

MEETING
STATE OF CALIFORNIA
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL

HOLIDAY INN
275 SOUTH AIRPORT BOULEVARD
PENINSULA ROOM
SOUTH SAN FRANCISCO, CALIFORNIA

FRIDAY, MAY 16, 2008

9:15 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison

Mr. Peter Mathews

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION

Dr. Joseph Frank, Senior Toxicologist

Mr. Randy Segawa, Senior Environmental Research Scientist

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT

Dr. George Alexeeff, Deputy Director

Dr. Joe Brown, Staff Toxicologist

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

Dr. Karen Riveles, Associate Toxicologist

Dr. Andrew Salmon, Chief, Air Toxicology and Risk
Assessment Section

Dr. Brice Winder, Staff Toxicologist

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1 PROCEEDINGS

2 CHAIRPERSON FROINES: So let's call the meeting
3 to order, the May 16th, 2008, meeting of the Scientific
4 Review Panel.

5 And the first topic on the agenda is the --

6

7 PANEL MEMBER GLANTZ: There's some feedback. Can
8 you --

9 CHAIRPERSON FROINES: Is that better?

10 PANEL MEMBER BLANC: It's Froines' wall of sound.

11 (Laughter.)

12 CHAIRPERSON FROINES: It's barely past 9 o'clock
13 and we're already into this.

14 (Laughter.)

15 CHAIRPERSON FROINES: Let's put the lid on it and
16 we will be fine.

17 (Laughter.)

18 CHAIRPERSON FROINES: So the first item on the
19 agenda is the discussion of the Panel's findings related
20 to the Endosulfan report.

21 So essentially comments from the Panel.

22 There's one change, by the way. That is, that
23 Toby pointed out that there's a sentence that says, "DPR
24 regulations specify MOEs of greater than 100 to be health
25 protective." And actually there's no regulation, so we --

1 just DPR considers MOEs of greater than 100 to be health
2 protective. So that's that.

3 Gary.

4 PANEL MEMBER BLANC: Where is that?

5 CHAIRPERSON FROINES: It's on page 3, numbered
6 under 9.

7 PANEL MEMBER FRIEDMAN: Well, I had sent in a
8 couple of comments on a previous draft. And I appreciate
9 that one of them was very well responded to in terms of
10 putting -- the first draft just said there were scenarios
11 where there's excess exposure. And now there's actually
12 some description of what those are, and I appreciate that.
13 But there's still something I don't -- there was another
14 change I suggested, which was not made. And probably I
15 don't understand it, but I'd like to just raise that
16 question again.

17 Item number 7 on page 2, the last two sentences:
18 The subchronic inhalation NOAEL of 0.194 milligrams per
19 kilogram-day is the critical NOAEL for evaluating both
20 inhalation exposures and seasonal inhalation exposures in
21 humans." Then the next sentence I don't understand. "The
22 estimated no-effect level (ENEL) of" -- the same number,
23 0. -- oh, it's 0.01. Pardon me. I thought from the last
24 draft they were the same. But 0194 for chronic effects in
25 animals is the appropriate value for evaluating chronic

1 inhalation exposures. That may answer the question,
2 because -- no, I missed the -- so I guess my question was,
3 isn't there supposed to be some kind of factor, you know,
4 taking into account intraspecies variation and within
5 species variation that would make one not look at the
6 animal level but what would be derived from that for
7 humans as the appropriate thing. But I guess I missed the
8 extra decimal place and that's -- does that answer the
9 question?

10 CHAIRPERSON FROINES: Um-hmm.

11 PANEL MEMBER FRIEDMAN: So if it's a tenth as
12 great in animals, that's a level that we accept for
13 humans?

14 CHAIRPERSON FROINES: As the value.

15 PANEL MEMBER FRIEDMAN: Yes. I mean we've always
16 translated values in animals by various factors --
17 uncertainty factors into humans. But now it just says
18 here's the value for animals and that's what we accept for
19 evaluating chronic inhalation exposures in humans.

20 PANEL MEMBER BLANC: I think -- I see now your
21 confusion. I think it's because of the use of the word
22 "for". And I think it should be based on --

23 CHAIRPERSON FROINES: That's right.

24 I'm sorry.

25 PANEL MEMBER BLANC: Do you think that's correct?

1 CHAIRPERSON FROINES: Um-hmm.

2 PANEL MEMBER BLANC: So I would suggest that if
3 it read, "The estimated no-effect level of 0.194" --
4 "0.0194 milligrams per kilograms-day based on chronic
5 effects in animals" --

6 OEHHA DEPUTY DIRECTOR ALEXEEFF: It's not based
7 on the --

8 PANEL MEMBER BLANC: It's not based -- isn't it
9 one-tenth of what the animal level is?

10 OEHHA DEPUTY DIRECTOR ALEXEEFF: Maybe -- George
11 Alexeeff of OEHHA.

12 No -- Joe Frank, is he here?

13 Okay, yeah. So he can correct me if I'm wrong.
14 But when you have -- this is the terminology that DPR
15 uses -- estimated no-effect level, that means they've --
16 they didn't have an exact -- there was not an exact study
17 of a no-effect level. So it's estimated by adding in an
18 uncertainty factor or an adjustment factor.

19 So they've simply taken the subchronic value,
20 added a tenfold adjustment factor, and estimated the
21 chronic value. So it's still based on that same study,
22 the same study as the subchronic study. Is that correct,
23 Joe?

24 DPR SENIOR TOXICOLOGIST FRANK: That's correct.

25 OEHHA DEPUTY DIRECTOR ALEXEEFF: That is correct.

1 Does that -- so the reason that you estimated is
2 because we did not have a study that specifically met the
3 chronic criteria.

