

MEETING
STATE OF CALIFORNIA
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
MILLBERRY CONFERENCE CENTER
500 PARNASSUS AVENUE
SAN FRANCISCO, CALIFORNIA

THURSDAY, JANUARY 6, 2005

9:00 A.M.

JAMES F. PETERS, CSR, RPR
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper(via teleconference)

REPRESENTING THE AIR RESOURCES BOARD

Mr. Jim Aguila, Manager, Substance Evaluation Section

Mr. Jim Behrmann, Office of Community Health

Ms. Peggy Jenkins, Manager, Indoor Exposure Assessment
Section

Mr. Robert Krieger, Air Pollution Specialist

Mr. Peter Mathews, Office of Community Health

Mr. Jim Stebbins, Air Pollution Specialist

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APPEARANCES CONTINUED

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT:

Dr. George Alexeeff, Deputy Director, Scientific Affairs

Dr. James Collins, Staff Toxicologist

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

Dr. Mark Miller, Air Toxicology and Epidemiology Section

Dr. Bruce S. Winder, OEHHA, Associate Toxicologist

ALSO PRESENT

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

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

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

Is that correct?

PANEL MEMBER PLOPPER: That's correct.

CHAIRPERSON FROINES: Charlie, can you hear me?

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

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

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

(Laughter.)

PANEL MEMBER GLANTZ: Sort of like God talking.

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

PANEL MEMBER PLOPPER: Well, you know --

(Laughter.)

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

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

1 ramifications.

2 So we are going to continue where we left off.

3 And, that is, with OEHHA continuing their presentation.

4 Peter Matthews is passing around a new set of
5 slides. Dr. Landolph has prepared some written comments.

6 And we're going to ask him to discuss them at some point
7 so we can have them on the record verbally.

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

9 (Thereupon an overhead presentation was
10 Presented as follows.)

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

12 Good morning. Thank you.

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

17 So Ken is in the second row.

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

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

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

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

2 Sorry. Actually it sounded really loud to me.

3 Is that better?

4 Okay. Good.

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

7 CHAIRPERSON FROINES: Can I interrupt you?

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

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

21 And Mark Miller and I will tag team this
22 presentation.

23 DR. MILLER: So this slide --

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, Sorry.

25 For the Panel members who have the handouts, page

1 16 is basically where we're starting. So there's a blank
2 on the top of your page 16. And then this slide is not
3 there, but we're just going to use it for a brief
4 introduction. And then the next slide will be starting
5 there.

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

9 PANEL MEMBER PLOPPER: The comments, right?

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

13 PANEL MEMBER PLOPPER: Okay.

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

22 CHAIRPERSON FROINES: Just one comment.

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

1 folks.

2 Are you going to address those issues today?

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

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

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

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

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

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

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

4 And --

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

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

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

1 Next slide.

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

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

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

16 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's
17 this slide.

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

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

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

9 CHAIRPERSON FROINES: Kathy.

10 PANEL MEMBER HAMMOND: The other piece of that
11 is, if you look at, for instance, the Morabia study where
12 you just gave -- we broke out the details as a dose
13 response, clearly there is a dose response when you do the
14 comparison to those who are not exposed to ETS, those from
15 2.2, 2.7, 4.6. And so only -- the only spot -- the plot
16 point that's up there is only two. So is that the one
17 that includes the ETS exposed in the referent group?

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

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

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

1 actually.

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

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

7 PANEL MEMBER HAMMOND: Right, with that study.

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

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

15 PANEL MEMBER HAMMOND: Actually I'm --

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

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

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

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

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

22 PANEL MEMBER BYUS: Go ahead.

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

1 extremely important.

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

8 DR. MILLER: Yeah. Well, they have.

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

19 --o0o--

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

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

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

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, this

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

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

13 PANEL MEMBER BYUS: That's quite interesting.

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: And in
15 addition --

16 PANEL MEMBER BYUS: What was the last statement?

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

21 PANEL MEMBER BLANC: Blunted.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Blunted.

23 PANEL MEMBER BLANC: Blunted.

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

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

11 This study in particular did not look at that.

12 PANEL MEMBER BYUS: Okay.

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

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

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

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

11 --o0o--

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

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

1 raising.

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

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

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

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

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

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

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

15 PANEL MEMBER BLANC: I understand.

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

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

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

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

12 And so one of the questions --

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

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

1 sense.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 OEHHHA SUPERVISING TOXICOLOGIST MARTY: We can do

1 that with more than one paper.

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

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

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

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

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

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

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

25 PANEL MEMBER PLOPPER: I had a couple of comments

1 if I could make them.

2 PANEL MEMBER GLANTZ: God is talking.

3 CHAIRPERSON FROINES: Dr. Plopper has a comment.

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

13 Does that make sense?

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

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

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

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

4 CHAIRPERSON FROINES: Can you hear him okay?

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

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

14 PANEL MEMBER PLOPPER: Oh, sure.

15 CHAIRPERSON FROINES: -- discuss that a bit
16 further?

17 PANEL MEMBER PLOPPER: Yeah.

18 CHAIRPERSON FROINES: Joe.

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

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

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

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

11 CHAIRPERSON FROINES: Stan.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 PANEL MEMBER BYUS: That's right.

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I --

25 CHAIRPERSON FROINES: There's a lot of people who

1 want to talk with Melanie and your --

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

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

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

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

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

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

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

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, it
16 does.

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

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

1 would be no reason why initiation would be impacted.

2 CHAIRPERSON FROINES: This exchange --

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: So I think
4 that --

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

8 PANEL MEMBER BYUS: Exactly.

9 (Laughter.)

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

12 PANEL MEMBER BYUS: I agree.

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

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

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

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

10 Maybe Mark should start with the overall and move --

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

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

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

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

19 CHAIRPERSON FROINES: Okay.

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

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

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

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

15 --o0o--

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

20 CHAIRPERSON FROINES: This is 1.9?

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

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

25 PANEL MEMBER GLANTZ: It's a log scale.

1 CHAIRPERSON FROINES: Okay.

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

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

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

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: Thanks,
13 Mark.

14 (Laughter.)

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

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

25 In premenopausal breast cancer it's relatively

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

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

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

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

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

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: The
25 chronologic trend?

1 PANEL MEMBER BLANC: Yes.

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

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

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

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

22 --o0o--

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

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

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

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

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

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: For --

16 PANEL MEMBER BLANC: In the whole document.

17 DR. MILLER: Suggestive evidence, causal --

18 OEHHA SUPERVISING TOXICOLOGIST MARTY:

19 Suggestive -- inconclusive, suggestive and
20 causal.

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

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

25 PANEL MEMBER BLANC: Inclusive, suggestive and

1 causal.

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

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

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

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

25 Do you have dose response data in the

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

6 There are some data --

7 CHAIRPERSON FROINES: Can I make one comment --

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

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

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

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

1 poison.

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

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

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

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

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

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

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

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

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

21 PANEL MEMBER BYUS: They're there.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 PANEL MEMBER GLANTZ: Well, I understand that.

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

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

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

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

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

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

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

17 OEHHA SUPERVISING TOXICOLOGIST MARTY:
18 -- inconclusive.

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

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

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

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

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

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

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

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

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

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

25 Secondly, the evidence definitely -- of the six

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

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

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

15 DR. MILLER: Yeah.

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

23 CHAIRPERSON FROINES: Joe.

24 Oh, sorry.

25 OEHHHA SUPERVISING TOXICOLOGIST MARTY: By the

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

3 DR. JOHNSON: It just came out in December.

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

7 CHAIRPERSON FROINES: Premenopausal?

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

9 DR. JOHNSON: And not postmenopausal.

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: And not
11 postmenopausal.

12 CHAIRPERSON FROINES: And does it look at
13 postmenopausal?

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes, it
15 does.

16 CHAIRPERSON FROINES: And it's not positive?

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

18 CHAIRPERSON FROINES: Joe.

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

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

1 although some of it is in the premenopausal exposure.

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

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

10 Really. I have the curve right here.

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

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

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

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

6 PANEL MEMBER GLANTZ: Ken keeps wanting to say
7 something.

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

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

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

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

23 PANEL MEMBER BYUS: Great.

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

1 as well.

2 And the postmenopausal was much more modest dose
3 response.

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

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

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

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

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

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

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

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

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

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

16 (Laughter.)

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

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

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

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

12 PANEL MEMBER GLANTZ: Could I just ask one
13 question?

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

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

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

22 CHAIRPERSON FROINES: There may be a little
23 bit --

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

25 CHAIRPERSON FROINES: We're going to get into

1 biomarkers.

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

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

10 DR. MILLER: We have talked about that.

11 DR. JOHNSON: Oh, okay.

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

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

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

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

7 DR. MILLER: And is positive.

8 DR. JOHNSON: And is positive.

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

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

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

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

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

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

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

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

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

15 So let's go ahead with your slides.

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

18 DR. MILLER: Okay.

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

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

23 PANEL MEMBER FRIEDMAN: Yes. And --

24 CHAIRPERSON FROINES: Because he hasn't said
25 anything.

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

4 (Laughter.)

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

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

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

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

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

3 CHAIRPERSON FROINES: Thanks, Gary.

4 Okay. Melanie.

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

8 --o0o--

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

10 There is some discussion in the report about the
11 differences chemically in side-stream versus mainstream
12 smoke. There are studies showing that some carcinogens
13 are more concentrated in side-stream smoke versus
14 mainstream smoke.

15 One of them is mentioned here. Lodovici, et al.,
16 2004, reported about ten times more carcinogenic PAH's in
17 side-stream smoke relative to mainstream smoke. And that
18 was in terms of they were looking at micrograms per -- I
19 forgot what it was. It was either -- darn it, I forgot
20 the units.

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

25 PANEL MEMBER HAMMOND: If we move on, this data

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

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

7 Thank you.

8 PANEL MEMBER HAMMOND: Just bring the pieces
9 together.

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

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

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

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

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

13 Okay. For the --

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

16 PANEL MEMBER HAMMOND: Right.

17 (Laughter.)

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

23 The ratio biologically is nonsmokers have 1
24 percent as much cotinine as smokers on average. And
25 4-aminobiphenyl in the study that I published we had 14

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

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

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

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

11 PANEL MEMBER HAMMOND: I'm talking internal dose.

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

17 PANEL MEMBER HAMMOND: I think -- I agree -- I
18 totally agree it's complicated. But I'm saying that in
19 fact -- I'm talking about a biologic dose. I mean it's
20 4-aminobiphenyl hemoglobins adducts. It's not the DNA
21 adducts, but it certainly is what got into the human body.
22 And of course you can go on and on and on about -- and
23 it's important to do it. But I think in terms of showing
24 that in fact the different ratios in side-stream and
25 mainstream smoke have some relevance, that definitely

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

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

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

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

21 CHAIRPERSON FROINES: It's okay to mention it.

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

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

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

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

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

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

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

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

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. I
14 think --

15 PANEL MEMBER BYUS: Is that fair?

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

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

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

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

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

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

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

1 ratios being different by different things.

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

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

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I
9 think just to back everybody up, the reason it's in Part B
10 is we're talking -- when we're talking about biological
11 plausibility, that what we're saying is there are
12 carcinogens in tobacco smoke, there are mammary
13 carcinogens in ETS, that mammary epithelium is capable of
14 metabolic activation of the carcinogens, that you can find
15 DNA adducts of these carcinogens in the breast tissue. In
16 other words, the carcinogens reach the breast tissue. And
17 in fact on page 179, we talk about several studies, one of
18 which looks at 4-aminobiphenyl DNA adducts in normal
19 breast tissue, and there is a linear trend from never
20 either active or passive, ever passive only, ever active
21 only to both. So there's a linear trend in the
22 4-aminobiphenyl DNA adducts in breast tissue.

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

1 That's all we're trying to say.

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

7 And so I agree with Kathy or whoever said it.

8 I'd put it in Part A. It's relevant information.

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

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

18 That's an easy effect. So we'll remove that --

19 PANEL MEMBER FRIEDMAN: Just respond to Stan.

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

1 CHAIRPERSON FROINES: Joe, did you --

2 OEHHA SUPERVISING TOXICOLOGIST MARTY: All right.

3 So --

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

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

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

23 (Laughter.)

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

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

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

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

8 PANEL MEMBER HAMMOND: She's had those up.

9 CHAIRPERSON FROINES: Did I miss --

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

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

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure.

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

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

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

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

6 --o0o--

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

8 So --

9 CHAIRPERSON FROINES: Onwards.

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

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

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

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

1 consistently showing stronger associations.

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

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

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

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

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

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

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

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

4 --o0o--

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

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

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

21 --o0o--

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 PANEL MEMBER BYUS: Methodologically here are the
13 strongest.

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

21 PANEL MEMBER BYUS: There you go.

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

24 CHAIRPERSON FROINES: Joe.

25 PANEL MEMBER LANDOLPH: And what might help you

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

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

25 PANEL MEMBER GLANTZ: Well, I agree with what

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

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

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

21 CHAIRPERSON FROINES: Let me make my point here.

22 PANEL MEMBER BYUS: Are we?

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

25 (Laughter.)

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

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

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

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

9 (Laughter.)

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

13 (Laughter.)

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

1 I think.

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

4 I'm just not --

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

8 (Laughter.)

9 PANEL MEMBER FRIEDMAN: Make it shorter.

10 DR. JOHNSON: Make it clearer, simpler.

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

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

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

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

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

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

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

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

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

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

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

12 --o0o--

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

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

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

1 PANEL MEMBER GLANTZ: Thun is with the Cancer
2 Society.

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

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

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

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

21 --o0o--

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

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

11 --o0o--

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

15 DR. MILLER: Pooled analysis.

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

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

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

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

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

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

5 --o0o--

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

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

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

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

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: So we
22 screwed up.

23 CHAIRPERSON FROINES: So it's --

24 PANEL MEMBER HAMMOND: The comment was
25 overestimate?

1 CHAIRPERSON FROINES: A typo in the comment?

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

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
5 so. Sorry.

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

9 --o0o--

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

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

20 In most studies the cases and controls that were
21 not ETS exposed actually ranged from 20 to 50 percent, not
22 10 percent, including the most recent Hanaoka, which is
23 also a prospective cohort study.

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

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

7 --o0o--

8 DR. JOHNSON: Just one comment.

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

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

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

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

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

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

22 --o0o--

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

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

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

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

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

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

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

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

1 we feel belongs with the more complete studies.

2 --o0o--

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

5 --o0o--

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

8 (Laughter.)

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

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

1 inter-individual variability.

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

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

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

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

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

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

1 control studies.

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

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

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

19 What is your response to that?

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

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

1 that trend, although there were few of them.

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

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

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

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

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

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

17 PANEL MEMBER GLANTZ: Okay.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 DR. JOHNSON: I think the other quick point on

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

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

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

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

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

3 PANEL MEMBER HAMMOND: Okay.

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

8 That was it for breast cancer.

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

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

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

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

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

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

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

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

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Jim.

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

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

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

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

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

16 (Laughter.)

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

19 PANEL MEMBER GLANTZ: There's a short answer.

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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

4 Joe.

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

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

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

24 --o0o--

25 OEHHHA SUPERVISING TOXICOLOGIST MARTY: This is a

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

10 --o0o--

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

19 --o0o--

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

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

10 --o0o--

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

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

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

1 think that was our plan. Right, Mark?

2 DR. MILLER: Yes.

3 CHAIRPERSON FROINES: Comments, questions?

4 Craig?

5 PANEL MEMBER BYUS: No.

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

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

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

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

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

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

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

22 CHAIRPERSON FROINES: Kathy.

23 PANEL MEMBER HAMMOND: Nothing.

24 CHAIRPERSON FROINES: Joe.

25 PANEL MEMBER LANDOLPH: I thought overall it's a

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

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

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

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

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

1 And then you go on to the Sorahan study which is
2 positive. Then you go to the Schuz study which actually
3 finds an odds ratio of 1.5. That's significant based on
4 39 cases. I can't -- I wouldn't exclude that and say that
5 that's a negative study, which is what you basically say.

