MEMBER GLANTZ: But also -- and I don't
23 want to delay this. But it's not that wide. I mean the
24 same people we've talked about before are the people who
25 wrote the IARC report. And, you know, they're -- well, I

1 don't know. I mean I can suggest some people who have
2 not -- who are very knowledgeable, who have not taken a
3 public -- who've been following this and not taken a
4 public position that would -- I think, if you can get them
5 to do it, would be very credible as scientific reviewers.
6 And, you know, I'll talk to you later about who that might
7 be.

8 CHAIRPERSON FROINES: Yeah, I talked to Kurt
9 Straif today, who's at IARC. And, you know, he reflected
10 the IARC report. So there are people who just don't know.
11 So the more you have some knowledge base out there, I
12 think the stronger it gets.

13 PANEL MEMBER GLANTZ: No, I agree, I agree. And
14 I think that the process of one of the things that this
15 report has done is it has forced people to actually
16 confront this newer evidence, and I think that's why some
17 people's views have been changing.

18 CHAIRPERSON FROINES: I think Kathy and some --
19 whoever else she chooses to work with should write
20 about -- I mean since she, you know, held her red book up
21 and said, "Froines cohort studies don't show any results
22 and" blah, blah, blah, that one should put that argument
23 in the literature.

24 PANEL MEMBER GLANTZ: Well, the red book was the
25 IARC report, not Chairman Froines, just for the record.

1 (Laughter.)

2 CHAIRPERSON FROINES: What?

3 PANEL MEMBER GLANTZ: The red book was the IARC
4 report and not Chairman Froines red book, just for the
5 record so we don't have any political ramifications.

6 CHAIRPERSON FROINES: My lips are sealed.

7 (Laughter.)

8 CHAIRPERSON FROINES: Motion to close the
9 meeting?

10 PANEL MEMBER BLANC: I so move.

11 PANEL MEMBER GLANTZ: Second.

12 CHAIRPERSON FROINES: All in favor?

13 (Ayes.)

14 CHAIRPERSON FROINES: Thanks, everybody.

15 (Thereupon the California Air Resources
16 Board, Scientific Review Panel meeting
17 adjourned at 4:15 p.m.)

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1 CERTIFICATE OF REPORTER

2 I, JAMES F. PETERS, a Certified Shorthand
3 Reporter of the State of California, and Registered
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5 That I am a disinterested person herein; that the
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11 I further certify that I am not of counsel or
12 attorney for any of the parties to said meeting nor in any
13 way interested in the outcome of said meeting.

14 IN WITNESS WHEREOF, I have hereunto set my hand
15 this 21st day of March, 2005.

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