4 CHAIRPERSON FROINES: So we should say based on
5 subchronic effects in animals.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Yes.

8 OEHHA DEPUTY DIRECTOR ALEXEEFF: Is that correct?

9 Yeah, that's correct.

10 PANEL MEMBER FRIEDMAN: So the previous sentence
11 has just taken and added an uncertainty factor to that, is
12 that -- of tenfold? Well, actually it's ten times as
13 great. So I guess I still don't fully understand what's
14 going on here.

15 PANEL MEMBER BLANC: No, it's ten times as
16 sensitive, Gary. Ten times more sensitive, ten times
17 lower.

18 PANEL MEMBER FRIEDMAN: But they're saying that a
19 ten times as great level in the previous sentence is the
20 critical for evaluating exposures in humans. So wouldn't
21 you want an even lower level than what's observed as no
22 effect -- or is estimated as no effect in animals?

23 CHAIRPERSON FROINES: That's the tenfold safety
24 factor -- uncertainty factor.

25 PANEL MEMBER FRIEDMAN: But it seems to be going

1 in the wrong direction.

2 CHAIRPERSON FROINES: I don't think so.

3 OEHHA DEPUTY DIRECTOR ALEXEEFF: George Alexeeff
4 again.

5 No, it's not going in the wrong direction. The
6 extrapolation -- the adjustment is not from animal to
7 human at this point. It is simply subchronic to chronic.
8 So in this case it's still the same animal study and we're
9 still ultimately trying to protect humans. But it's not
10 an actual interspecies adjustment at this point. So it
11 would --

12 CHAIRPERSON FROINES: That's how I understood it.

13 PANEL MEMBER FRIEDMAN: Well, I don't want to
14 take up -- you know, I guess I don't fully understand it.
15 But if everyone else accepts it, you know, that's fine.
16 I'll just talk to somebody afterwards and better
17 understand it.

18 CHAIRPERSON FROINES: It is -- the point is it is
19 what it is, and it's the basis around which MOEs are
20 calculated. And so the only -- what I would like -- what
21 I think we would all like to avoid is getting into some
22 explanation -- I mean we could add in, although I'm not
23 sure I'm for it, but add in what George said, is that this
24 is a subchronic to chronic adjustment.

25 We're saying the estimated no-effect level of

1 .0194 based on subchronic effects in animals is the
2 appropriate value for evaluating chronic inhalation
3 exposure in humans. So I think it's clear.

4 PANEL MEMBER BLANC: Yeah, with that change I
5 think it's fine.

6 PANEL MEMBER FRIEDMAN: Okay.

7 CHAIRPERSON FROINES: You're okay?

8 PANEL MEMBER FRIEDMAN: I mean it's -- I don't
9 want to take up more time of the Committee. I mean I
10 respect you guys. And I just need to talk to somebody off
11 line about it just for my own education.

12 CHAIRPERSON FROINES: Okay. George, what's the
13 history of this term -- Randy -- what's the history of the
14 ENEL? Because that's historically not the way we've
15 talked about this?

16 OEHHA DEPUTY DIRECTOR ALEXEEFF: I mean the
17 history is that -- I mean OEHHA has --

18 CHAIRPERSON FROINES: Randy may want to --

19 OEHHA DEPUTY DIRECTOR ALEXEEFF: Or Joe -- I
20 think Joe Frank is probably the appropriate person, from
21 DPR.

22 But the history is that we've always done this
23 type of adjustment. DPR has always explicitly called it
24 an estimate. And we just -- we never used that word. We
25 just said the NOAEL is such and such. But in there there

1 might be an adjustment factor from a LOEL or a subchronic
2 to chronic or something like that. They just explicitly
3 state that it's -- we didn't have the exact study on which
4 we got this number. We had to make an adjustment, so call
5 it the ENEL.

6 CHAIRPERSON FROINES: It's just that I -- for me,
7 and maybe this is my fading memory as I age, especially
8 with this Panel, but I think the ENEL is a new term, isn't
9 it?

10 PANEL MEMBER FRIEDMAN: Yes, I've never seen it
11 before.

12 CHAIRPERSON FROINES: Is it? Because I --

13 OEHHA DEPUTY DIRECTOR ALEXEEFF: They've --

14 CHAIRPERSON FROINES: Well, give him a chance.
15 He's with DPR.

16 OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, Joe, why
17 don't you just come on up and explain --

18 PANEL MEMBER GLANTZ: Why don't -- yeah, because
19 I have the same reaction. Why don't you just delete the
20 paren ENEL close paren. Then it's just an estimated
21 no-effect level.

22 CHAIRPERSON FROINES: We could do that.

23 PANEL MEMBER GLANTZ: Then we don't have a new
24 acronym introduced that's causing us all --

25 DPR SENIOR TOXICOLOGIST FRANK: Yes, I'm Joe

1 Frank from DPR.

2 It's something we've used for a number of years.
3 And the reason we throw "estimated" in front of a NOEL is
4 to just make it a little more clear that we're not using
5 an actual calculated NOEL. But we've done that in the
6 past as well. For example, when we don't have a NOEL, we
7 have a LOEL, then we'll do an adjustment factor of 10 and
8 call it an estimated NOEL. And some people just make it
9 shorthanded and call it an ENEL. But it's an estimated
10 NOEL with some sort of adjustment. And the rationale in
11 the document should always be clear.