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: We're

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

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

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

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

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

20 CHAIRPERSON FROINES: Okay.

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

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

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

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

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah,
18 okay.

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

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

24 CHAIRPERSON FROINES: Okay.

25 PANEL MEMBER GLANTZ: Could I ask one question?

1 CHAIRPERSON FROINES: Please.

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

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

9 CHAIRPERSON FROINES: Melanie.

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

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

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

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

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: ARB's here

1 prepared to do that. So --

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

4 Are you talking about reproductive separate from
5 developmental?

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

7 CHAIRPERSON FROINES: You're not talking about
8 developmental?

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

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

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

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

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

23 CHAIRPERSON FROINES: Jeanette, do you have
24 slides?

25 ARB AIR QUALITY MEASURES BRANCH CHIEF BROOKS:

1 Yes, we do.

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

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

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

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

10 (Laughter.)

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

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

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

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

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

25 I think that there's an interesting problem we

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

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

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

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

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

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

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

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

23 PANEL MEMBER BYUS: He didn't tell you, did he?
24 (Laughter.)

25 CHAIRPERSON FROINES: But it raises some -- you

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

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

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

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

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

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

16 PANEL MEMBER BYUS: Came from plant products.

17 CHAIRPERSON FROINES: -- as well.

18 PANEL MEMBER BYUS: Originally, right?

19 CHAIRPERSON FROINES: So --

20 PANEL MEMBER HAMMOND: More so --

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

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

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

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

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

19 What do we think, 45 minutes is sufficient?

20 PANEL MEMBER HAMMOND: How long are the lines?

21 PANEL MEMBER GLANTZ: It's not a long line.

22 There's a food --

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

24 (Thereupon a lunch break was taken.)

25 CHAIRPERSON FROINES: Shall we begin?

1 Let me try that one again.

2 Shall we begin?

3 PANEL MEMBER GLANTZ: Sure.

4 CHAIRPERSON FROINES: Melanie?

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

11 CHAIRPERSON FROINES: They need an hour.

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: An hour.

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

15 So we need an hour --

16 ARB AIR QUALITY MEASURES BRANCH CHIEF BROOKS:

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

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

25 That's fine.

1 PANEL MEMBER GLANTZ: That will let Melanie
2 recuperate.

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

6 (Thereupon an overhead presentation was
7 Presented as follows.)

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

11 The 1997 document reviewed 18 studies. This
12 document, I've indicated here 11 studies. In fact that's
13 8 original studies and 3 meta-analyses.

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

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

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

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

4 --o0o--

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

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

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

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

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

1 --o0o--

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

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

11 In the study by Wells, he broke out just adult
12 exposures in all work place exposures. And again the
13 ratios -- the odds ratios are in the neighborhood of 1.2,
14 1.23, something of this nature.

15 --o0o--

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

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

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

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

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

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

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

25 ARB ASSOCIATE TOXICOLOGIST WINDER: Yes, it was.

1 PANEL MEMBER GLANTZ: That they followed for like
2 20 years. And they drew blood at the beginning of the
3 study. And so the cotinine levels that the analysis is
4 based on was the cotinine at study entry 20 years ago.
5 And they only had that single exposure measurement from 20
6 years ago.

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

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

1 were being discussed this morning.

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

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

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

1 discussion of cohort versus case control studies of ETS.

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

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

7 --o0o--

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

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

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

1 response to a single exposure of ETS.

2 --o0o--

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

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

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

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

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

4 ARB ASSOCIATE TOXICOLOGIST WINDER: Sure. There
5 we go.

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

8 --o0o--

9 ARB ASSOCIATE TOXICOLOGIST WINDER: These are
10 workers that are exposed for eight hours a day or more for
11 2 to 20 years. And what they report is there's a
12 significant difference between people so exposed and those
13 not exposed to ETS in terms of the same flow-mediated
14 dilatation.

15 --o0o--

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

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

25 CHAIRPERSON FROINES: How do they measure the

1 drop in --

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

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

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

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

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

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

25 It is also not so easy to tell from the tables

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

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

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

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

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

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

15 PANEL MEMBER GLANTZ: Pardon me?

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

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

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

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

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

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

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

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

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

22 And so it's --

23 PANEL MEMBER GLANTZ: Well, I think --

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

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

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

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

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

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

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

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

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

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

1 electrophilic and an oxidated stress processes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 (Laughter.)

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

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

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

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah,
12 right.

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

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

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

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

1 PANEL MEMBER HAMMOND: I didn't say that.

2 PANEL MEMBER BLANC: Stan.

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

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

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

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

14 So this is very well understood.

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

17 PANEL MEMBER GLANTZ: Maybe it isn't --

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

23 PANEL MEMBER GLANTZ: Right, those --

24 CHAIRPERSON FROINES: They are not health
25 outcomes.

1 PANEL MEMBER GLANTZ: No --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Um-hmm.

25 CHAIRPERSON FROINES: Joe.

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

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

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

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

11 PANEL MEMBER GLANTZ: Well, see, I --

12 PANEL MEMBER HAMMOND: Maybe a new table would --

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

17 You know, the --

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

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

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

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

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

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

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

19 CHAIRPERSON FROINES: Well, I can accept that.

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

22 (Laughter.)

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

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

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

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

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

15 PANEL MEMBER BLANC: Yes.

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

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

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

23 PANEL MEMBER BLANC: No.

24 PANEL MEMBER HAMMOND: No? Okay.

25 (Laughter.)

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

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

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

1 in this report.

2 It's different than having a heart attack.

3 CHAIRPERSON FROINES: Joe.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 PANEL MEMBER BLANC: For what?

9 ARB ASSOCIATE TOXICOLOGIST WINDER: For the
10 atherosclerosis.

11 We're looking for it here.

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

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

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

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

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

8 PANEL MEMBER GLANTZ: Yes.

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

13 PANEL MEMBER GLANTZ: Right.

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

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

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

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

1 talked about before.

2 I mean the report will -- I mean I won't vote
3 against the document if this is taken out. But I think
4 it's an important thing to keep in there. But I've said
5 this five times. Let --

6 CHAIRPERSON FROINES: I think we're talking more
7 about the structure of the chapter rather than the --

8 PANEL MEMBER GLANTZ: Right. And I can work with
9 Melanie to clarify this.

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly.

11 PANEL MEMBER GLANTZ: If it's all mixed up
12 together, it shouldn't be.

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: It looks
14 like, just paging through, first we did the epi studies on
15 heart disease risk, then we got into more epi studies that
16 were looking at slightly different things, and then we
17 started getting into the pathophysiology. Some of it
18 should probably have been moved into a different section.
19 I think it's pretty easy to do.

20 And then I have a suggestion about the table that
21 it hopefully would make Stan happy and Paul happy and
22 others happy. That if we -- instead of calling it --

23 (Laughter.)

24 PANEL MEMBER BYUS: Are you going to make me
25 happy?

1 (Laughter.)

2 OEHHA SUPERVISING TOXICOLOGIST MARTY: You know,
3 instead of just saying altered vascular properties, which,
4 you know, you can argue whether that's a clinical effect
5 or not -- it's certainly a subclinical effect -- we might
6 want to just say other toxic effects dash vascular -- or
7 cardiovascular system, and then indicate that these were
8 human studies, short-term exposures, they do see acute
9 effects. And then keep the discussion we have in here
10 about how that might be related to triggering an acute
11 coronary event.

12 Would that be better?

13 PANEL MEMBER HAMMOND: I certainly think Section
14 8.1 could be divided up. It is a very long section. And
15 if you divided it up and put a few subtitles, I think that
16 that might help.

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: A lot.

18 CHAIRPERSON FROINES: I guess I'm still the
19 person who would argue that there are effects that you
20 measure that have relevance to the mechanism that I
21 wouldn't classify necessarily as a subclinical effect.

22 The inhibition of various enzymes by lead may
23 lead to subclinical effects like --

24 PANEL MEMBER GLANTZ: -- hypertension. That was
25 the report.

1 CHAIRPERSON FROINES: But I wouldn't call the
2 inhibition of the enzymes nor the oxidation of LDL nor the
3 inhibition of nitric oxide synthase nor the Glutathione
4 GSSG ratio, all those things, I wouldn't classify those as
5 subclinical effects. Those are at a stage before. And
6 I'm arguing that it's a -- that what we wanted in the long
7 run is to be able to combine the various steps of the
8 process that ultimately lead you to the heart attack. And
9 the complicating feature about cardiovascular disease is
10 the chronic versus acute elements of it that add
11 complexity to it.

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I
13 think that -- you know, part of the problem might be the
14 way we put together the presentation, because we're -- we
15 talk about it in the summary as a mechanistic basis for
16 some of these observations might be this compromise
17 anti-oxidant defenses and so on.

18 There are clearly studies that we're talking
19 about that directly measured vascular properties. And
20 that's in a class in itself. But that the rest could be
21 by the miscellaneous.

22 CHAIRPERSON FROINES: Well, then I would put a
23 section on saying mechanisms -- mechanistic studies that
24 enhance our understanding of the ultimate health outcomes,
25 and not necessarily just throw it in as a sentence or two

1 in the conclusion.

2 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We
3 can do that.

4 PANEL MEMBER BLANC: What you might do as the
5 first step, Melanie, is add a -- before you divide up the
6 first huge table -- that's not the first table, but the
7 big table -- into sub-tables, put in an extra column
8 there, which actually says what the health outcome is that
9 this study is -- or health outcomes if it looked at more
10 than one. See if you have a sense of what the actual
11 health endpoint was. Was it acute MI? Was it
12 atherosclerosis, you know, measured angiographically or
13 radiographically? I mean what was it?

14 And then once you do all that, then why don't you
15 see. Because what you've got -- what you're promising the
16 reader in Table 8.0 is that you now have 18 plus 11
17 studies of coronary heart disease. And I guess that's the
18 term that you used before, so that's the term you want to
19 use now?

20 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. We
21 did that to avoid confusion.

22 PANEL MEMBER BLANC: Instead of atherosclerotic
23 heart disease or coronary artery disease or -- it's not
24 the most common term.

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: No, it's

1 not. But it sort of lumps those things together.

2 We do have, I might note, on Table 8.1 an
3 "outcome" column. So it does have like MI --

4 PANEL MEMBER HAMMOND: Well, that's the
5 numbers --

6 OEHHA SUPERVISING TOXICOLOGIST MARTY:

7 -- death --

8 PANEL MEMBER BLANC: Anyway, and then you promise
9 the reader six previous studies about altered vascular
10 properties with nine additional ones, which makes you go
11 from suggestive to conclusive. That's your big change,
12 right, in this chapter?

13 So maybe one of the reasons I focused on it is
14 because it is the one that you're going to have to defend
15 the most. And it seems to be a bit of a grab bag. There
16 is heterogeneity views here clearly on whether or not that
17 is a health condition or whether it is an important series
18 of studies that need to be included and need to be
19 analyzed but aren't in and of themselves a health outcome.
20 And partly you're locked into it because I guess the last
21 document was structured that had this, and so you didn't
22 really think much about it. You just went forward and did
23 again what you did last time.

24 And maybe what in the end will solve the problem
25 will be a paragraph in the introduction which says, "We

1 recognize that altered vascular properties are not in and
2 of themselves a health outcome. However, we have treated
3 them for the purposes of this analysis partly because they
4 were treated that way in the last document and we wish to
5 be consistent and avoid confusion that might arise by
6 combining it with others, and also because it is relevant
7 to two types of outcomes that we can't tease out
8 effectively from the epidemiologic data. One is chronic
9 coronary artery disease and the other is acute
10 exacerbation of preexisting coronary artery disease."

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I
12 think that's good.

13 PANEL MEMBER BLANC: "We have one epidemiologic
14 study which is quite relevant to that which we'll be
15 discussing at some length, as you will see in Section
16 8.3," blah, blah, blah, blah, blah.

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Another
18 thing is we could have two separate tables, outcomes CHD
19 and stroke, which are clear, and then a separate table
20 talking about altered vascular properties in exercise
21 tolerance. I'm not sure exercise tolerance would be
22 considered a --

23 PANEL MEMBER HAMMOND: You don't have anything --
24 you have nothing to put into that --

25 OEHHA SUPERVISING TOXICOLOGIST MARTY: -- disease

1 or --

2 PANEL MEMBER HAMMOND: -- you have nothing to put
3 into that table.

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah,
5 we --

6 PANEL MEMBER HAMMOND: Because there are no new
7 studies.

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: There's no
9 new studies. But we want to report what we did before and
10 so on.

11 PANEL MEMBER BLANC: Would you live with that,
12 Stan?

13 PANEL MEMBER GLANTZ: Yeah, I mean, well, I'll --
14 I mean they definitely shouldn't be all mixed up.

15 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

16 CHAIRPERSON FROINES: There is a difference
17 between some of the biochemical things --

18 PANEL MEMBER GLANTZ: Yes.

19 CHAIRPERSON FROINES: -- and the altered vascular
20 properties. I mean -- so there are stages on the
21 gradient.

22 PANEL MEMBER GLANTZ: Right. No, I think this
23 can be -- I think --

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: We can fix
25 it.

1 PANEL MEMBER GLANTZ: We'll work together and
2 come back with something that will hopefully make
3 everybody happy.

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We
5 can keep going on the presentation.

6 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now,
7 based on the idea that this ETS is causally associated
8 with myocardial infarction, in '97 you see the estimates
9 up here for excess cardiovascular death, both for
10 California and the U.S. And in our update we're
11 indicating about 1700 to 5500 deaths in California and
12 roughly 23,000 to about 70,000 in the U.S.

13 These are based on -- the range here is based on
14 a lower odds ratio of about 1.2 and the upper one
15 roughly -- what is it? -- 1.6, 1.8.

16 CHAIRPERSON FROINES: Can I just quickly go back
17 to the previous debate and discussion.

18 When you work on this Stan and get something
19 drafted, can I take a look at it? Because we're working
20 on cardiovascular disease and air pollution all the time.
21 And I just for personal reasons would be interested in
22 what we're doing versus what you're writing about, because
23 I think there are things that overlap.

24 Go ahead. Sorry.

25 PANEL MEMBER HAMMOND: On this table, I think --

1 when I first saw this I was going like "huh?" There's
2 some things that seem strange. Because if you look at the
3 U.S. numbers, the numbers go lower and higher than the '97
4 estimates; whereas the California numbers go lower and
5 lower. But actually then I thought about it some, and I
6 had some idea of why. But I think it's worthwhile
7 discussing those reasons. You know, in other words,
8 part -- certainly in California the estimates for lower
9 risks relate partly to the fact that there are fewer
10 people exposed now to secondhand smoke, right?

11 ARB ASSOCIATE TOXICOLOGIST WINDER: Uh-huh.

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

13 PANEL MEMBER HAMMOND: So I think -- but it's
14 important to say that and to say how that's done.

15 And I'm not quite sure why the -- and I think
16 there's also an underlying lower rate of death from heart
17 disease. I don't know if that's true from '97. But, you
18 know, the trends have been lower. So that's another
19 reason that this goes down. But that should have then
20 made the U.S. numbers go down. So I'm not sure why the
21 U.S. interval becomes wider. Is there a wider confidence
22 interval in the actual understanding of the point estimate
23 of the relative risk or --

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes,
25 the --

1 PANEL MEMBER HAMMOND: And so I just think it's
2 worth -- you know, what are the contributors to make these
3 numbers change? Because its confusing to look at it
4 first.

5 ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, we can
6 add some clarity to that.

7 PANEL MEMBER HAMMOND: I mean I have all these
8 thoughts in my own head. But I think it should just be
9 there.

10 --o0o--

11 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now,
12 if we look at these studies regarding stroke, here we have
13 two studies, one by You, et al., one by Bonita.

14 The study by You, et al., is a case control
15 study. And the one by Bonita is looking at all forms of
16 stroke, both fatal and nonfatal.

17 And what they show is that -- with respect to
18 You, spousal smoking, that is to say exposure to ETS from
19 the spouse, is associated with -- significantly associated
20 with stroke in this whole group. Now, whole group in this
21 particular instance also included active smokers.

22 The ever smokers, this -- you see the ever
23 exposed on the left-hand side. And it's making reference
24 to just ETS exposure. So You, et al., finds that among
25 just ETS exposed there is an elevated risk that is now

1 significant. Whereas for the whole group, which includes
2 those ex-smokers, stroke is in fact elevated.

3 Bonita on the other hand finds that from both men
4 and women there is a significant elevation in the risk of
5 strokes associated with ETS exposure.

6 Now, this is -- the involvement of ETS is further
7 emphasized over here on the right. This is an analysis
8 looking at the effect of active smoking on stroke risk in
9 comparison to nonsmokers with and without ETS versus
10 nonsmokers totally without ETS.

11 And the important point here is that when your
12 referent group has no ETS exposure at all, the risk is
13 substantially higher, as opposed to this estimate in which
14 the ETS -- or, excuse me -- the referent group includes
15 those exposed to ETS. So this again supports the role of
16 ETS in the stroke risk.

17 PANEL MEMBER HAMMOND: And I guess I would just
18 ask how -- is the comparison group in the You or the
19 Bonita for the passive smoking -- is the comparison a
20 group of people who its well established don't have ETS
21 exposure?

22 ARB ASSOCIATE TOXICOLOGIST WINDER: Not terribly
23 well.

24 PANEL MEMBER HAMMOND: And I think that's
25 worth -- I think that's a message that needs to kind of

1 keep bringing brought out. When the comparison group
2 probably has some ETS exposure, we need to say that.

3 ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, that's
4 the reason we pointed out this right here.

5 But you're right, I need to emphasize it more for
6 You.

7 PANEL MEMBER HAMMOND: Well, I would assume that
8 in that. But that's what I couldn't tell is looking -- at
9 least from this, you know.

10 So that if you look at the -- the NS there is
11 nonsmokers?

12 ARB ASSOCIATE TOXICOLOGIST WINDER: That's
13 correct.

14 PANEL MEMBER HAMMOND: It's all nonsmokers?

15 ARB ASSOCIATE TOXICOLOGIST WINDER: In this
16 particular -- this one is all nonsmokers.

17 PANEL MEMBER HAMMOND: No, to the left.

18 ARB ASSOCIATE TOXICOLOGIST WINDER: Oh, over
19 here.

20 PANEL MEMBER HAMMOND: Are these -- I'm confused
21 what those three bars are. Are those --

22 ARB ASSOCIATE TOXICOLOGIST WINDER: Oh, okay.
23 These are nonsmokers. This is men and women. And all
24 I've done here is separate out the men.

25 PANEL MEMBER HAMMOND: And they're non -- this is

1 ETS exposed nonsmokers compared to -- or is this
2 nonsmokers married to smokers compared to nonsmokers not
3 married to smokers?

4 ARB ASSOCIATE TOXICOLOGIST WINDER: Well, it
5 includes that. And I believe it's ETS exposed work and
6 home.

7 PANEL MEMBER HAMMOND: Work and home?

8 ARB ASSOCIATE TOXICOLOGIST WINDER: Yes.

9 PANEL MEMBER HAMMOND: Okay. So it's at least a
10 little better effort to deal with.

11 ARB ASSOCIATE TOXICOLOGIST WINDER: Right. But
12 you're right in terms of the comparison group. It's--

13 PANEL MEMBER HAMMOND: But I think it's an
14 important message that could be carried through the
15 document. Kind of the stage can be set in Part A, you
16 know, that the comparison group is very important. Pick a
17 few of the good examples, even within -- maybe Part A
18 could add that in too to say how important the exposure
19 assessment is. But the comparison -- you're absolutely
20 right, the bars to the right and earlier in the breast
21 cancer used similar information that when you compare
22 smokers to all nonsmokers or to nonsmokers who also have
23 no passive smoking, you get different results implies that
24 there's an effect from the passive smoking. And I think
25 all studies should always be looked at in terms of how

1 good is the comparison -- how clean is the comparison
2 group.

3 PANEL MEMBER BLANC: When you did your key word
4 search in terms of stroke, what were the words that you
5 used?

6 ARB ASSOCIATE TOXICOLOGIST WINDER: Stroke,
7 ischemic, and hemorrhagic. And then picked out many
8 others that were just -- that came up in searching for ETS
9 and cardiovascular effects, since many papers showed up in
10 that kind of search.

11 PANEL MEMBER BLANC: And you use CVA, cerebral
12 vascular accident?

13 ARB ASSOCIATE TOXICOLOGIST WINDER: No.

14 PANEL MEMBER BLANC: And did you use amaurosis
15 fugax?

16 ARB ASSOCIATE TOXICOLOGIST WINDER: No.

17 PANEL MEMBER BLANC: Or carotid?

18 ARB ASSOCIATE TOXICOLOGIST WINDER: No.

19 PANEL MEMBER BLANC: Just as a double check, I
20 think you -- it seems a -- the literature seems a little
21 sparse. There were two studies that came out in 1999.
22 You'd think somebody would have said, "Hmm, I have a data
23 set I can analyze for that outcome."

24 PANEL MEMBER GLANTZ: Yeah, I think -- I mean I
25 think that doing those extra red lines searches that Paul

1 suggests is a good idea. But I think it's pretty sparse
2 literature.

3 PANEL MEMBER HAMMOND: Actually the Whincup paper
4 has a stroke in it.

5 ARB ASSOCIATE TOXICOLOGIST WINDER: Yeah, They
6 did mention stroke.

7 PANEL MEMBER HAMMOND: Yeah, they have -- it's a
8 negative. They don't -- they actually had a negative
9 result, but the Whincup paper has stroke.

10 PANEL MEMBER GLANTZ: I don't think there's been
11 a lot done. I think it's worth doing those other checks,
12 but...

13 --o0o--

14 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Now,
15 with respect to responses to comments.

16 This is a comment from Lee. And hes' suggesting
17 that recent study show little association between spousal
18 smoke and CHD, especially two largest studies in 1995 and
19 2003.

20 Well, it was never specified in the comment to
21 what studies he was referring, but we can pretty well
22 guess it was probably either the LeVois & Layard paper of
23 '95 or just the Layard paper in '95 and Enstrom & Kabat's
24 paper in 2003.

25 Now, with these studies we have concern with

1 respect to misclassification. For example, with the
2 Enstrom & Kabat, they're looking at CPS data on a cohort
3 of women who are -- what they're effectively doing is
4 comparing women who allegedly are not exposed to spouse --
5 spousal smoking with women who are. But it doesn't take
6 into account ETS exposures outside the home and elsewhere.
7 So there's some question in mind as to how the control
8 group -- how exposed they are to ETS.

9 Furthermore, for example, in the LeVois & Layard
10 paper ex-smoking spouses are included in this study as
11 though they are continually smoking. Well, if they stop
12 in the process, this is going to skew the results toward
13 no effect.

14 In addition, in Layard's study the cases were
15 older than the controls. So had the controls lived as
16 long as the cases, maybe they would have become cases
17 themselves. So this particular difference in the ages
18 here is a concern with respect to their analysis.

19 And as I mentioned with respect to Enstrom &
20 Kabat, it seems very likely that the controls were
21 exposed. And at that point in time there's a lot of
22 smoking and a lot of ambient ETS exposure.

23 OEHHA SUPERVISING TOXICOLOGIST MARTY: 1959 was
24 their baseline.

25 PANEL MEMBER BLANC: These papers with these

1 limitations are cited and discussed in the document.

2 ARB ASSOCIATE TOXICOLOGIST WINDER: That is
3 correct.

4 --o0o--

5 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. LeVois
6 commented that the studies in the update do not find a
7 significant association with coronary heart disease.

8 Well, on the contrary, several studies,
9 Rosenlund, Ciruzzi and Whincup, all relatively recent, all
10 of which find significant association with respect to ETS.
11 And some are based on just report, some are based on serum
12 cotinine. And, again, it's a significant association in
13 all three.

14 The comment in the stroke studies by Bonita and
15 You, et al., have severe limitations. And as we indicate
16 up here, that's part of the reason that we think that
17 these studies should be considered as suggestive of an
18 association. But they're nothing upon which we can base
19 any conclusion of causality.

20 --o0o--

21 ARB ASSOCIATE TOXICOLOGIST WINDER: And this
22 particular comment by LeVois is risk from ETS is close to
23 active smoking risk at a fraction of the exposure.

24 Well, this is one of the things that's come up
25 earlier in the discussion of carcinogenesis. And that's

1 the idea that ETS is not just diluted mainstream smoke.
2 They're different constituents. With respect to the heart
3 disease, perhaps some with the most interest are carbon
4 monoxide, PAH's, and nicotine. They happen to be higher
5 in the side-stream smoke.

6 Furthermore -- and again this has been alluded to
7 earlier in the morning regarding the dose response
8 effect -- the CHD response to smoking is nonlinear. So
9 that at low levels a fairly small increase in the amount
10 of exposure results in a relatively high increase in
11 effect. Whereas at higher levels of exposure, this seems
12 to plateau.

13 Also we've mentioned this morning regarding the
14 nature of the particles to which we're exposed. Now, in
15 ETS the particulates tend to aggregate less than in
16 mainstream smoke. So that these -- in ETS-exposed
17 individuals are getting better penetration in the lungs by
18 these smaller particles with whatever is on those
19 particles.

20 PANEL MEMBER HAMMOND: I'm not sure I find that
21 argument convincing.

22 What size do the mainstream aggregate to?

23 ARB ASSOCIATE TOXICOLOGIST WINDER: I don't know
24 the aerodynamic size right now. But the studies read
25 indicate or tend to aggregate such that they precipitate

1 or deposit in the upper airways better than the more
2 dilute ETS smoke does.

3 PANEL MEMBER HAMMOND: I guess, you know -- the
4 other thing is ETS particles tend to aggregate to about
5 .3, which is like the hardest size to deposit. It's the
6 least likely to deposit, and so it's actually going to be
7 exhaled. So you actually exhale a higher percentage of --
8 I mean I think that's a difficult argument to go down. I
9 think it's a complex issue and I'm not sure I would find
10 that really compelling, because there are other studies
11 that show that a smaller percentage a ETS particles
12 actually get deposited in the lung. And it's not the
13 penetration. It's the deposition that matters.

14 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. And to
15 what extent in terms of exchange of material is adhering
16 to those particles is observed in, for example, ETS versus
17 mainstream?

18 PANEL MEMBER HAMMOND: Well, I'm just saying -- I
19 can't answer that right now. I'm saying it's very
20 complex. I think it's taking a one-dimensional approach
21 to a multi-dimensional problem. So if you want to pursue
22 that argument, I think you have to pursue all those
23 aspects.

24 ARB ASSOCIATE TOXICOLOGIST WINDER: Sure. Okay.

25 Now, further in this development we find that

1 cells respond differently to ETS versus mainstream smoke
2 in the study by Wong, et al., in 2004.

3 This was kind of an interesting study in that
4 the -- in many respects the mainstream-smoke-exposed cells
5 tended to be more like the unexposed, whereas the ETS
6 cells were radically different.

7 This is suggesting that the different cell types
8 will have a very different response to ETS --

9 PANEL MEMBER GLANTZ: What kind of cells are
10 these?

11 ARB ASSOCIATE TOXICOLOGIST WINDER: I believe
12 these were fiberglass.

13 PANEL MEMBER GLANTZ: Pardon me?

14 ARB ASSOCIATE TOXICOLOGIST WINDER: I think they
15 were fiberglass.

16 At least I think so.

17 And then --

18 CHAIRPERSON FROINES: This one seems a little
19 abstract to me.

20 PANEL MEMBER HAMMOND: Can you explain that --
21 explain this bulletin.

22 CHAIRPERSON FROINES: When you say respond --

23 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. What
24 Wong, et al., were doing was taking and creating a
25 solution of mainstream smoke, so they have this extract in

1 solution, as well as an extract of ETS in solution. And
2 they were exposing cells in culture to both these kinds of
3 solutions in addition to controls, and then looking at
4 various properties of that exposure.

5 CHAIRPERSON FROINES: Like what?

6 OEHHA SUPERVISING TOXICOLOGIST MARTY: They
7 looked at the cells microscopically, in particular looking
8 at the endoplasmic reticulum, which in control cells was
9 well developed, concentrated around the nucleus.

10 In cells exposed to side-stream smoke containing
11 media they showed punctate staining, reflecting
12 fragmentation and coalescence of the endoplasmic reticulum
13 around the nucleus. Whereas the endoplasmic reticulum in
14 cells exposed to the mainstream smoke looked more like
15 that of the control cells.

16 They also looked at the integrity of Golgi
17 vesicles.

18 And they looked at the distribution of the
19 chemokine IL8 compared to control and mainstream smoke.
20 And the mainstream smoke looked in both cases more like
21 the control cells. And the side-stream smoke had a higher
22 level of effect.

23 PANEL MEMBER BLANC: Wouldn't it just be simpler
24 to say that "We acknowledge that the relationship between
25 the risks consistently associated with ETS and the risks

1 associated with direct smoking in terms of cardiovascular
2 outcomes are not directly proportional. However, there
3 are multiple plausible biological reasons why this maybe
4 the case and we do not find it necessary to find a
5 proportional and linear dose response in order to support
6 this effect."

7 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

8 PANEL MEMBER BLANC: "And briefly we refer you to
9 a series of articles about the" -- "series of sources
10 about the make-up and potential biological effect
11 difference between these two mixes"?

12 PANEL MEMBER GLANTZ: Yeah, I think --

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think
14 that's actually the gist of our response in the report.

15 PANEL MEMBER GLANTZ: Yeah, I think -- I'd like
16 to agree with Paul. I think all you need to say here -- I
17 think the Law & Wald paper from 2003 deals with that issue
18 quite, you know, directly at least in terms of platelet
19 activity. And Terry Pechacek and Stephen Babb from the
20 CDC had an editorial in the BMJ commenting on the Helena
21 study, where they dealt -- it was almost like a -- it
22 wasn't an editorial. It was like a little review dealing
23 with exactly this issue of the nonlinear dose response
24 relation and bringing in a lot of the stuff that had been
25 published since then.

1 And I think if you just go to those two papers,
2 that answers the question, rather than trying to build up
3 the argument yourself.

4 CHAIRPERSON FROINES: I agree with Stan and Paul,
5 Melanie, and Kathy for that matter. I think the last
6 three bullets up there are all complex issues. And you
7 just get yourself into a lot of speculation. And, you
8 know, they are probably very reasonable explanations for
9 the differences that they saw. There may have been some
10 cell death at the site of toxicity. There are all sorts
11 of reasons why things are different that have nothing to
12 do with what you're talking about.

13 So those last three bullets are the kinds of
14 things that I would say fit into the category that you can
15 refer to them but not really get into a discussion of
16 them, the way Paul -- I think Paul suggested.

17 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We
18 can go back and look at our response to that comment and
19 see how it plays out with respect to what Paul just said.

20 PANEL MEMBER BLANC: Can I just make a time
21 comment?

22 You know, unless the Panel members have a
23 specific comment, I think that there's some really
24 pressing things I'd like to discuss rather than going
25 through in this format with each and every one of your

1 point-by-point responses, you know, to these, you know,
2 consultant very voluminous comments. I understand that
3 it's your responsibility. And it's our responsibility to
4 overall see that your response is coherent, which I think
5 it is. We could tweak it here and there. But I think
6 that there are some more fundamental issues that warrant
7 our consideration today. If indeed you're going to be
8 most effective in your work in revising the document for
9 our forthcoming meeting.