12 CHAIRPERSON FROINES: So, Stan, taking out the
13 acronym is -- it is the estimated no-effect level.

14 PANEL MEMBER GLANTZ: Yeah. But the acronym, I
15 had the same reaction. I never heard of ENEL for that.

16 It's not worth arguing about.

17 CHAIRPERSON FROINES: So, okay, let's -- I think
18 there's agreement that this is -- these changes clarify
19 a --

20 PANEL MEMBER FRIEDMAN: But, again, George was
21 saying that what really the tenfold difference is from
22 chronic to subchronic --

23 CHAIRPERSON FROINES: Subchronic to chronic.

24 PANEL MEMBER FRIEDMAN: Beg your pardon?

25 CHAIRPERSON FROINES: Subchronic to chronic.

1 You're taking a subchronic study and you're -- and you
2 don't know if that's appropriate -- entirely appropriate
3 for a chronic value. And so you're adding a safety factor
4 of 10 -- uncertainty factor, whichever. In other words
5 the subchronic study is not a chronic study. And so
6 they're simply saying, "We're going to add an uncertainty
7 factor of 10 to take that into consideration."

8 PANEL MEMBER FRIEDMAN: Okay. But we've
9 always -- there's always been uncertainty factors when we
10 go from one species to humans. And that last sentence
11 seems to deny that.

12 PANEL MEMBER BLANC: But you're mixing apples and
13 oranges, because in their system instead of doing that,
14 what they do is this ratio of possible exposure to NOEL.
15 And then they put the safety factor in after that
16 essentially by saying that the -- if the margin of the
17 ratio isn't a thousandfold or a hundredfold, then the
18 potential for an effect is possible. And so that's how
19 they do it in the DPR thing. That's what's confusing you,
20 I think, is that that's where -- whereas in the other
21 system we're used to where we're talking about action
22 levels or whatever they -- I forget what they call it --
23 MACs or whatever the hell they are, that's where they
24 start using those multiplication factors in that way. So
25 that I think is what's essentially confusing you.

1 PANEL MEMBER FRIEDMAN: Well, what's confusing me
2 is the appearance of the word "chronic" in the last
3 sentence twice. "The estimated no-effect level for
4 chronic effects in animals is the appropriate value for
5 evaluating chronic inhalation exposures in humans."

6 CHAIRPERSON FROINES: We changed that. We
7 changed it to: "The estimated no-effect level of .0194
8 milligrams per kilogram-day based on subchronic effects in
9 animals is the appropriate value for evaluating" --

10 PANEL MEMBER FRIEDMAN: Okay, thank you. That
11 takes care of it.

12 CHAIRPERSON FROINES: So --

13 PANEL MEMBER BLANC: I'll move to accept the
14 findings as stated, with the modifications as noted.

15 CHAIRPERSON FROINES: Is there a second?

16 PANEL MEMBER FRIEDMAN: Second.

17 CHAIRPERSON FROINES: Is there discussion?

18 Hearing no discussion.

19 All those in favor of adopting the motion.

20 (Hands raised.)

21 CHAIRPERSON FROINES: Unanimous.

22 PANEL MEMBER BLANC: The Chair's voting too?

23 CHAIRPERSON FROINES: Sure.

24 So that's good.

25 I wanted to raise one issue with you and not

1 overstate it. But in this document, we are -- we are
2 making findings that one could say at a minor level or a
3 not so minor level, whatever -- however one wants to
4 characterize it -- we are differing from DPR in our
5 findings. And my view is that -- as you noticed, I didn't
6 write anything to call attention to that in these
7 findings. But I thought that it might be -- we shouldn't
8 just leave it in that way. So I thought when I wrote the
9 transmittal letter to Mary-Ann, that I would actually
10 bring to her attention that there is a difference of
11 opinion.

12 The other alternative is to just not mention it
13 at all. But, for example, there was very -- there was
14 very active discussion about the safety factor for
15 children. And my view is that DPR should be aware that
16 the Panel thinks that there should be a safety factor to
17 take into account that particular issue.

18 So I assume that won't create any problems. But
19 we can go either way. We can just ignore the differences
20 in terms of our communication with DPR or we can call
21 attention to it.

22 PANEL MEMBER GLANTZ: I think you should point it
23 out in a cover letter.

24 PANEL MEMBER FRIEDMAN: I do. And specify what
25 they are and not just say there are differences and people

1 have to search for them. But specify what you were just
2 saying.

3 CHAIRPERSON FROINES: Yeah. It would be very
4 brief. It may be just a couple, three --

5 PANEL MEMBER BLANC: That's on point 11, right?

6 CHAIRPERSON FROINES: Well, there are three
7 issues --

8 PANEL MEMBER BLANC: But there's also the
9 genotoxicity issue --

10 CHAIRPERSON FROINES: -- genotoxicity. And their
11 document basically spends a lot of time saying it's not a
12 carcinogen. And in true academic form we would prefer to
13 say further studies would be relevant.

14 So there are three issues. I frankly don't
15 understand why they -- every academic always says more
16 research is needed, and that's all we were saying. And so
17 the fact that they didn't adopt that seems to me to be
18 unfortunate. But, again, it's not something to make a big
19 deal out of, because I think that the history of
20 Endosulfan is that it's on the way out. And so whether --
21 actually whether one wants to do chronic bioassays at a
22 national toxicology program, that's -- whether it's worth
23 it on Endosulfan is a good question.