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's
11 fine. We can stop here.

12 PANEL MEMBER BLANC: Is that okay with the
13 Chairman?

14 CHAIRPERSON FROINES: I agree and disagree. I
15 think Paul's point about speeding things along is fine. I
16 think that we also want to be sure that we have
17 addressed -- the Panel has seen how you addressed the
18 comments from the interested parties so that we have a
19 complete understanding of those comments so that we don't
20 give short shrift to the commenters.

21 So I think that to follow his model is fine. But
22 I don't think we should sacrifice the record in that
23 respect if we have --

24 PANEL MEMBER BLANC: No, I don't mean to
25 sacrifice the record. And I'll say for my part, looking

1 at your slides, which summarize your detailed responses to
2 the next 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 points by LeVois,
3 it seems as if you've given them very full and detailed
4 and legitimate consideration.

5 PANEL MEMBER GLANTZ: Can I --

6 PANEL MEMBER BLANC: And I feel fine that the
7 record could show that from my point of view.

8 PANEL MEMBER GLANTZ: Well, I've looked through
9 them too and think the same thing.

10 What I would suggest is that you go through them
11 quickly. And then if any member of the Panel has a
12 pressing point to make, we could make it. But I would try
13 to go through them quickly. I also while you were talking
14 looked through them. And I think a lot of the issues have
15 already been addressed actually in the discussion we've
16 had.

17 Why don't you just quickly run through them just
18 for the record and to make sure nobody notices something
19 that isn't obvious.

20 --o0o--

21 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Well,
22 as this comment here, they're suggesting that the
23 endpoints that we reported are not unique to ETS and may
24 not increase CHD.

25 And the point of this one is that in fact these

1 endpoints that we reported -- that are listed here are
2 supported by other researchers being associated with
3 cardiovascular disease.

4 And ETS increases the measurement of these
5 endpoint.

6 --o0o--

7 ARB ASSOCIATE TOXICOLOGIST WINDER: Says there's
8 a smoker misclassification likely in Rosenlund and most
9 ETS studies.

10 And we agree that it -- if you have a smokers in
11 control group, that would bias the results toward the
12 null.

13 And if smokers are in the exposed group, that
14 would inflate our apparent risk.

15 But the point is that these population-based
16 studies when they have studies looking at
17 misclassification level, this is generally relatively low.
18 In this case a study by Nyberg, et al., it's running 1.2
19 percent. And at that level if that's applicable to
20 Rosenlund, that wouldn't affect the results substantially.

21 PANEL MEMBER HAMMOND: And one other point that I
22 would add and, that is, that for heart disease the
23 relative risk is relatively small. Lung cancer, which
24 where you really have much more of a serious impact,
25 there's a high relative risk if you've got a smoker in

1 your exposed -- in your nonsmoker group that's exposed to
2 passive smoke. And that's going to have a significant
3 impact, but not when the relative risk is small. Even if
4 they're there, they're not going to have a significant
5 impact.

6 --o0o--

7 ARB ASSOCIATE TOXICOLOGIST WINDER: Here it's
8 saying Steenland, et al., were inconsistent in the
9 inclusion of ex-smokers.

10 This and the next slide they're mainly
11 criticizing Steenland's general analysis. But his
12 analysis included here three different -- or excuse me --
13 four different ones, three which looked at the effect of
14 the spousal smoking, which examined all source.

15 He tended to limit his analyses to those in which
16 the couples were both participating in CPS-II. So they
17 can validate the exposure both by self-report and by
18 spousal report. The idea is that this would tend to give
19 a more certain discrimination of who was actually exposed
20 and who wasn't. That analysis resulted in significant
21 risk.

22 Also the small increased CHD risk associated with
23 marriage to current smokers but not ex-smokers.

24 And then an increased risk with ETS from all
25 sources. But only home exposure in males was

1 statistically significant.

2 --o0o--

3 ARB ASSOCIATE TOXICOLOGIST WINDER: This says
4 here that Steenland's focus on never-smokers married to
5 current smokers at baseline ignores relevant data.

6 We're saying again that this -- he excluded
7 exposure to former smokers because CHD risk does appear to
8 drop rapidly after cessation of exposure. And in these
9 studies listed here, Steenland, Raitakari, and Rosenlund,
10 the risk decreases rapidly after cessation of exposure to
11 ETS as well.

12 --o0o--

13 ARB ASSOCIATE TOXICOLOGIST WINDER: It says here
14 the CPS-II data do not show evidence of decreased risk
15 after cessation of ETS exposure. So criticism of use of
16 ever-smokers is not justified.

17 The list is related to the slide before this.
18 And the CHD risk is attenuated after ETS exposure. So
19 including ex-smokers would tend to skew the results toward
20 the null.

21 --o0o--

22 ARB ASSOCIATE TOXICOLOGIST WINDER: Steenland's
23 analysis of concordant exposure data excludes subjects not
24 reporting home ETS which likely meant no ETS exposure.
25 Therefore the data did not reflect true CPS-II exposures

1 and the analyzed subjects may be a biased subset.

2 Well, this is speculation on the author's part
3 because the analysis of the concordant data was only one
4 of several analyses. And these several analyses did find
5 significant associations. But it's also the analysis it
6 would be most likely to give the least misclassification.
7 And that the assertion of the data represent no ETS
8 exposure is just speculation.

9 --o0o--

10 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. This
11 is the Enstrom & Kabat studies. Analysis of CPS-I data
12 for California may be more valid than the studies based on
13 CPS-II.

14 Well, as I mentioned on one of the earlier
15 slides, we have some real concerns about the background
16 exposure to ETS in that group that was analyzed by Enstrom
17 & Kabat. And that when you -- there's several curious
18 things about this study. And one example is that the
19 spousal smoking in that study reportedly increased with
20 education, which is contrary to what most studies find, in
21 that individuals with more education tend to smoke less.

22 --o0o--

23 ARB ASSOCIATE TOXICOLOGIST WINDER: Okay. Oh,
24 yeah, this is the same group.

25 Further in that study by Enstrom & Kabat there

1 was no update on the spousal smoking during this 26 years
2 of follow-up from 1972. So this has the same problem that
3 we've reported on many of these other studies that says
4 exposure at baseline and then not during the follow-up.
5 So we figured there maybe substantial chance of
6 misclassification there.

7 The age of the never smoking women at baseline in
8 that study decreased with increasing spousal exposure --
9 spousal smoking.

10 Well, this is important because during the study
11 period the CHD mortality in general fell about 5 percent
12 for every four years. So as a result of these women being
13 younger that had the higher ETS exposure, that effect
14 would be counteracted by the fact that there's a decreased
15 CHD mortality compared to the older controls. And we
16 would not expect that the control for age in this study
17 would necessarily compensate for that. So we have some
18 concerns that the results were biased or nil.

19 --o0o--

20 ARB ASSOCIATE TOXICOLOGIST WINDER: This comment
21 says weight of evidence for causal ETS-CHD association has
22 gotten weaker. Our report ignores studies not supporting
23 the conclusion. And laboratory studies are not convincing
24 regarding mechanisms.

25 We disagree. We say on the contrary that newer

1 studies do continue to support a causal association. And
2 we cite here, for example, the Whincup study.

3 We mention here the fact the study by Wong, et
4 al., suggesting a difference between ETS versus some
5 mainstream smoke.

6 And we think the studies that they're concerned
7 that we're ignoring are the ones by Le Vois and Layard
8 that, as we mentioned before, have some serious concerns
9 about the program.

10 OEHHA SUPERVISING TOXICOLOGIST MARTY: In which
11 we did not ignore. They're in the document.

12 And that's it for Chapter 8.

13 PANEL MEMBER BLANC: I'd like to ask -- I know
14 that there was discussion at this point switching to the
15 ARB presentation relating to Part A, I guess it is? The
16 exposure assessment?

17 But I would like to make a request to the group
18 if we could have the discussion which I assume did not
19 happen this morning on the general approach to causality,
20 suggestiveness and inconclusiveness, unless I missed it.

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: It didn't
22 happen. We have a --

23 PANEL MEMBER BLANC: That it happen now, because
24 I'm probably not going to be able to remain here until 4
25 o'clock.

1 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. We
2 have just a few slides relevant to that.

3 PANEL MEMBER BLANC: If that's okay, with the
4 Chair's indulgence.

5 CHAIRPERSON FROINES: I'm afraid so. I know --
6 hopefully we can finish this in a half hour and have an
7 hour for Jeanette.

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: It should
9 be fairly quick.

10 CHAIRPERSON FROINES: We certainly -- I think
11 that it's important, but I think we can probably get
12 through it.

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: This
14 primarily relates to our description of -- no, we do not
15 have handouts, I'm sorry to say. We weren't sure we were
16 going to actually even talk about this today.

17 But it basically goes to Chapter 1's description
18 of what we are saying is the basis for describing
19 something as causal. And I'm looking for that.

20 It's on page 1-9 in the gray-covered document.

21 And the bottom paragraph of page 1-9 we
22 somewhat -- we're somewhat short in our description. Dr.
23 Blanc sent us a document from the Institute of medicine,
24 which said it much more clearly, and which we feel is
25 certainly applicable to how we looked at all of these

1 studies. So we are suggesting adding a few sentences to
2 that paragraph on the bottom of page 1-9.

3 (Thereupon an overhead presentation was
4 Presented as follows.)

5 OEHHA SUPERVISING TOXICOLOGIST MARTY: And this
6 slide, the first sentence is what is already in the
7 document. And the second italicized sentence is what we
8 want to add, which we think more clearly states what we
9 actually did when we looked at all of the studies.

10 So what we're saying is it's causally associated
11 when there's a positive relationship and the effect can't
12 really be attributed to chance, bias, or confounding. The
13 sentence you want to add is: "The evidence must be
14 biologically plausible and satisfy several of the
15 guidelines used to assess causality such as strength of
16 association, dose response relationship, consistency of
17 association, and temporal association."

18 So I think that makes it more -- makes it a
19 little clearer what we've done.

20 --o0o--

21 OEHHA SUPERVISING TOXICOLOGIST MARTY: IOM has a
22 few more layers than we actually used when we were looking
23 at these studies. We have conclusive, suggestive,
24 inconclusive.

25 The bottom part of that page starts where we

1 discussed when we say something is effect that we consider
2 to be suggestive. And that is for which you could
3 interpret it as causal. That could be credible. But we
4 don't have the same amount of confidence that chance, bias
5 or confounding is not playing a large role.

6 So we added two more sentences there to indicate
7 what we mean by that. So, for example, at least one high
8 quality study reports a positive association that is
9 sufficiently free of bias, including adequate control for
10 confounding. Alternatively several studies of lower
11 quality show consistent positive associations and the
12 results are probably not due to bias and confounding.

13 So, you know, hopefully that is a little bit
14 clearer description of how we differentiated between a
15 causal effect and a body of evidence where it's suggestive
16 of an association.

17 PANEL MEMBER FRIEDMAN: The first sentence in
18 italics sounds like it could be consistent with a causal
19 association. I think it would help me if you specified
20 what's missing -- what is missing that would make that not
21 be a -- regarded by you as a causal association? You mean
22 the fact that the criteria such as strength and so on were
23 not considered or --

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, they
25 may have been considered but may not have satisfied

1 several of the guidelines. So, for example, if we're
2 talking about a causal association, we have some
3 biological plausibility evidence and we also have the
4 strength of association, dose response, consistency and
5 temporal association all satisfied.

6 PANEL MEMBER FRIEDMAN: So I think it would help
7 me if you said in terms of the suggested one that, "but it
8 lacks those things."

9 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. So
10 make a clearer differentiation.

11 --o0o--

12 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, what
13 we're saying is that I think we can't really rule out
14 chance, bias or confounding.

15 PANEL MEMBER BLANC: What does rule out mean to
16 you?

17 PANEL MEMBER FRIEDMAN: When you say one high
18 quality study, you know, is free of bias and has
19 controlled confounding, that sounds pretty persuasive to
20 me. So what's missing?

21 PANEL MEMBER BLANC: Multiple studies.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Multiple
23 studies, exactly. To some -- you know, if you have one
24 study it's really hard to hang your hat on it.

25 PANEL MEMBER FRIEDMAN: You said that there's

1 only one study or something --

2 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right, if
3 you have study. But it's pretty hard to hang your hat on
4 it, particularly if you have other studies that didn't
5 show that effect.

6 PANEL MEMBER HAMMOND: So I guess -- yeah, I
7 mean -- I agree with Gary. I think you do have to be a
8 little clearer. So whether it's to say, for example, one,
9 only one, rather than at least one high quality study? Or
10 is it that, for instance, it doesn't suit -- if you go
11 back a slide, it doesn't suit biologic plausibility or it
12 doesn't answer several -- it does not in fact answer
13 several of these guidelines, is that what you're saying?

14 OEHHA SUPERVISING TOXICOLOGIST MARTY: That's
15 basically what we're saying.

16 PANEL MEMBER HAMMOND: So maybe it's -- and
17 actually I think strength of association I think is
18 becoming, to my mind -- I know that's been out there for a
19 long time. But I think that we're kind of moving beyond
20 that now. We're looking at low level effects. And I
21 don't think that one has to have a relative risk of five
22 for it to be believable. And I actually feel that that's
23 an old criteria that is no longer valid.

24 OEHHA SUPERVISING TOXICOLOGIST MARTY: But I
25 think --

1 PANEL MEMBER FRIEDMAN: But it does -- a low
2 relative risk does leave open a greater chance of
3 confounding, explaining it. So I think in your --

4 PANEL MEMBER HAMMOND: But if people have
5 addressed it, that's what you have to look at.

6 PANEL MEMBER FRIEDMAN: Right. I think it has to
7 be addressed. We still believe it even though it's low
8 level because --

9 PANEL MEMBER HAMMOND: You certainly have to do
10 more to address those issues when it's a low level. But I
11 don't think strength of association is actually as
12 important as some other issues.

13 PANEL MEMBER FRIEDMAN: If it's there it's just
14 like -- like CRAIG was saying for a dose response, if it's
15 there it really helps a lot.

16 CHAIRPERSON FROINES: Wait, wait, wait, Kathy. I
17 want to stop.

18 We have one issue on the table, which is the
19 difference between 1 and 2.

20 PANEL MEMBER HAMMOND: That's what I'm talking
21 about.

22 CHAIRPERSON FROINES: I know. But people are now
23 into the details. And I want to talk about dose response
24 obviously. And so -- but I'm holding back. I think we
25 should address this issue of what's the difference between

1 1 and 2 and then move on to the other topics, like
2 strength of association.

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I
4 think that the number of studies clearly always comes into
5 play, the number and quality of the studies. We
6 already --

7 CHAIRPERSON FROINES: But what is the --

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: We've
9 already described that in the paragraph above when I'm
10 talking about that.

11 CHAIRPERSON FROINES: What does the number mean?
12 Because with diesel we had 50 studies, and we've made
13 decisions on methylene chloride with one study. And so I
14 don't know what more than one study means unless you mean
15 confirming study or -- or what are the criteria?

16 OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. Let
17 me read the paragraph above that on page 1-9, and maybe
18 that will help people understand what we're saying.

19 We say, "A weight of evidence approach has been
20 used to describe the body of evidence on whether or not
21 ETS exposure causes a particular effect. Under this
22 approach the number and quality of epidemiological studies
23 as well as other sources of data on biological
24 plausibility are considered in making a scientific
25 judgment. Associations that are replicated in several

1 studies of the same design or using different
2 epidemiological approaches or considering different
3 sources of exposure are more likely to represent a causal
4 relationship than isolated observations from single
5 studies.

6 If there are inconsistent results among
7 investigations, possible reasons are sought such as
8 adequacy of sample size for a control group, methods used
9 to assess ETS exposure, range and levels of exposure. And
10 results of studies judged to be of high quality are given
11 more weight than those of studies judged to be
12 methodologically less sound.