24 PANEL MEMBER BLANC: No, but it has to do with
25 what criteria one might use to assess genotoxicity.

1 CHAIRPERSON FROINES: Right.

2 PANEL MEMBER BLANC: And I think that there
3 was -- I think the emphasis you might put on that in the
4 letter is that we perhaps lean more towards a holistic
5 assessment of genotoxicity, without using carcinogenicity
6 as the trump card. In other words, I -- I mean if I had
7 to summarize the discussion around the table, it was, yes,
8 okay, the carcinogenicity studies are weak. But because
9 those studies were equivocal in the face of other studies
10 that are convincing of genotoxicity short of
11 carcinogenicity, it's important to not discard that, which
12 seemed to be less equivocal, the evidence. So I think
13 that would be a sort of positive spin to put on it. Not
14 that we thought that they should have said it was a
15 carcinogen, but that there were studies that would have
16 seemed to put it more squarely as genotoxic even if you
17 couldn't establish carcinogenicity.

18 CHAIRPERSON FROINES: Well, in fact, that's what
19 our finding says. We say, "The Panel has concluded
20 Endosulfan is likely genotoxic." We acknowledge that
21 "Endosulfan has not consistently induced tumors in rats
22 and mice. However, due to its genotoxicity and
23 tumor-promoting ability, Endosulfan has the potential to
24 be carcinogenic with further studies required."

25 That seems to me to be --

1 PANEL MEMBER BLANC: Yeah, yeah.

2 CHAIRPERSON FROINES: -- exactly what you're
3 saying.

4 PANEL MEMBER BLANC: Right.

5 CHAIRPERSON FROINES: And in the transmittal
6 letter you're saying --

7 PANEL MEMBER BLANC: Right, exactly.

8 CHAIRPERSON FROINES: So with the changes that we
9 just made, we are finished on Endosulfan.

10 So, Randy, I'll write a transmittal letter next
11 week and send it over to you guys. And Kathy and --

12 PANEL MEMBER BLANC: -- Joe.

13 CHAIRPERSON FROINES: -- Joe got it down to three
14 pages. I got it back to four pages with Gary's comments.
15 But this may be a new record. Probably is a model.

16 We finally after how many years, Gary, have
17 gotten to you're argument of --

18 PANEL MEMBER FRIEDMAN: No. Well, you got it
19 back to the way it used to be.

20 CHAIRPERSON FROINES: No, it's only four pages.

21 PANEL MEMBER FRIEDMAN: Oh, yeah. But that's
22 what it -- that's good. I mean I --

23 PANEL MEMBER BLANC: Oh, you're saying that's
24 good.

25 PANEL MEMBER FRIEDMAN: Yeah. I mean the first

1 report we got was huge. And so this is just right.

2 CHAIRPERSON FROINES: I wonder how many pages we
3 had with diesel? Do you remember, George? I'm sure it
4 wasn't four.

5 (Laughter.)

6 CHAIRPERSON FROINES: Melanie, we'll move ahead.
7 (Thereupon an overhead presentation was
8 Presented as follows.)

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Good morning. Melanie Marty.

11 PANEL MEMBER BLANC: Good morning, Melanie.

12 PANEL MEMBER GLANTZ: Morning, Melanie.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: So this morning we're going to be going over our
15 revised methodology for non-cancer risk assessment. And
16 as you'll recall, the Panel got first the public review
17 draft to look at while we were busy responding to public
18 comments. And then once we did that, the Panel received
19 our revised version plus the responses to comments for
20 their review.

21 So what we're going to do today is go over,
22 first, the methodology section, which is the big part of
23 the document, and then individually the chemicals that we
24 developed Reference Exposure Levels based on the revised
25 methodology.

1 So I'm going to have Andy present the technical
2 support document and the main -- just the main issues.
3 And we had given a presentation at the last SRP meeting,
4 so we didn't want to just repeat that whole thing. So
5 we're going to again hit the highlights and then focus on
6 a few changes that were made, including changes in
7 response to the lead on the methodology section, who is
8 Dr. Glantz. So --

9 CHAIRPERSON FROINES: Could I do two things.

10 First is, Randy, just before we get off DPR, in
11 terms of planning for future meetings, do you have a sense
12 of when the next pesticide will come to the Panel? And if
13 you don't, that's fine.

14 DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

15 SEGAWA: Good morning. I'm Randy Segawa with the
16 Department of Pesticide Regulation.

17 The next chemical we think will be chloropicrin
18 and will probably come to you this fall, is our hope.

19 CHAIRPERSON FROINES: Fall.

20 DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

21 SEGAWA: Yes.

22 CHAIRPERSON FROINES: It would be September or
23 closer to December?

24 DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST

25 SEGAWA: I would say closer to December.

1 CHAIRPERSON FROINES: Okay. So that will affect
2 our planning.

3 Thank you very much.

4 Melanie, since we just went through the findings,
5 historically we've never -- we've voted on issues like
6 this, but we've not written findings. Is that your
7 general view of this? Do you want findings from the
8 Panel?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: You're right, that historically for these
11 documents you have not written findings. The findings
12 have only been for identification of a chemical as a toxic
13 air contaminant.

14 If you want to write findings, it's up to you
15 guys. But we didn't anticipate that you would.

16 CHAIRPERSON FROINES: Well, here's what I
17 think -- and I'm certainly willing to be a minority. But
18 that I've become aware that throughout the world and
19 within the United States that there are a lot of agencies
20 and groups that actually pay attention to what OEHHA is
21 doing. And so you've been -- you are a leader both in
22 terms of the risk assessment values that you derive but
23 also in the risk assessment methodology to lead to those
24 values.

25 So there's a lot of attention to OEHHA's findings

1 in a very wide spectrum of organizations and groups. And
2 so my sense would be that having a very short couple of
3 sentence, a page even, findings in which an established
4 scientific panel blessed what you have done would
5 reinforce the credibility of your effort. So my sense
6 would be that it would be valuable -- it might be helpful,
7 not necessarily valuable, to have short findings.