13 "General considerations made in evaluating
14 individual studies include study design, appropriateness
15 of the study population, methods used to ascertain ETS
16 exposure as well analytic methods such as the ability to
17 account for other variables that may potentially confound
18 the ETS effect.

19 "Increased risk with increasing levels of
20 exposure to ETS is considered to be a strong indication of
21 causality, although absence of a graded response is not
22 necessarily evidenced against a causal relationship."

23 And then we would have these two sentences and
24 then those sentences. So, you know, I -- we don't want to
25 sit here and say you have to have ten studies or you have

1 to have five studies or you have to have thirty-five
2 studies. You know, it's clear that there is some judgment
3 based on the science that goes into your decision.

4 PANEL MEMBER BLANC: For practical purposes now
5 in retrospect though, can't you go back, look at all of
6 your decisions and say there is no -- the minimal number
7 of studies that we have used to classify any health
8 endpoint as causally related in this document is 5, is 7,
9 is 4, whatever it is? Isn't there some minimum if you
10 actually went through?

11 OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, we
12 have the number of studies that have been considered both
13 in the '97 report and this report. I mean we could go
14 back and say, yeah, there was a minimum of 15 or whatever
15 it is.

16 PANEL MEMBER HAMMOND: I would be careful though.
17 I think you want this statement to stand for other risk
18 assessments you do for other materials. So, you know, as
19 John said, you might have another compound for which you
20 have one superb study that looks fabulous and fulfills
21 every criteria you can think of. And you don't want to
22 say that you're locked in because we happen to have five
23 wonderful studies here, as we set five as the criteria.

24 Well, you should do it intellectually like what
25 you think is actually necessary to come to that

1 conclusion.

2 PANEL MEMBER BLANC: I'd sort of take a middle
3 ground, where I would do one but I would leave the door
4 open that, you know, just doesn't preclude that, you know,
5 fewer studies might serve that purpose. But there's
6 certainly not a scenario where you see where one study in
7 fact would be sufficient; is that correct?

8 OEHHA SUPERVISING TOXICOLOGIST MARTY: I wouldn't
9 be comfortable with that.

10 PANEL MEMBER BLANC: Would two?

11 PANEL MEMBER BYUS: I disagree. I think one --
12 these days, especially with these low risk studies, one
13 large study funded could be conclusive, and it would be
14 virtually impossible to reproduce --

15 CHAIRPERSON FROINES: Well, we made a decision
16 to --

17 PANEL MEMBER BYUS: -- if it was good. You know
18 what I mean?

19 CHAIRPERSON FROINES: We accepted the risk
20 assessment for naphthalene based on one health input in
21 animals.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Right. I
23 think that's a different -- that's a different issue. Are
24 we talking about risk assessment now or are we talking
25 about epidemiologically?

1 CHAIRPERSON FROINES: No, but the committee also
2 was saying that the qualitative evidence of it being a
3 toxic air contaminant was adequate, you know. I mean in
4 other words the qualitative issue was being dealt with as
5 well as the quantitative one.

6 PANEL MEMBER HAMMOND: Actually -- I mean that
7 gets -- your comment just got me to think about it. This
8 is a section on weight of the evidence. So it's not like
9 just what epidemiologic studies are sufficient to make a
10 judgment, as is implied in your italicized section here.
11 We add to the epidemiology other data such as toxicology
12 data, which is biologic plausibility -- I mean there are
13 many other things that go into it.

14 It is there. It's in your -- or it's been one
15 before. I'm sorry. I'm in the wrong slide. But in the
16 conclusive one, italicized section.

17 But it actually -- and that's when I think of
18 weight of evidence is were adding epidemiology,
19 toxicology, all our knowledge of the world. And yet the
20 way it's written actually here -- and, you know, the
21 discussion is focused very much in epidemiology. Of
22 course it's important. But I think it's important to keep
23 this sense that one good epidemiology study along with
24 good senses of biologic plausibility, a dose response
25 function, consistency of -- you know, all these -- if all

1 these things -- I can imagine one study that would be very
2 convincing to all of us.

3 PANEL MEMBER GLANTZ: Well, see, I -- the problem
4 I -- I want to expand on that, because I think that -- I
5 mean every time I hear the term "biological plausibility,"
6 I think of ye olde English, because the idea of biological
7 plausibility, I don't know when that all got cooked up a
8 long time ago, but that was before we had a tremendous
9 amount of mechanistic understanding or experimental
10 toxicology and things like that.

11 And so, you know, these criteria are really based
12 almost exclusively on statistical and epidemiological
13 considerations. And we're way past that on a lot of these
14 things. I mean if you look at the whole discussion this
15 morning, if you look at the discussion about heart
16 disease, you know -- so it would be nice to, you know,
17 instead of talking about biological plausibility, to me
18 when you talk about the weight of the evidence is you look
19 at the epidemiology if you have it. And, as John said,
20 we've often dealt with things where we don't have any
21 human epidemiology. You look at what you know about the
22 mechanistic effects of the compound in question and any
23 biological effects. Rather than biological plausibility,
24 I would say biological effects. And to me, you know, when
25 I look at these things, it's sort of when you step back

1 and look at the whole picture, the question is: Does the
2 evidence hang together?

3 You know, do you have -- do you have, you know,
4 things where you're showing effects, not to reopen an
5 old -- the discussion we had before. But, you know, when
6 you look at heart disease, we see these changes in oxidant
7 loads, oxidant LDL affects the dose, things you have on
8 Nitric Oxide Synthase, which affects vascular reactivity
9 and the development of atherosclerotic plaque and acute
10 events, and then you see it in the epidemiology. So the
11 whole -- you have this whole train of evidence going from
12 very molecular things and mechanistic things up to where
13 you can see something at the level of an entire
14 population. And that to me is like -- that's like really
15 nice when you have that.

16 Now, often we don't have that full range of
17 evidence. And so to me the question is like how -- and I
18 don't know how you would put this in these words, but sort
19 of how long is the chain and how strong are the links.
20 And that to me is how you make these judgments. So I
21 think that -- you know, and is what evidence you have
22 internally consistent, you know. So I don't know quite
23 how you would write that.

24 But I'd like to see this move away from such sort
25 of a traditionalist strict epidemiological statistical

1 paradigm, which was developed before a lot of these other
2 more experimental tools were even around.

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: You know,
4 I think -- I'd like to point out too on page 110 that we
5 discussed this issue in the context of the Toxic Air
6 Contaminant Program, which, you know, Dr. Froines just
7 pointed out we have naphthalene based solely on animal
8 data, we have perchlorate. I mean there's like a ton of
9 them that we've already identified as text.

10 We point out that because the epi data are
11 extensive for ETS, they serve as the primary basis on
12 which findings of ETS effects are made. Experimental data
13 are also reviewed to determine the extent to which they
14 support or conflict with the human data. In some cases
15 studies of ETS constituents in animal -- experimental
16 animals are used to support the weight of evidence
17 judgment. As noted above, this is standard practice in
18 risk assessment.

19 In many instances in the toxic air contaminants
20 program chemicals have been identified as TAC's and
21 emissions have been regulated based on animal
22 toxicological data alone. This is important in the public
23 health setting because often times adequate
24 epidemiological data do not exist.

25 So I think that -- what I'm trying to say is

1 basically what Stan just said, only much more
2 articulately --

3 (Laughter.)

4 OEHHA SUPERVISING TOXICOLOGIST MARTY: -- that
5 there's a whole chain of events, you know, and a whole --

6 CHAIRPERSON FROINES: We're going to let this --
7 assessment's going to take ten more minutes. And then
8 you're going to take what was said here, unless somebody
9 makes a specific suggestion, and work on it and bring it
10 back next time. So we have ten more minutes and then --
11 because I'm not going to keep ARB from...

12 I want to strongly support Stan's point of view
13 in this, Melanie. Because when I served on and chaired
14 the NTP Carcinogen Committee, every time a chemical came
15 up, various intervenors came in and said, "There's no dose
16 response information. There's no dose response
17 information. There's no exposure information." Well, the
18 fact of the matter is when you go out there and look at
19 who collects exposure information, for the most part it
20 isn't collected routinely. And so we always have to -- we
21 always have the problem that there's inadequate exposure
22 information.

23 So then we set our ourselves this criteria of
24 dose response, which we can never adequately meet, for the
25 most part, except in the very, very most expensive and

1 best studies. So, yes, I agree with you about dose
2 response. But we already talked earlier about it
3 doesn't -- everything doesn't just keep going up. And so
4 we need to understand that -- whether it be strength of
5 association or dose response, we have to have a modern
6 understanding of what reality's all about in order to make
7 decisions. Otherwise we get our own rhetoric -- we get
8 trapped in our own rhetoric. And what happens is we
9 become criticized for inadequacy of, for example, exposure
10 information that isn't routinely collected.

11 And so it seems to me that the epidemiologists
12 did very well with tobacco smoke because they get such
13 a -- an enormous dose. They have very, very powerful
14 findings. But for most things that we deal with, the
15 levels of exposure in the environment are so low as to be
16 very -- that we're always forced to extrapolation because
17 we can't measure in the regions where people are actually
18 breathing the chemical. So what does strength of
19 association mean in a lot of circumstances? We simply
20 can't get to it.

21 So I think that we have to be very careful not to
22 set ourselves up with a goal standard which we're going to
23 have consistent difficulty in meeting and develop criteria
24 for decision making that is realistic within that
25 particular context.

1 PANEL MEMBER BLANC: Well, I think I would differ
2 to an extent. And, that is, that I think it is important,
3 as you have tried to do, to lay out what is generally
4 considered the traditional approach to causality. I think
5 it would help you to the extent that it's publicly
6 available to actually cite explicitly what the IOM
7 approach has been. Perhaps if the EPA has struggled with
8 a causality guideline, you might look at what they have.

9 I think it's not absurd to even go back to sort
10 of the classic tobacco-related diseases, hypertraditional
11 causality framework. And then having done that, talk
12 about those ways in which that, as in an overly
13 prescriptive or overly narrow version of causality, is to
14 an extent not applicable to this situation. I think
15 that's the context in which you could have your discussion
16 about cigarette smoking in relationship to -- direct
17 cigarette smoking relationship to the outcomes. I think
18 you weaken your direct cigarette smoking argument by not
19 saying first, "Well, in general, yeah, we do think that
20 it's supportive when cigarette smoking is related." You
21 go immediately into this sort of backpedaling, well, but
22 it's problematic and there's this and there's that. But
23 in fact, you know, you don't start off by saying, "Well,
24 yeah, you know, generally speaking, yes. But here are a
25 few caveats. We don't expect to be linear. For some

1 things there may be a threshold." So it's well
2 understood, you know, gathering epidemiologic data is, you
3 know, indicated -- and this is particularly the case for
4 certain health outcomes such cardiovascular disease -- see
5 Chapter 6 -- as you'll see in Chapter 8, whatever it is.

6 And, similarly, I think that this is the area in
7 which you should have your generic discussion of the
8 issues of defining exposure for the purposes of the
9 referent group, since this is something that's come up
10 again and again and again in your analyses: Is your
11 referent group actually free of secondhand smoke exposure
12 or not? And how do you know it? And is a -- you know,
13 Stan's points from earlier today about even though
14 traditionally cohort studies -- longitudinal cohort
15 studies are argued to be more free of bias, for your
16 purposes longitudinal studies which don't have multiple
17 measures of changes in secondhand smoke over the
18 observation period are perhaps less useful than
19 retrospectively ascertained exposure data. And I would
20 lay out all of the generic issues that you've struggled
21 with the various epidemiologic and non-epidemiologic
22 analyses. And I think this is also the point in which you
23 should make clear what drives you to do your own
24 meta-analyses and what role you believe they serve in
25 raising the threshold perhaps from suggestive to

1 causative.

2 You know, by implication it's not that nothing
3 could be causative without a meta-analysis. However, when
4 there is a meta-analysis, you believe it is further
5 substantive strengthening in the area of consistency of
6 results, particularly if there are multiple studies but
7 all of them have fairly small populations because of the
8 nature of the endpoint being studied. And therefore
9 pooling data substantively increases the power or the
10 analytic power to answer the question. And I think if you
11 use these pages to do all those things, it would first of
12 all free you up from a lot of gobbledegook later on,
13 because you could just simply say, "Refer to perform
14 to" -- "We performed a meta-analysis as part of our
15 causality evaluation (see Chapter 1)."

16 CHAIRPERSON FROINES: Paul, I certainly would
17 support what you've said almost completely. But I still
18 reserve -- I still think one has to have a section where
19 you talk about limitations and realistic considerations.
20 Otherwise you're stuck with Bradford Hill. And Bradford
21 Hill just doesn't work under circumstances that we live
22 in. And we have to have ways of making decisions. So
23 that I would agree that everything you said can go as a
24 front piece. But I think there needs to be some sort of
25 paragraph or paragraphs that talk about some limitations

1 as well. And that doesn't have to be defensive?

2 PANEL MEMBER BLANC: No, no. In fact you can set
3 up Bradford Hill as a kind of strawman where you say, "We
4 love Bradford Hill. It's great for the following
5 reasons:" But of course there is this other problem and
6 this problem and so on. And so, you know, we've tempered
7 our application of it to be consistent with the reality.
8 Although actually this particular body of subject matter
9 is heavily epidemiologic as it turns out for most of the
10 endpoints that you're interested in.

11 PANEL MEMBER GLANTZ: Yeah, but, you know, I
12 don't want to prolong this. But in terms of breast cancer
13 though I think the toxicology studies contribute a lot
14 though to the conclusion of causality. The fact that
15 there are elements -- you know, that there are elements in
16 the smoke that we know are delivered to breast tissue,
17 that they are causing cellular damage in breast tissue,
18 and that they are mammary carcinogens in animals. And I
19 think those facts add a lot to the epidemiology.

20 CHAIRPERSON FROINES: I would even argue that
21 given what we have in tobacco smoke, it should be the
22 burden of the person who wants to not consider it a
23 carcinogen to make the argument. Because we have lots of
24 epidemiology showing human carcinogenesis from those
25 chemicals. And so the burden shouldn't be on us to prove

1 at some level. But given the way the process works, we
2 are going to take that tack basically.

3 PANEL MEMBER GLANTZ: Right. But what I'm just
4 saying is is that to me when you look at the breast cancer
5 data, the toxicology is more than just, quote, biological
6 plausibility. I mean I see the toxicological evidence as
7 very, very strong all by itself. And the fact that you
8 have this strong toxicological evidence in combination
9 with what I would call reasonably good epidemiology is
10 what I think justifies a causal conclusion.

11 I think that the epidemiology on its own without
12 the toxicology might, but it's much, much stronger when
13 you put the two of those together.

14 CHAIRPERSON FROINES: And given that you're
15 talking about toxicology, that leads us right into
16 Jeanette's talk, discussion.

17 So thank you, Melanie. Thank you everybody from
18 OEHHA.

19 PANEL MEMBER GLANTZ: I think you get to come
20 back later.

21 CHAIRPERSON FROINES: Jeanette, you want to take
22 five minutes to give our guy a chance to take a break.

23 (Thereupon a recess was taken.)

24 CHAIRPERSON FROINES: We can go till 4:15 I
25 think, Jeanette. As long as there's a cab outside at

1 4:15.

2 CHAIRPERSON FROINES: We're in business.

3 (Thereupon an overhead presentation was
4 Presented as follows.)

5 ARB MANAGER AGUILA: We're in business? Okay.

6 Well, good afternoon to the Panel. I'm Jim
7 Aguila with ARB. I realize it's kind of late in the day.
8 We'll try to get through this as efficiently as possible
9 here.