8 What do you think about that?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: That's a good point.

11 CHAIRPERSON FROINES: Stan, what do you think?

12 PANEL MEMBER GLANTZ: Well, I always sort of
13 thought that the fact that it was approved -- the report
14 was approved by the Panel was all you needed. But I don't
15 see any harm in it. And I'd be happy to work with Melanie
16 to prepare some brief findings.

17 CHAIRPERSON FROINES: I mean I think it should be
18 brief and --

19 PANEL MEMBER GLANTZ: No more than 12 pages.

20 (Laughter.)

21 CHAIRPERSON FROINES: Do you want to write 12
22 pages?

23 PANEL MEMBER GLANTZ: No, no, no. No, I think
24 that -- you know, that would be like an executive summary
25 almost. But, yeah, if you think that's a good idea, I

1 don't think that would be hard to do.

2 My only thing was I didn't know if we were
3 going to -- my predilection is that we should approve the
4 parts of the report that are here today.

5 CHAIRPERSON FROINES: Yeah, we'll get to that.

6 PANEL MEMBER GLANTZ: So I mean creating a
7 findings document, would that in any way delay anything?
8 That would be my only concern.

9 CHAIRPERSON FROINES: I don't think so.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Just a reminder. We do have another meeting
12 scheduled for June 18th. So things that carry over, we
13 can --

14 CHAIRPERSON FROINES: And I asked Melanie today
15 is there enough substance for a meeting a month from now?
16 And she assured me that there was. So we'll go ahead with
17 the planning.

18 I think that Melanie said that manganese is
19 probably going to elicit a lot of interesting comment.
20 And Paul Blanc is just waiting with bated breath on
21 manganese, I know.

22 PANEL MEMBER GLANTZ: Okay. Well, I'd just
23 say -- I mean I don't know -- I can't prejudge what the
24 Panel's going to do. But I'm happy with the methodology
25 part of the document now. So I would hope we would be

1 able to approve it today. Although if people raise
2 issues, then we won't. But I suppose we could approve the
3 document and then approve an additional set of findings in
4 a month.

5 CHAIRPERSON FROINES: Anyway, let's go ahead.

6 --o0o--

7 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

8 CHIEF SALMON: Is this okay?

9 Yeah, I think so.

10 Okay. I'm Andy Salmon with OEHHA.

11 As Melanie said, I've got a short presentation
12 here which just picks out some of the highlights of the
13 document.

14 --o0o--

15 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

16 CHIEF SALMON: You saw the previous draft version there of
17 course. And this version which you have received is in
18 response to comments -- first round of comments from
19 particularly Dr. Glantz. And also we now do have the
20 public comments assembled, and we have responses for
21 those, which you also have.

22 I'm just going to provide a very brief summary
23 here. But obviously if there are any points either in
24 that or during the rest of the presentation that you want
25 to amplify, then please do so.

1 question?

2 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

3 CHIEF SALMON: Certainly.

4 CHAIRPERSON FROINES: Going back a long time ago
5 when we did methylene chloride, I remember George's
6 presentation where he went through all the uncertainties
7 in the PVPK models. And we've come a long way since that
8 time and obviously the models are much more accepted. But
9 there's still some -- in my view, some ambiguity about the
10 uncertainty associated with them.

11 And in terms of the models, I assume that you
12 spend a fair amount of time looking -- still to this day
13 looking at those uncertainty issues, because they are
14 rampant I think.

15 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

16 CHIEF SALMON: Absolutely. I think that the standard
17 practice in using pharmacokinetic models now definitely
18 includes things like sensitivity analysis. And we have in
19 fact used things like, you know, a Monte Carlo
20 distributional analysis in some of the models. Exactly
21 how explicit that is in the narrative about the model is a
22 little bit variable, because there's an underlying
23 principle that some degree at least a basic sort of -- at
24 least an informal sensitivity analysis to figure out
25 whether we know enough to make use of the model.

1 And of course one of the things about the
2 uncertainties that you uncover in the use of the model is
3 that these are all -- it may look as if the model is
4 making things worse rather than better. But what it's
5 actually doing is pointing out that your previous
6 assessment based on an uncertainty factor didn't
7 necessarily cover all the variables adequately. So I
8 think even if a model in fact displays some relatively
9 large and serious uncertainties, it's still a useful way
10 of looking at the situation, or at least that's the
11 general analysis which we're offering in this document.

12 So, obviously, you know, when it comes to a
13 particular assessment, then everything is case by case and
14 we either do or do not use the model depending on whether
15 it's reasonable, appropriate and sufficiently -- we're
16 sufficiently confident in it.

17 CHAIRPERSON FROINES: And I'm embarrassed to say
18 that I've forgotten whether what you just said verbally is
19 actually in the document.

20 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
21 CHIEF SALMON: I believe it is, yes.

22 CHAIRPERSON FROINES: So, that's okay. I just
23 think it -- the issue of sensitivity and uncertainty I
24 think just need to be explicitly stated that you -- so
25 nobody has any illusion that you just accept the --

1 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

2 CHIEF SALMON: Well, certainly I think, you know, we do
3 take that as a point. And, you know, we'll go through and
4 check to make sure whether -- see whether there isn't
5 something we ought to underline in the document. But I
6 believe that statement is there. But we'll check to
7 make --

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: We'll check.

10 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

11 CHIEF SALMON: -- we'll check to make sure that it's
12 sufficiently emphatic.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: I think it's safe to say that nobody thinks that
15 PBPK models erase all uncertainty.