10 But we actually have the ARB team here this
11 afternoon to kind of talk about some of the issues and
12 questions that were raised last time. And to my right I
13 have Robert Krieger and Jim Stebbins. And to my -- or
14 actually to my left, to your right. To my right is Bruce
15 Winder, who's going to cover some of the biomarker
16 information.

17 So Robert will take us through most of the
18 presentation and then I'll kind of chime in on the
19 particulate matter discussion.

20 MR. KRIEGER: Okay. Thank you, Jim.

21 Today ore presentation will focus on the comments
22 that you presented at the November 30th meeting.

23 Next slide.

24 --o0o--

25 MR. KRIEGER: As discussed at the November SRP

1 meeting, you, the Panel, had several comments on the
2 report which we'll address now.

3 The first comment deals with your concern over
4 the regards for the statewide ETS PM outdoor estimate.
5 This is the number that we had previously in the report
6 that we submitted to you that estimated a state -- overall
7 statewide concentrations of ETS fine PM.

8 --o0o--

9 MR. KRIEGER: To address this comment we actually
10 did a Los Angeles-area-only estimate based on several
11 studies that we'll talk about here. We felt that this
12 estimate better reflects what most people are exposed to
13 in urban areas. And we felt that this could be kind of
14 tagged along top of some of the estimates that we already
15 have in our report.

16 As a reference point ARB staff used the results
17 from the Schauer and the Rogge studies to estimate the
18 2003 Los Angeles ETS fine PM outdoor ambient background
19 concentrations.

20 Cigarette sales data, taken from the Board of
21 Equalization, and cigarette emission rate data, taken from
22 several studies were used to determine the percent
23 reduction in cigarette emissions from the data presented
24 in the Schauer and Rogge studies to 2003 year.

25 Next we applied this percent reduction to the

1 1982 fine ETS PM estimates that were presented in the
2 Schauer and Rogge studies to calculate the annual average
3 Los Angeles fine ETS particle concentration.

4 --o0o--

5 MR. KRIEGER: This next slide shows actually the
6 calculations that we used to get to this level. The top
7 half of that graph shows the statewide emissions for
8 cigarettes in California -- or actually in California, the
9 statewide. And it shows that the percent reduction in
10 actually just cigarette sales was about 59, 60 percent
11 reduction. The ETS emission rate was based on -- that was
12 based on the 1982, was 20.4 milligrams per cigarette.
13 That was based on the Schauer and the Rogge study.

14 Actually that number came from a Hildeman study
15 in 1991. But that emission factor we believe decreased.
16 We have newer data that shows that the emissions from the
17 cigarettes are at 13.4 milligrams per cigarette.

18 You take the total difference between the two
19 cigarette sales and the emission rate and you come to
20 roughly an estimate about 73 percent reduction. And we
21 just simply -- from that point we simply took that percent
22 reduction, applied it to the 1982 data set emissions or at
23 least ambient calculations to come up with a 2003 fine PM
24 estimate ranging from about .06 to .10 micrograms per
25 cubic meter.

1 Next slide.

2 --o0o--

3 MR. KRIEGER: The SRP also had a comment on the
4 percentage of indoor cigarette smoking that makes it
5 outdoors. That was a comment that was made by Dr. Blanc.
6 And Dr. Hammond raised this issue as well. And we'll
7 address that in this next slide.

8 --o0o--

9 MR. KRIEGER: As we mentioned before, there is
10 limited information -- or limited information is available
11 to allow an accurate estimate of indoor to outdoor ETS
12 emissions. No direct measurement of indoor versus outdoor
13 cigarettes consumed in California have been done. But
14 there are several actually data sets that are available
15 that we could make kind of a reasonable assumption the
16 percentage of cigarette that is smoked indoors makes it to
17 the outdoor environment.

18 Some of these are based on the current laws that
19 limit most smoking in public indoor places, like the AB 13
20 that was adopted in 1988. The work place, bars and
21 restaurants, et cetera.

22 Also the 2002 California adult tobacco survey
23 data from the Department of Health Services indicates that
24 about 95 percent of Californians report a smoke-free
25 indoor work environment.

1 cigarettes per day, those who smoke only.

2 Fifty to Eighty percent -- it was the number that
3 was used in the previous slide -- of the ETS ventilates
4 indoor to outdoor.

5 With those assumptions here we go through Case 1.
6 And Case 1 we just wanted to show that if you're a smoker
7 and you follow the rules of the work place exposure and
8 not smoke indoors, you're smoking outdoors the majority of
9 day, and if you do not smoke at home, virtually a hundred
10 percent -- and it may vary a little bit -- but virtually a
11 hundred percent of your smoking occurs outdoors.

12 What we want to point out here is that Case 2 is
13 the scenario where the smoker does not smoke outdoors but
14 smokes, let's say, 50 percent -- or smokes at home the
15 rest of the time or the six hours of the time, but at a 50
16 percent ventilation rate. So 50 percent of the cigarettes
17 smoked actually is smoked indoors, 50 percent makes it
18 outdoors.

19 So we add those two together. And with the total
20 cigarettes they smoked per day we come up with an 80
21 percent calculation or rate that smoked indoors make it
22 outdoors. And so we believe that this would sort of
23 comprise maybe the lower end of a range for emissions that
24 would actually make it from the indoor environment to the
25 outdoor. It could be much higher.

1 And this is for smokers only too. For nonsmokers
2 it's -- we assume it's much more higher than 80 percent.

3 PANEL MEMBER FRIEDMAN: Can I ask a question?

4 MR. KRIEGER: Yes.

5 PANEL MEMBER FRIEDMAN: Maybe I don't have this
6 correctly. But you said that 20 percent -- 80 percent of
7 children live in smoke-free homes. And isn't it true that
8 about half of smokers -- I mean that the percentage of the
9 smoking adults in California is about 20 percent -- about
10 20 percent or 18 percent?

11 MR. KRIEGER: That's correct.

12 PANEL MEMBER FRIEDMAN: And if half of them don't
13 smoke in their home, then there should only be about 10
14 percent of homes with smokers.

15 ARB MANAGER AGUILA: Okay. I think that refers
16 to the nature of the survey itself. And what they did is
17 they surveyed homes. But homes may have more than one
18 child. So that's not really factored in.

19 PANEL MEMBER HAMMOND: There's another factor
20 too. And, that is, that something like 40 percent of
21 children have parents who smoke. So in other words
22 smokers and nonsmokers don't have the same percent of --
23 the children aren't evenly distributed among smokers
24 and -- all right. So it doesn't follow that. So it turns
25 out the higher percentage of children have a parent who

1 smokes than the percent of the adult population who
2 smokes.

3 PANEL MEMBER FRIEDMAN: I'm surprised.

4 PANEL MEMBER HAMMOND: You can start working out
5 the scenarios, but it -- yeah.

6 --o0o--

7 MR. KRIEGER: The next slide.

8 The comment is actually an easy comment to
9 address. It dealt with Dr. Blanc's comment on the Eisner
10 study. We presented in a final slide, which you will see
11 here today too, that we presented an outdoor number that
12 was taken from the Eisner study. And he asked us to go
13 back and confirm whether this was an ETS-monitored
14 measurement or not. And in doing so we did -- the next
15 slide.

16 --o0o--

17 MR. KRIEGER: Just a summary real quick. The
18 Eisner study dealt with actually 50 subjects who were part
19 of the asthma study. They used passive samplers to
20 measure personal exposures to nicotine. They actually had
21 a category that had 12 that it had only outdoor exposures
22 only. So there was a category for outdoor exposures only.
23 And they reported concentrations from the outdoor ambient
24 environment to be .025 micrograms per cubic meter
25 nicotine. And it's important to note too -- and I will

1 show this on the last slide too, our summary slide -- that
2 the results are consistent with all the other studies,
3 measurements and estimated results.

4 --o0o--

5 MR. KRIEGER: Another comment that was brought up
6 by Dr. Froines mentioned about our ARB air monitoring
7 study -- near-source nicotine, our monitoring study. And
8 I will present some of the findings from that study in the
9 next few slides.

10 --o0o--

11 MR. KRIEGER: The ARB staff conducted an ambient
12 air monitoring at outdoor smoking areas for nicotine, in
13 part to address some of the gaps that existed in outdoor
14 measurement studies.

15 To obtain data on current levels of ETS in
16 ambient air where people spend part of their day the ARB
17 monitored nicotine concentrations at several outdoor
18 smoking areas in California. These sites included
19 sampling at an airport, college, public building, office
20 complex, and an amusement park.

21 At each of the study sites sampling was conducted
22 for nicotine over a three-day time period during typical
23 business hours, usually between 8 and 5 p.m. Two of the
24 days were devoted to eight-hour samples; six one-hour
25 samples were collected on one of the sampling days. QA/QC

1 samples were obtained for this study.

2 The estimated quantitation limits shown for the
3 eight and one-hour samples is the level that we have
4 confidence in showing the nicotine levels that we
5 measured.

6 Sampling was done by ARB's monitoring laboratory
7 staff and analyzed by UC Davis's trace analytical lab.

8 --o0o--

9 MR. KRIEGER: Here we have -- next few slides
10 have a couple pictures of our actual sampling equipment.

11 During this monitoring period nicotine was
12 collected with XAD-4 absorbent resin by pulling air
13 through the sampling cartridges you see up there at a rate
14 of 15 liters per minute. The sampling cartridges
15 contained about 30 milliliters of XAD-4 resin.

16 Analysis was conducted by a gas chromatography
17 with mass selective detector. And the pump is shown on
18 the right too as well with the tubing.

19 Next slide.

20 --o0o--

21 MR. KRIEGER: This next slide shows a picture of
22 our actually monitoring set up. The slide on the left
23 shows the -- kind of the typical height of our monitoring
24 device. The slide on the right shows that -- the
25 importance of this slide is actually to show where the

1 monitors are located. And you see the one on the right,
2 which obviously is the airport there you can tell, is
3 located right outside the baggage claim area where several
4 people congregate. And smoking occurs right next to the
5 monitor. So we would expect higher, you know, ETS levels
6 to occur there.

7 The picture on the bottom left is from the
8 college. And -- well, at that time there's no smokers
9 there. But there were a few.

10 And the one on the right's the office building.

11 --o0o--

12 MR. KRIEGER: This slide shows in a graphic
13 form -- and the next slide will be a table with the same
14 results. But some of the results here. The results of
15 our monitoring show that actually the number of cigarettes
16 smoked on the right correspond to the levels found in the
17 areas -- and the levels are on the left, the concentration
18 levels. So basically the number of cigarettes smoked
19 corresponds to the levels that you see on the table.

20 The background concentration are in red. I don't
21 know if you can read that. And the kind of green color is
22 actually the mean concentrations for each one of those
23 sites.

24 --o0o--

25 MR. KRIEGER: This table shows actually the

1 throughout each one of the monitoring sites.

2 --o0o--

3 MR. KRIEGER: That's all I -- oh, we have one
4 last slide. And this is actually the pretty important
5 slide which will become part of our Table 5 of my report.

6 This slide summarizes the data we have found on
7 the outdoor levels of ETS exposure.

8 The results from the studies themselves are
9 indicated by the black text. And the estimated levels of
10 either nicotine or fine ETS PM are shown on the blue text.

11 The estimated levels were calculated by using an
12 adjustment factor for the conversion of nicotine to the
13 fine ETS PM. And the ratio we used for this calculation
14 was eight. And that was supported by data by Nelson in
15 1994 and Martin in 1997, who tested a number of cigarettes
16 for fine ETS and nicotine as well. So we had the ratio
17 that occurred from nicotine to fine PM.

18 And as you can see on the slide there, both
19 columns actually match up fairly consistently. And the
20 levels are not too far off from even the estimated
21 concentrations. So there's like a convergence there
22 between all the data that's presented in our outdoor
23 estimates.

24 --o0o--

25 MR. KRIEGER: Any questions on that?

1 But more importantly it's important to point out that in
2 general ETS does fall within the ultrafine and fine
3 particulate matter range. And I think this kind of talks
4 a little bit to what was discussed earlier regarding ETS's
5 role in terms of overall air pollution.

6 So we would make a point to point out that, you
7 know, it is kind of overlapping between the two. Not to
8 mention that, you know, ETS has several carcinogens. And
9 of course there's literally thousands. We put 50 here
10 because that's what we found in our literature. But I'm
11 sure there's probably more.

12 Not to mention as well that there's also many
13 that are reproductive toxicants and possibly even
14 developmental toxicants too.

15 --o0o--

16 ARB MANAGER AGUILA: As far as the PM research is
17 concerned, you know, we'd just like to point out that just
18 the nature of how PM is generated, it leads to a nice
19 normal distribution and that's typically how it's viewed.
20 Most of the studies typically look at particle mass. But
21 there's also other studies that have looked at number
22 counts, that is, the number of particles per cubic
23 centimeter or meter, in addition to the actual length of
24 the particle itself.

25 But, by and large, when you talk about

1 conclusions of some of these studies, they're put in
2 basically statistical terms in terms of median modes,
3 standard deviation and the like. So we'd like to point
4 that out in our report, especially since we're going to be
5 presenting some data that would be in that form.

6 It's also important to note that, you know, over
7 time detection methods and techniques have changed. And,
8 in fact, there's studies that we looked at that have
9 actually done comparison work to point out that, depending
10 on what kind of analyzer you use, there could be
11 differences and, in fact, stark differences in some cases.
12 And then also to point out the differences between
13 research that's done on mainstream versus side-stream.
14 There are differences in terms of its, not only the
15 chemical make-up, but also the particle mass distribution
16 as well.

17 --o0o--

18 ARB MANAGER AGUILA: As far as the aging process
19 goes, typically what we point out is that the ETS would
20 dilute rather rapidly in the air in most cases. But
21 depending on the conditions that its generated in, there's
22 a number of chemical reactions that could occur. The ones
23 listed on the slide here are simply the main ones that we
24 were able to find in the literature.

25 And of the list there, probably the coagulation

1 captured mainstream smoke and was able to filter the
2 mainstream smoke so you have only the gaseous component of
3 ETS, which the author terms as smoke vapor. And this was
4 kind of an interesting analytical apparatus that they used
5 here.

6 But basically it was a 50 milliliter syringe
7 where they stuck a cigarette on the top of it and pulled a
8 plunger and were able to generate smoke. And they looked
9 at that smoke in two ways. One way they looked at it was
10 through light scattering techniques. And another one was
11 just an optical counter -- a Lasik optical counter.

12 And the bottom line here what you see is that
13 basically after about 100 second or 150 seconds the
14 particle number stays relatively flat until you get to
15 about 500 minutes -- or seconds. Excuse me. But the
16 diameter of the particles do increase over time. And the
17 authors theorize that this is mainly due to condensation
18 of particles.

19 --o0o--

20 PANEL MEMBER HAMMOND: How large was that
21 chamber?

22 ARB MANAGER AGUILA: It was 50 milliliters lit
23 ease

24 PANEL MEMBER HAMMOND: Fifty milliliters?

25 ARB MANAGER AGUILA: Yes, it was rather small.

1 And the author -- by the way, on the previous
2 slide the author also theorized that one of the chemical
3 processes that could be happening is the combination of
4 NO2 with isoprene. So they note that as one of the
5 chemical reactions that would lead to this increase in
6 diameter effect.

7 Next slide.

8 --o0o--

9 PANEL MEMBER LANDOLPH: To come up with the
10 particle diameter, what did they use, low angle forward
11 scattering --

12 ARB MANAGER AGUILA: Actually they used a
13 horizontal and a vertical scattering technique and they
14 compared the light intensity of the two measurements. And
15 based on theoretical calculations of angle of defraction,
16 they were able to determine the response curve between the
17 ratio of the horizontal to the vertical light scattering
18 intensity to this theoretical graph that allowed them to
19 actually plot the diameters on that.

20 CHAIRPERSON FROINES: I don't understand
21 something. You said that they attribute the increase in
22 diameter to isoprene NO2, is that what you said?