16 CHAIRPERSON FROINES: Well, but the other side of
17 it is when you get into Monte Carlo simulation, then of
18 course the number of options you have becomes this
19 monster. And so --

20 PANEL MEMBER GLANTZ: Well, yes and no. I mean
21 you can -- the value of doing the Monte Carlo simulations,
22 you can introduce uncertainty and a whole bunch of
23 parameters in the model, but at the end you have one
24 number popping out at the end. And so what you end up
25 with is the distributional characteristics of the net

1 result. In this case it would be the REL.

2 So the fact that there's a lot of -- a lot of
3 uncertainty in different elements of the model, what you
4 end up with is the net effect on the output variable. So
5 what you end up with is just some measure of uncertainty
6 in what the REL is. There's this sort of cumulative
7 effect of all the other uncertainties.

8 CHAIRPERSON FROINES: Well, but with the -- if
9 you look at some of Dale Hattis's work, and he gives you a
10 list of options to choose from that's, you know, pages
11 long, and his input. And what he is saying is that there
12 then needs to be a decision about what you intend to
13 adopt.

14 PANEL MEMBER GLANTZ: Sure. But that's true in
15 anything.

16 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
17 CHIEF SALMON: Yeah, I think one of the problems which you
18 inevitably face with this sort of modeling approach is
19 that, you know, on the one hand you've got things which
20 are essentially variability, where you can relatively
21 easily at least -- you know, you can get some idea of what
22 the distribution of the variability is likely to be. And,
23 you know, following Dale Hattis of course we tend to
24 assume it's not normal. But at least, you know, that you
25 have some kind of a handle on the issue with that.

1 obviously we'd use the chronic REL. But this covers
2 certain particular situations such as off-site workers,
3 children in schools, and some other special situations
4 which apply in some Hot Spots risk assessments.

5 We're considering also, again in response to
6 comments we've received, that we may in cases where it's
7 needed develop separate values for adults and for infants
8 and children because of the nature of the special
9 situations that the assessments might be facing.

10 The 8-hour reference exposure levels which you
11 see in the package, and which we'll be talking about in a
12 few minutes, are designed to be protective of children.
13 But we are considering the possibility in the future of
14 developing ones which would be protective of adults but
15 not children as a later development.

16 PANEL MEMBER BYUS: Yeah, I have a comment --
17 shall we comment now or -- as we go along or --

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
19 CHIEF SALMON: Go ahead.

20 PANEL MEMBER BYUS: I had one comment in regard
21 to that last statement. And, that is, you've done a very
22 nice job for the most part about children. But the other
23 major variable is the geriatric, older, elderly.

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
25 CHIEF SALMON: Yes.

1 PANEL MEMBER BYUS: And in terms of
2 pharmacokinetics, toxicokinetics it's even -- potentially
3 even more dramatic than the difference between adult and
4 children is the difference between geriatric and adult.
5 As you know, clearance -- virtually all the clearance
6 mechanisms are significantly reduced in geriatrics as you
7 age: Renal clearance, secretion, filtration markedly
8 diminished; lung capacity's markedly diminished;
9 distribution effects or cardiac output is significantly
10 reduced. So in terms of toxicokinetics and then the SIP
11 enzymes, there's a both quantitative and qualitative
12 difference among geriatric patients -- or geriatrics, not
13 patients -- drugs here.

14 The other difference is disease -- the disease
15 overlay. As you age, you have much more likelihood to
16 have disease processes which could affect your sensitivity
17 for the toxicodynamic aspects. Environmental exposures.

18 And also geriatric -- elderly are usually taking
19 a lot more drugs, so their clearance mechanisms can be
20 saturated in terms of environmental.

21 So really, you know -- and I think somewhere in
22 here you should mention this. Now, whether you want to
23 discuss it in detail, but I think you should mention it
24 because it's sort of strikingly absent as you read it.
25 And I like the way this is written and I like the way it's

1 done -- don't get me wrong -- for the most part. But I
2 think it's -- when I read it, that's what I was struck by.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: We will add a paragraph. I think that's a good
5 point. There is some effort underway in the risk
6 assessment community to try to get a better handle on
7 that, because it's absolutely true.

8 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

9 CHIEF SALMON: I think we do say somewhere that we -- you
10 know, we have a concern for sensitive sub-populations of
11 any type, of which children obviously are an example. But
12 we should make --

13 PANEL MEMBER BYUS: But then the drug analogy
14 which you've used in here. And the drug analogy, there's
15 much more data on a geriatrics, there's much more interest
16 in it, and there's much more information available. So in
17 a sense I think it would almost be easier than to do the
18 children. But not that the children are not important,
19 because it is, very clearly.

20 But, as I said, it's strikingly not stated. You
21 should at least have a paragraph. Say what I just said
22 and that your more detail analysis will come later.
23 Because I think because it's not said here, it's like
24 maybe you're not aware of it and that it makes your other
25 arguments about the children less valid.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: We'll add a paragraph. Also, Dale Hattis has done
3 some work looking just exactly at that.

4 CHAIRPERSON FROINES: Yeah, but it -- Melanie, I
5 think that's a really important point that is not really
6 going to be dealt with by a paragraph in the long run; in
7 the short run perhaps. But in the long run it seems to me
8 that we ought to develop a project on geriatric --

9 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

10 CHIEF SALMON: Well, as Melanie says, there is in fact
11 some ongoing investigation into this area going on inside
12 of OEHHA; not specifically in this context but in general.
13 So you will likely be seeing some product or response to
14 that at some point.

15 CHAIRPERSON FROINES: It would be interesting to
16 actually do a worst-case scenario and, say, look at, you
17 know, these chemicals being blocked because you're
18 metabolism is -- your clearance is saturated and so on.
19 And I don't want to get into --

20 PANEL MEMBER BYUS: But, as you say, clearance is
21 the -- clearance is what allows drugs and chemicals to
22 accumulate. So if clearance is impaired, that's like the
23 worst thing that could happen for accumulation. I mean
24 exposure -- repeated exposure is important, but its
25 clearance is the controlling factor. And because

1 clearance is generally decreased in all aspects in the
2 geriatric patients, plus the disease sensitivity,
3 toxicodynamic aspect, you know, because they would be much
4 more likely to have any of a variety of overlaying
5 diseases than you would be in a child, it really -- you
6 know, and it struck me as I was reading it, and just what
7 you just said, that geriatrics people could be the most
8 sensitive out there in the environment.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Well, you know, it's certainly true for
11 particulate matter air pollution, among other things. I
12 mean, you know, we can see that in Epi studies.

13 PANEL MEMBER BYUS: Sure.

14 PANEL MEMBER GLANTZ: Do you have any specific
15 references you think they ought to --

16 PANEL MEMBER BYUS: I was going to give you a
17 reference site. There's actually a very good paper, I
18 think it was in Nature about four or five years ago --
19 that has -- I use it in my lectures to medical students.
20 It has great graphics about the changes in the SIP
21 enzymes' clearance, from child through adult to geriatric.
22 They show you the continuum. It's a very nice series of
23 graphics. And I can get you the reference for that.

24 CHAIRPERSON FROINES: Okay. That would be great.
25 Thank you.

1 PANEL MEMBER FRIEDMAN: Would you send it to all
2 of us?

3 PANEL MEMBER BYUS: Sure, sure.

4 PANEL MEMBER FRIEDMAN: Thank you.

5 PANEL MEMBER GLANTZ: It's becoming more relevant
6 every day.

7 (Laughter.)

8 PANEL MEMBER BYUS: Shocking though. That's why
9 I -- I keep looking at those diminished organ capacities
10 with age. And it's a wonder I can even walk and go to the
11 bathroom properly.

12 (Laughter.)

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
14 CHIEF SALMON: The next thing I was just going to mention
15 in passing is this idea that the inter and intraspecies
16 uncertainty factors originally were just -- you know,
17 they're ten because we have ten fingers, and they were
18 considered as a monolithic item. But more recently people
19 have started to think of both of these uncertainty factors
20 as consisting of both a pharmacokinetic and a
21 pharmacodynamic component. And the advantage of doing
22 that is, firstly, it gives you a slightly more refined way
23 of deciding whether the value you're using is sufficient;
24 and, secondly, it gives you the opportunity to
25 individually replace these with specific models. Whereas

1 is often the case, one might, for instance, have a
2 pharmacokinetic model which was compound and species
3 specific but not of a dynamic model -- not a model toxic
4 response.

5 --o0o--

6 CHAIRPERSON FROINES: Do you think -- Do you
7 think -- sorry. Going back to that.

8 Do you think that you are going to have enough
9 information on pharmacodynamic issues?

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: I was just going to add that --

12 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

13 CHIEF SALMON: Seldom.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

15 MARTY: Yeah, exactly. That's going to be really rare.

16 And I can't think of an example that actually exists right
17 now where we're confident that the pharmacodynamics is
18 adequately modeled.

19 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

20 CHIEF SALMON: It's possible that the OP people might be
21 able to do something. But I don't think we want to go
22 there at this point.

23 CHAIRPERSON FROINES: I mean the toxicokinetics
24 is much simpler. That's --

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: It's better understood at least.

2 CHAIRPERSON FROINES: It's better understood.

3 Simpler's not the right word. But you know what I mean.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

5 CHIEF SALMON: Yes. I would certainly agree with that in
6 general.

7 The other thing we've talked to you about already
8 at some length is the use of benchmark concentration
9 methodology. And this we now prefer -- when we can use
10 it, which is actually most of the time, we prefer the
11 benchmark concentration approach. And we specifically
12 define our benchmark or point of departure so that it has
13 properties which are similar to a NOEL, so we would be
14 using the same uncertainty factors with that point of
15 departure as we do for a NOEL.

16 CHAIRPERSON FROINES: As we move into the new
17 era, however rapidly it emerges, when we are going to be
18 using, quote, biomarkers and high throughput assays and
19 all the other things that were in that NRC report that
20 Lauren Zeise was on, as we get into that, then the issue
21 of a threshold becomes much more difficult because you're
22 looking at changes in NRF keep-one, you know, changes or
23 oxidated stress or whatever the -- glutathione
24 depletion -- you begin to have the potential to look at
25 things for which there is, if anything, a very low

1 threshold. And so you'll have data that one could use at
2 a very different stage in understanding the process. And
3 I assume that that's going to affect everything.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
5 CHIEF SALMON: Yes.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Yes, I think it's safe to say it will affect risk
8 assessment. And that at this point a lot of the people
9 doing risk assessment are asking ourselves, how are we
10 going to deal with those types of data? Not that we
11 haven't dealt with them in the past before. Perchlorate
12 is one example where our drinking water group based the
13 public health goal on what was considered a precursor
14 effect, that is, inhibition of iodine uptake by the
15 thyroid.

16 So, you know, it is a very interesting problem.
17 And it's going to -- it's going to require a lot of
18 thought on how to apply this, because you're absolutely
19 right, the meaning of a threshold is certainly going to
20 change in that context.

21 CHAIRPERSON FROINES: Well, it's also going to
22 require major policy and legal considerations. Because if
23 you say that inhibition of various phosphatase is an
24 adverse effect that you're going to regulate, you're going
25 to end up in court with people saying that's a biochemical

1 marker, that's not a rat study.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Amen.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

5 CHIEF SALMON: Well, yeah, there's a huge debate about
6 this going on at the moment. I mean there are some actual
7 technical approaches including one which you will see in
8 one of the -- in the acetaldehyde REL coming up, where you
9 can actually use a severity score for a particular
10 response as an input to what essentially is a
11 pseudo-continuous variable as input to a benchmark model.