23 ARB MANAGER AGUILA: Yeah, the combination of NO2
24 and isoprene was one of the chemical reactions that they
25 noted in the paper.

1 CHAIRPERSON FROINES: Well, wait. There's no
2 chemical reaction we're talking about. I assumed that the
3 increase in diameter occurs basically by coagulation and
4 condensation, not by chemistry.

5 ARB MANAGER AGUILA: Yeah, I simply mentioned
6 that because it was mentioned in the paper. But, you're
7 right, there's other reasons why --

8 CHAIRPERSON FROINES: Vapor is -- you know, is a
9 molecule.

10 PANEL MEMBER HAMMOND: Well, those kinds of
11 reactions will actually give you smaller particles, not
12 larger ones. So I think John's right.

13 ARB MANAGER AGUILA: Okay. Well, we'll make sure
14 we get that straight.

15 PANEL MEMBER HAMMOND: Well, it's probably not
16 important for where you're going.

17 --o0o--

18 ARB MANAGER AGUILA: Okay. This is the next
19 slide here. This is another study. Ingebretsen, who
20 looked at particle evaporation.

21 In this case this was a side-stream diluted with
22 air in a -- and an optical particle counter was used with
23 an electrical mobility analyzer.

24 And in this particular study we're looking at the
25 time relationship to mass mean diameter. And what it

1 indicates is that there's an initial dip, which the author
2 explains as an evaporation effect happening. Before other
3 chemical processes take over, that actually would increase
4 the mass mean diameter. But essentially this is important
5 within the first 100 minutes or so.

6 PANEL MEMBER LANDOLPH: Well, you know, that last
7 side, I was trying to thinking of what confused me. The
8 particle concentration is on a log scale. The diameter is
9 on a linear scale. So you see the diameter going up fast.
10 And you see that the particle number looks like it's
11 decreasing slowly, but actually it's on a log scale, so
12 it's going down much faster.

13 ARB MANAGER AGUILA: Yes. And actually that's a
14 good -- I appreciate that you pointed that out, because
15 this actually is a bit of an artifact of how they took the
16 measurement. Because what you're seeing there is you're
17 seeing the tail-end of the smoke that's in this 50
18 milliliter syringe. So, you know, the authors basically
19 state that there's probably a limit to the detection
20 accuracy once you get that far out.

21 PANEL MEMBER LANDOLPH: Thank you.

22 CHAIRPERSON FROINES: Well, it's probably pretty
23 turbulent and you're not getting much drop off by growing.
24 So it's a phenomenon of the production of the particles
25 probably more than anything else.

1 elemental carbon core and on the surface have PAH's
2 condensing. That's the point you're trying to make?

3 CHAIRPERSON FROINES: And so as you take two
4 diesel particles, it's not as though all those PAH's then
5 become monolayers on top of what already exists. But you
6 get this factual kind of thing that Sheldon Freedlander
7 shows pictures of, you know. So that the actual number of
8 monolayers of absorbed compound stays relatively constant,
9 which means that they may be. It means we should be
10 regulating on the basis of surface area, I think.

11 PANEL MEMBER HAMMOND: But I think it's less of
12 an issue for tobacco smoke.

13 CHAIRPERSON FROINES: Why?

14 PANEL MEMBER HAMMOND: I think it's more uniform.

15 CHAIRPERSON FROINES: You think so?

16 PANEL MEMBER HAMMOND: I think so. I mean I --
17 don't guess an elemental carbon core.

18 CHAIRPERSON FROINES: It's so sticky, you mean?

19 PANEL MEMBER HAMMOND: I mean there are
20 differences, but I doubt it, as -- in that sense, as
21 different on the inside and the outside as a diesel
22 particle would be.

23 CHAIRPERSON FROINES: I'm still in favor of
24 regulating on the basis of surface area.

25 (Laughter.)

1 ARB MANAGER AGUILA: Well, just in general, I'd
2 like to summarize here and just state for the record that
3 we are changing the report. We'd like to add a lot more
4 detail. Basically the information that we presented today
5 was the bulk of the new information that we'd present in
6 the report. And I think the main take-home message here
7 would be that ETS really is a -- it's an air pollutant, a
8 concentrated air pollutant, as I heard earlier this
9 morning, that kind of -- it has an overlap between
10 ultrafines and fine particulate matter. And even though
11 it's subject to quite a few chemical processes, it still
12 tends to stay in the same range.

13 CHAIRPERSON FROINES: What's at the core of going
14 just -- Kathy. What's the core of tobacco smoke? It's
15 not carbon obviously. Although there must be some carbon.

16 PANEL MEMBER HAMMOND: Well, I mean -- one of the
17 examples I gave you was something that had no particles to
18 start out with, right? And so it was entirely
19 condensation -- for those particles that were formed was
20 entirely condensation of vapors, semi-volatile organic
21 compounds.

22 I'm not actually familiar with an analysis of --
23 a surface analysis as opposed to the core analysis. But I
24 think there's a lot more of what it is is a condensation
25 of smoke as opposed to there being these elemental carbon

1 cores. There probably are little bits of tobacco leaf, I
2 guess. But I don't really know.

3 ARB MANAGER AGUILA: No, I think that's our
4 understanding as well. And it's really obvious in the
5 literature when you study semi-vol -- and how they dilute.
6 It's pretty obvious that they're condensing and forming.

7 CHAIRPERSON FROINES: Well, you have -- a
8 tailpipe of a vehicle is like a hot tube, right? And so
9 you have all sorts of chemistry going on within the hot
10 tube. And then there's what happens when all the vapors
11 come out and condense and form particles.

12 So you have particles in the tailpipe or exhaust
13 and you have particles that are formed after the exhaust
14 comes out. So there are two. Now, do you form all sorts
15 of particles -- you smoke -- the hot part of the cigarette
16 is at the end. Now, we're talking about ETS here, so it's
17 more complicated.

18 PANEL MEMBER HAMMOND: The hottest part is when
19 the smoker's smoking the cigarette and they're inhaling so
20 they're pulling oxygen here. So that's like 300 degrees
21 warmer than when it's smoldering. And during that time
22 most of the particles actually go into the smoker's lungs.
23 That's one of the differences in mainstream to
24 side-stream. But when it's smoldering it's only 600
25 degrees roughly. So it's a little different. But you

1 still would have vapor phase semi-volatile compounds that
2 will later condense.

3 CHAIRPERSON FROINES: But the particles that are
4 formed in the cigarette are -- do they have -- what is
5 their core?

6 PANEL MEMBER HAMMOND: Partly -- if they're
7 totally condensations, then they would be the same as --
8 that would be uniform, right?

9 And then the other, I don't know. But I was
10 suggesting it could be unburned tobacco. I don't know
11 though.

12 MR. KRIEGER: Yeah, there is a percentage of
13 elemental carbon in the smoke --

14 PANEL MEMBER HAMMOND: It's a tiny percent --

15 MR. KRIEGER: It's a very tiny percent, but there
16 is --

17 PANEL MEMBER HAMMOND: One or two percent.

18 MR. KRIEGER: Yeah.

19 PANEL MEMBER HAMMOND: It's only one or two
20 percent. And I don't think that that's -- it's not like
21 diesel.

22 MR. KRIEGER: It's not like diesel. Diesel's
23 much more elemental carbon.

24 ARB MANAGER AGUILA: And I mean as far as being
25 able to compare the combustion effects of a vehicle versus

1 a tobacco column, which is what we refer to it, they could
2 be different because in a vehicle you have the catalytic
3 converter, which is supposed to create chemical reactions
4 in the engine before it gets exhausted. And there's a
5 possibility that some of those reactions might occur after
6 it leaves the tailpipe. But you wouldn't have anything
7 like that with tobacco.

8 CHAIRPERSON FROINES: We should run some tobacco
9 smoke in our tox systems and see what it looks like.

10 PANEL MEMBER GLANTZ: I just had one question.

11 All this stuff was about particulates. What
12 about the gas phase? Is there anything to say about that?

13 ARB MANAGER AGUILA: Yeah, actually we do cover
14 it in the report. The reason why we covered PM is because
15 that was a question that was specifically brought up last
16 time. But actually the report does have a discussion of
17 the gaseous components, including a table of what -- you
18 know, the chemicals that have been identified either
19 through Prop 65 or ARB or IARC.

20 PANEL MEMBER GLANTZ: I know -- I remember the
21 table on the particulates -- the amount of particulate
22 pollution put into the air. Is there anything you could
23 do for the gas phases? Or does that get even like harder?

24 ARB MANAGER AGUILA: Right. Well, we were
25 talking about that. And we are aware of at least one

1 study where people looked at emission rates. And to the
2 extent that we could look at a cigarette and what
3 chemicals are being emitted from the cigarette, we could
4 compare gaseous components that way. But there's pretty
5 limited data. I think that's pretty much what we had in
6 mind looking at that. And also that same data set also
7 looks at side-stream versus mainstream as well. So we
8 could look at those separately as well in terms of their
9 generation rates per cigarette. So that's more like an
10 emission factor. It doesn't really tell you much about
11 the concentrations or anything. But at least it will tell
12 you from a cigarette where the relative differences among
13 different chemicals. It's not in the report now, but we'd
14 be happy to put that in.

15 PANEL MEMBER GLANTZ: I mean I don't want to
16 create a huge amount -- I mean this is something I know
17 very little about, but I wouldn't want to create a huge
18 amount of extra work. But if you could give -- I was
19 pretty impressed with the emissions that you quantified
20 there. And if you could add something about some of the
21 gas phase emissions, that would be entertaining. I don't
22 know that it's worth a huge amount of work. But if you
23 can do it easily, and it would make sense -- Kathy is
24 holding her head.

25 PANEL MEMBER HAMMOND: Well, no. I'm thinking,

1 if the left hand can talk to the right hand at ARB, and
2 probably they're all the -- they're probably on the same
3 bodies in between. There's a report that they recently
4 did on indoor air pollution that I happen to be a little
5 aware of. And there was some discussion about --

6 PANEL MEMBER GLANTZ: Wasn't Peggy Jenkins in
7 the --

8 PANEL MEMBER HAMMOND: And there was some
9 discussion there, you know -- and this is well known --
10 that in smoker's homes there are higher benzene levels in
11 the homes than in nonsmokers' homes, you know. But those
12 are the kinds of things that would be relevant. Obviously
13 the cigarette smoke as the benzene loads.

14 ARB MANAGER AGUILA: Okay. Would that be
15 something relevant to a discussion of absorption and
16 desorption? Because we are aware of a couple of studies
17 where they did look at benzene, they looked at nicotine.

18 PANEL MEMBER HAMMOND: Oh, I thought we were
19 talking about something different. I thought we were
20 talking about -- Stan was trying to talk about the
21 composition of the emissions. And that's where I was kind
22 of going with that.

23 PANEL MEMBER GLANTZ: Yeah, I mean I think the --

24 PANEL MEMBER HAMMOND: The only trouble I'm
25 thinking is since -- there's a lot that's been written on

1 that. I mean is that something you want to also reproduce
2 here?

3 PANEL MEMBER GLANTZ: Well, it depends how much
4 work it is. I mean I just -- I mean my main focus in
5 looking at the document was to Part B. But in reading
6 through Part A I just thought all this was very
7 interesting. And I was impressed with what some of the
8 numbers were. And I think it would be -- you know,
9 there's a lot of other toxins in the smoke that are in the
10 gas phase.

11 CHAIRPERSON FROINES: Vapor.

12 And some people even think some of those are the
13 most biologically active. So to the extent that you could
14 without doing massive amounts of work give some sense of
15 the levels of emissions, I think it would be interesting.
16 I don't think it will make a huge difference in whether
17 the report is approved or not. But just in the interest
18 of completeness, if you could do it easily, I think it
19 would be worth doing.

20 And I think Kathy brought up a different point
21 about the indoor air and the load of benzene and things
22 like that and indoor environments where people are
23 smoking. And, again, if that could be added in without
24 too much trouble, I think it would be interesting and make
25 the report more valuable.

1 ARB INDOOR EXPOSURE ASSESSMENT SECTION MANAGER

2 JENKINS: Peggy Jenkins, Air Resources Board.

3 I think we can do that very easily. Dr. Joan
4 Daisy from Lawrence Berkeley Laboratory actually did a
5 study. It was under contract to CARB. But she did look
6 at direct emissions and also aged emissions in a chamber
7 setting. But also attempted to do kind of some realistic
8 aging. Unfortunately some of the side-stream aging
9 results weren't crisp. But I think the initial emissions
10 were very good. She looked at aldehydes. Actually quite
11 a few of our toxic air contaminants were -- I think she
12 had about 17 toxic air contaminants that she looked at.

13 And one interesting result she did have was kind
14 of an increase in formaldehyde over time, which was not
15 totally unexpected, but I don't think it had been
16 measured. So there are a few studies -- a couple of
17 others like that that she cited we could certainly include
18 in a report without any difficulty. And I don't think
19 it's in there right now.

20 CHAIRPERSON FROINES: Are those smoking studies?

21 ARB INDOOR EXPOSURE ASSESSMENT SECTION MANAGER

22 JENKINS: This was a smoking machine chamber study of
23 mainstream and side-stream and initial and aged.

24 --o0o--

25 ARB ASSOCIATE TOXICOLOGIST WINDER: One of the

1 Now, I've not used most of these, and these are
2 the reasons. For example, carbon monoxide in the measure
3 of carboxyhemoglobin as an indication of the exposure to
4 carbon monoxide has been reported in several studies. But
5 carbon monoxide exposures occur from a variety of
6 different sources. So in and of itself this is not a
7 particularly useful indicator of ETS exposure.

8 Thiocyanate, which is derived from hydrogen
9 cyanide and smoke, also occurs to a certain extent in the
10 diet. So once again it's difficult to distinguish between
11 individuals who are exposed and not exposed to ETS.

12 Now, the next category of protein and DNA
13 adducts, some of that discussion we've had this morning,
14 are quite a number of these that have been reported.
15 They're used for indicating a certain amount of exposure.
16 But what is this connection to ETS versus active smoking?
17 Usually we can't distinguish on the basis of that.

18 Now, there's one example that is somewhat
19 different and that's the 4-aminobiphenyl. As Dr. Hammond
20 mentioned this morning, it is roughly 30 percent higher,
21 which means 30 times higher in side-stream versus
22 mainstream smoke. This is one of those compounds it looks
23 like it might have some use, but it's really not been used
24 widely. So from the standpoint of ETS exposure, this is
25 not particularly useful.

1 --o0o--

2 ARB ASSOCIATE TOXICOLOGIST WINDER: One that's
3 looking a little more promising is the
4 NNAL/NNAL-glucuronide. Now, this is a compound that's
5 metabolized from NNK, that is to say a carcinogen that
6 results as the consequence of combustion in nicotine.
7 Now, this is -- in the use of this it's possible to
8 distinguish between ETS, active smoking, and then exposure
9 to other non-tobacco nicotine sources. But, again, this
10 isn't widely used at this point. I think it's becoming
11 more widely used. But for our purposes it hasn't been
12 around long enough.

13 And the next two, nicotine and cotinine, these
14 are the two substances that are most commonly used in this
15 particular respect.

16 Now, nicotine is abundant and it's relatively
17 specific to tobacco. Although it is present in certain
18 dietary components. And we run into a problem with
19 individuals who are taking nicotine in the form of patches
20 or gum or something like this. So in that sense it
21 becomes a little more difficult to distinguish active
22 smoking, ETS exposed, et cetera.

23 Now, it has a very short half-life in body
24 fluids, so it's useful for determining very recent
25 exposures. And in a matrix like hair, it has a much

1 longer half-life. So this is useful from the standpoint
2 of measuring -- for seeing exposures over several weeks to
3 months.

4 Perhaps the most useful one in this context has
5 been cotinine. Now, as I mentioned here that this is
6 relatively abundant, that is to say 70 to 80 percent of
7 the absorbed nicotine is reportedly converted to cotinine.
8 This number derives from studies by both Dempsey and
9 Benewis. Now, this has been well developed for a variety
10 of matrices, hair, urine, saliva, this kind of thing.

11 And it's good principally for recent or
12 continuous exposure. And one of the things that was
13 mentioned last time was some concern that, well, what if
14 he had episodic exposures. Well, in that case our
15 measurements of cotinine could prove to be the same. On
16 the other hand in conjunction -- if you use it in
17 conjunction with nicotine, wouldn't even address that
18 issue. Most of the studies that we deal with have not
19 measured both, nicotine and cotinine.

20 Also, as with nicotine, since nicotine is found
21 in a variety of foods, the cotinine levels will to some
22 extent be influenced by that, not substantially.

23 PANEL MEMBER FRIEDMAN: Could you give a few
24 examples of the foods that it's found in?

25 ARB ASSOCIATE TOXICOLOGIST WINDER: Well, tea,

1 tomatoes, things like eggplant. All these contain small
2 amounts.

3 PANEL MEMBER GLANTZ: I think though this is a --
4 this is something that the tobacco companies have made a
5 big deal out of. And Jim Repace some years ago had a
6 letter to the editor. And I think it was BMJ. Kathy's
7 laughing. But it turns out that the food because of the
8 tomatoes and eggplant, I think are the two foods that have
9 it, that eggplant parmesan would be the --

10 (Laughter.)

11 PANEL MEMBER GLANTZ: Except that when you cook
12 it, most of the nicotine boils off. So you'd have to eat
13 it raw. And Repace --

14 PANEL MEMBER HAMMOND: How many pounds you had to
15 eat --

16 PANEL MEMBER GLANTZ: Yeah, Repace figured out it
17 was several pounds of eggplant -- raw eggplant parmesan
18 every day in order to get the levels typically seen in a
19 passive smoker. So it's true that there is some nicotine
20 in foods, but I think this is a pretty hypothetical
21 problem.

22 PANEL MEMBER HAMMOND: Well, in the M. Haynes
23 study where they actually had diet information as well,
24 you know, basically again did not see increased levels in
25 people who had the foods that are most thought to be the

1 problem. So it's really -- it's kind of a red herring.

2 CHAIRPERSON FROINES: But it's a good substance
3 to use on Fear Factor.

4 (Laughter.)

5 PANEL MEMBER BYUS: Again, this is a joke.

6 (Laughter.)

7 CHAIRPERSON FROINES: The eggplant industry will
8 be after us, right.

9 (Laughter.)

10 PANEL MEMBER BYUS: You know this.

11 PANEL MEMBER GLANTZ: The raw eggplant industry.

12 ARB ASSOCIATE TOXICOLOGIST WINDER: Next slide
13 please.

14 PANEL MEMBER GLANTZ: That was a joke too.

15 --o0o--

16 ARB ASSOCIATE TOXICOLOGIST WINDER: So based on
17 this, that we recognize the cotinine, nicotine and NNAL,
18 they're probably the best biomarkers so far demonstrated.
19 But of these, only cotinine and to some extent nicotine
20 had been widely used and the first to be able to use in
21 our studies with respect to ETS exposure. And so for that
22 reason -- this is the reason we rely on cotinine for
23 targeting at this kind of stuff. And the rest of the
24 biomarkers, some of them may have some potential use in
25 the future but at this point are really not of much use.

1 Any questions?

2 CHAIRPERSON FROINES: Kathy.

3 PANEL MEMBER HAMMOND: Well, I think that you've
4 all done a lot of work, and I commend you for the work
5 you've done and move this along quite a bit.

6 I think it's particularly -- since there are a
7 lot of issues here that you've dealt with, maybe
8 quickly -- you've put a lot of energy, for instance, into
9 talking about some things like the formation, the
10 complexity, which they're all there, but I actually think
11 they again are kind of a little bit red herrings. I mean
12 I suppose you have to address them because they're out
13 there. But, you know, the fact that it's very complex
14 doesn't make it not real, and the attempts to study it
15 require very artificial situations like 50 milliliter
16 chambers, you know, that just don't reflect what happens
17 in reality. So it's -- we shouldn't get bogged down on
18 some of those issues.

19 I think more to the point is the attempt to make
20 some estimates of what are background exposures. These
21 may be the most important things, you know, later. And I
22 think you've done some very nice things where you've
23 pulled together multiple sources of data, and I think that
24 this is very important. So on the one hand you've made
25 estimations from the source apportionment work that was

1 done by others that you cited as one of your slides -- it
2 would have been your nineteenth slide -- that summarizes
3 that. So you have Schauer and the Rogge data where you've
4 made estimates of the background levels of ETS and then
5 you've tried to extrapolate those down for the reduced
6 rates of smoking. And then what's interesting is when you
7 kind of compare that to some measurements that you all
8 made in your monitoring and Mark Eisner made in his study,
9 if anything I would say what you might note is that your
10 estimates are actually maybe underestimates, because the
11 observed values in your studies and in the Eisner studies,
12 which were personal samples for seven days, were all
13 actually higher than the numbers that you estimate. So,
14 if anything, you're underestimating.

15 But I think that you've got a relatively robust
16 number. I mean we're looking at -- to be agreeing within
17 a factor of 2 is pretty astounding, I think, and that's
18 where we are. The caveat -- that's a background level.
19 And then the caveat's not to lose the idea of the hot --
20 well, I'm going to -- the area where people are smoking,
21 when people are smoking outdoors, that near there you can
22 have higher levels.

23 PANEL MEMBER GLANTZ: I think that you call hot
24 spot.

25 PANEL MEMBER HAMMOND: But meanwhile the

1 background level, that's this other issue that you're
2 exposed to, even when you think you're not near a smoker,
3 is not insubstantial. And I think that you've got an
4 amazingly robust estimate of that coming out of -- kind of
5 triangulating it. So I commend you for that.

6 So I think you've done a nice job.

7 CHAIRPERSON FROINES: Other comments?

8 Why does passive smoking ETS cause cardiovascular
9 disease?

10 PANEL MEMBER GLANTZ: Why?

11 PANEL MEMBER HAMMOND: Which chemical, you mean?

12 CHAIRPERSON FROINES: Yeah.

13 PANEL MEMBER GLANTZ: Well, I think it's a whole
14 lot of different things. I think the particulates have a
15 lot of effects in terms of triggering inflammatory
16 responses.

17 CHAIRPERSON FROINES: In the lung?

18 PANEL MEMBER GLANTZ: Probably in the lung, but
19 releasing C-reactive protein, which then has
20 cardiovascular effects. There was a very nice study done
21 in Canada some years ago where they took fine particle air
22 pollution out of the air and stilled it into I think it
23 was rabbit lungs and got atherosclerosis. Controlled
24 study. So the particulates I think are very important.

25 The particulates seem to cause reductions in

1 heart rate variability that are associated with acute
2 events, heart attacks. I think the stuff we talked about
3 earlier about oxidant loads are important. Acrolein is an
4 important oxidant with a long half-life in blood. A
5 lot -- most of the oxidants don't have lung half-lives but
6 some do. And there's a lot of acrolein in cigarette
7 smoke. The 1-3 butadiene and benzopyrene have both been
8 shown to be atherogenic on their own.

9 So there's a whole lot of different, you know,
10 mechanisms that are at work here. I mean I think probably
11 one of the most important pathways is the stuff that was
12 being talked about earlier about the oxidant loads
13 reducing the amount of available NO, which screws up all
14 kinds of things related to endothelial function. But all
15 these different things are happening.

16 I don't think that nicotine is particularly
17 important. So there's a whole lot -- because there's so
18 many pathways that lead to cardiovascular disease, there's
19 a lot of places to stimulate those pathways in bad ways,
20 and cigarette smoke acts through a lot of them.

21 CHAIRPERSON FROINES: So the reason I asked that
22 question with you guys from ARB sitting there is precisely
23 the answer I got, which is -- and Donaldson from England
24 in terms of air pollution suggests the same kinds of
25 things, namely, that you have deposition in the lung which

1 produces inflammatory responses and then the inflammatory
2 responses produce cytokines and immunoglobulins and a
3 whole range of things and -- in other words, the particle
4 doesn't necessarily have to reach the heart to act in this
5 way.

6 So that the size distribution, the
7 characteristics of deposition, and so on and so forth
8 become very, very important in that respect.

9 PANEL MEMBER GLANTZ: Yeah. And the fine
10 particles are the worst.

11 CHAIRPERSON FROINES: Yeah. And acrolein's a
12 very interesting compound because it is an alpha beta
13 unsaturated aldehyde undergoes electrophilic addition to
14 form irreversible products and -- now whether -- what --
15 presumably that's a reaction with thiol groups and so it's
16 a protein -- it affects proteins. And so thiols are going
17 to -- may inhibit the nitric oxide synthase. So a lot of
18 things can happen.

19 So, anyway, so that both vapors and particles are
20 probably important.

21 PANEL MEMBER GLANTZ: Yeah. And actually that
22 was why I'd asked the question about trying to get some
23 estimate of the vapor phase loads too, because those are
24 important for some of these effects. It isn't just the
25 particulates.

1 CHAIRPERSON FROINES: A butadiene is more likely
2 to be a carcinogen rather than cardiovascular
3 implications. So that different chemicals --

4 PANEL MEMBER GLANTZ: Although butadiene does --
5 it's atherogenic.

6 CHAIRPERSON FROINES: Yeah.

7 So thanks, everybody. That was very useful.

8 Joe.

9 PANEL MEMBER LANDOLPH: I just have some minor
10 editorial comments I'll transmit to you and not take up
11 any time here.

12 Very nice job.

13 CHAIRPERSON FROINES: I assume that there's no --
14 I didn't mean to -- Stan and I were talking. I assumed
15 that there weren't other -- people would have jumped in if
16 there were other comments.

17 So, Melanie, we'll see where we can get this next
18 time.

19 PANEL MEMBER HAMMOND: John, Just a process
20 question.

21 Do we see another version of these things? Or
22 are we just kind of done with them now or what?

23 CHAIRPERSON FROINES: I'm assuming that Melanie's
24 going to try and get us a draft, as well as ARB, by --
25 certainly by the end of February so that we have two weeks

1 ahead of time to take a look at it for the March 14th
2 meeting.

3 OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we
4 have to do that in view of the number of reorganizations,
5 et cetera, that we're going to be doing to those chapters.
6 So I think it's important in this case. We don't always
7 have a draft -- a whole new revised report. But I think
8 we need to in this case.

9 CHAIRPERSON FROINES: So it's important for
10 people who have comments, just like Joe just said, to get
11 them to Melanie as soon as possible.

12 And so we will assume that by March first we'll
13 see a draft so we'll be prepared for the meeting. And if
14 that's the case, we may be able to take a vote in March
15 and we should be able to discuss findings.

16 So we'll draft some findings. And I say that,
17 knowing Gary's to my right and has very strong views of
18 how long those findings should be.

19 (Laughter.)

20 CHAIRPERSON FROINES: So we're going to have to
21 figure out what the --

22 PANEL MEMBER GLANTZ: And then Paul is to your
23 left with opposing views.

24 CHAIRPERSON FROINES: And I understand that too.

25 But we'll try and have -- we'll try and put

1 together some findings for discussion and hopefully be at
2 a place where we can take a vote unless there's violent
3 disagreement.

4 PANEL MEMBER FRIEDMAN: Will the new draft
5 show -- you have, a track changes feature so we know
6 what's added?

7 ARB MANAGER AGUILA: Yes, strike out, underline.

8 PANEL MEMBER FRIEDMAN: The same thing with the
9 OEHHA version?

10 PANEL MEMBER GLANTZ: It may be hard though if
11 you happen to strike out --

12 PANEL MEMBER HAMMOND: It may be this thick.

13 OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly.
14 I think where there's -- for example, Chapter 6. Paul
15 wanted lots of reorganization, which we've already almost
16 completed. If we did that in track changes mode, it would
17 be unreadable. So, you know, it's just wholesale
18 switching of sections is what happened.

19 PANEL MEMBER FRIEDMAN: Somehow if we could have
20 some kind of guidance as to what changes to focus on
21 rather than rereading the whole thing.

22 OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah,
23 exactly.

24 CHAIRPERSON FROINES: You could send them both
25 ways, with track changes and without track changes, and

1 let the reader decide.

2 PANEL MEMBER HAMMOND: Be electronically.

3 CHAIRPERSON FROINES: Electronically, yeah.

4 PANEL MEMBER GLANTZ: What I would suggest is --
5 I think there are parts of the report where the changes
6 are going to be fairly modest. And I think that could be
7 done with the track changes. I think for like Chapter 7,
8 the stuff we were talking about this morning -- and if
9 they do the kind of editing you'd suggested, Gary, I think
10 it would be pretty cumbersome.

11 So maybe what you could do, Melanie, is if it's
12 just -- if you're reorganizing something when you send
13 a -- maybe you could send like a memo with the report
14 saying in Chapter 6 the major change was this way, it was
15 reorganized. Or, you know -- and then if there are parts
16 where the changes were so extensive that you actually
17 rewrote big hunks of them, just say sections 7-1 through
18 7-10 were extensively rewritten and you need to read the
19 whole thing, or something like that.

20 PANEL MEMBER HAMMOND: And maybe on top of that,
21 I would say a track changes for any changes in the
22 executive summary or the summary or conclusions. Those
23 should be very clearly done probably.

24 CHAIRPERSON FROINES: I just had one general
25 comment. There was a fairly spirited debate between a

1 number of people with vis-a-vis cardiovascular. And Stan
2 actually -- paul made the original comment and I made --
3 and I followed up. And when Stan articulated the whole
4 process, beginning to end for cardiovascular disease, he
5 did it very effectively. That I think Stan should work
6 with you on to get that into the document, because it does
7 go from the biochemical, biological to the downstream
8 processes to the health endpoint. And the more we can get
9 on that level, the better off we're going to be because it
10 gives us the linkage between mechanistic findings to
11 health outcomes.

12 So I would urge you to drag out of him everything
13 that he knows that can help that --

14 PANEL MEMBER GLANTZ: I already said everything I
15 know.

16 CHAIRPERSON FROINES: He said -- he volunteered.
17 I'm just --

18 PANEL MEMBER GLANTZ: No, I'm happy to help.

19 CHAIRPERSON FROINES: -- putting it as a --
20 clearly he's got it here.

21 PANEL MEMBER GLANTZ: Just read the transcript,
22 because I said everything I know.

23 That was a joke.

24 CHAIRPERSON FROINES: We hope it is.

25 (Laughter.)

1 CHAIRPERSON FROINES: Because you certainly
2 sounded more -- can we get a motion to adjourn?

3 PANEL MEMBER HAMMOND: I move we adjourn.

4 PANEL MEMBER LANDOLPH: Second.

5 CHAIRPERSON FROINES: All those in favor?

6 (Hands raised.)

7 CHAIRPERSON FROINES: It's unanimous.

8 Thank you very much, folks. This was a very good
9 meeting and very useful.

10 Oh, and I just really want to say, a couple --
11 some of the Panel members have complimented both ARB and
12 OEHHA on the document. But just coming from the Chair I
13 want to say that this is really an extraordinary amount of
14 work that's been done and it's very, very well done. And
15 so everybody should feel good about where we are. We've
16 had two meetings and we've come a very long way. And
17 we'll bring it to closure next time, I hope.

18 (Thereupon the California Air Resources Board,
19 Scientific Review Panel meeting adjourned
20 at 4:10 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
4 Professional Reporter, do hereby certify:

5 That I am a disinterested person herein; that the
6 foregoing California Air Resources Board, Scientific
7 Review Panel meeting was reported in shorthand by me,
8 James F. Peters, a Certified Shorthand Reporter of the
9 State of California, and thereafter transcribed into
10 typewriting.

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 13th day of January, 2005.

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