12 So there are actually some technical measures we
13 have in hand which will assist us in responding to that
14 dilemma. But it certainly doesn't relieve us of, as you
15 point out, the basic sort of policy-based decision as to
16 how we're going to be able to respond to that.

17 CHAIRPERSON FROINES: I meant activation of
18 phosphatase. It's not inhibition. So --

19 PANEL MEMBER BYUS: You mention in here about
20 defining the effect as a toxicological effect, not a
21 biological effect.

22 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

23 CHIEF SALMON: Yes.

24 PANEL MEMBER BYUS: I mean that's really where
25 the argument is, are these markers biological or

1 toxicology -- toxicological? And the strength of that
2 association is where the discussion will lie. And you do
3 mention that in here, that -- and that when you set these
4 values, you're looking at the toxicological endpoint as
5 best that you can.

6 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

7 CHIEF SALMON: Yes.

8 CHAIRPERSON FROINES: So if you have activation
9 of NRF2 and you're seeing more Phase 2 enzymes, is that a
10 toxicologic effect? It's trying to prevent a toxicologic
11 effect.

12 PANEL MEMBER BYUS: Not necessarily

13 toxicological.

14 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

15 CHIEF SALMON: We don't necessarily --

16 PANEL MEMBER BYUS: You have to go further on

17 that association.

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

19 CHIEF SALMON: Yeah, it depends on what's going on. And
20 there are certainly circumstances in which activation of
21 Phase 1 or Phase 2 enzymes could actually have adverse
22 consequences. I mean some of the -- actually some of the
23 endocrine impacts of certain chemicals involve activation
24 of enzymes which also degrade things like T3 or steroid
25 hormones or whatever.

1 The traditional value of the UFA, the
2 interspecies uncertainty factor, has been 10, which we now
3 regard by default as consisting of a toxicokinetic factor
4 of root 10, or approximately 3, and a toxicodynamic factor
5 again of root 10, or approximately 3. The reason for root
6 10 obviously is if you put two together, then you get the
7 results of 10 because these are multiplicative factors.

8 PANEL MEMBER FRIEDMAN: May I ask, is the
9 subscript A -- just to help me remember these subscripts,
10 does that stand for animals?

11 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
12 CHIEF SALMON: Yes, it does. A stand for animal, K stands
13 for kinetic, and D stands for dynamic.

14 PANEL MEMBER FRIEDMAN: And H for human?

15 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
16 CHIEF SALMON: H for human, yes. You'll see these coming
17 through repeatedly, but that's the convention.

18 And as I mentioned previously, when we have the
19 opportunity to do so, we would replace either one or both
20 of these with a model. So if we have what we consider an
21 adequate model, then we would drop, say, the kinetic
22 factor. So you'd have an overall -- a UFA of 3.

23 But there's what we consider a partial model,
24 which was being used quite a bit in the past, which is the
25 U.S. EPA's health -- human equivalent concentration

1 calculation based on their regional gas dose distribution
2 model, an RGDR model. That we regard as a partial model.

3 And so unlike previous practice, we're now
4 actually just reducing the UFA to 6 rather than 3, because
5 we don't see that model as covering all the kinetic
6 uncertainties. It doesn't deal with metabolism. It
7 doesn't deal with distribution outside of the -- and it's
8 a fairly generic model of what goes on in the lung as
9 well. But it's nevertheless useful when we don't have
10 anything better.

11 And as we commented previously, unfortunately
12 there are few cases where we have a workable toxicodynamic
13 model. Although we may feel that we know enough about the
14 toxicodynamic situation that we might feel we should
15 choose a non-default value of the UFA-d if we know
16 something about the dynamics.

17 And so in all these cases what we're recommending
18 is defaults for which we can choose something different
19 based on specific information that we might have.

20 --o0o--

21 CHAIRPERSON FROINES: I worry a little bit about
22 your only giving a factor of 3 for toxicokinetics. If you
23 take Craig's comments earlier, the toxicokinetics could be
24 much greater.

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: That is particularly true of the
2 intraspecies variability, which is what -- which is the
3 next one I'm just about to speak to. And you will see
4 that I heartily endorse your sentiments.

5 The big question for intraspecies toxicokinetic
6 variability obviously is, is the previous use of the value
7 of root 10 for UFH-k adequate to protect, well, children
8 or other sensitive sub-populations. And the answer is, in
9 our opinion, no. We have some specific reasons for
10 thinking that based on particularly the studies in drugs
11 where there's been a lot of work describing kinetics. And
12 we refer particularly to work by Hattis and Ginsberg as
13 well as several other authors. And also we did some work
14 on our own account, which is reported in the Appendix E of
15 the document.

16 And based on that, it appears an increase of
17 UFH-k is necessary for many chemicals.

18 --o0o--

19 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

20 CHIEF SALMON: And so what we're proposing is that the
21 default value of UFH-k would increase to 10. Although
22 obviously this would be varied, firstly, for chemicals
23 which are not metabolized and which are having -- had a
24 local site of action rather than distributed. In fact,
25 there isn't very much pharmacokinetics going on there. So

1 we wouldn't propose the increase in that case.

2 And also in general, if we have a better model or
3 we have some other reasons showing why some value other
4 than 10 is appropriate in a specific case, then we would
5 use that.

6 --o0o--

7 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

8 CHIEF SALMON: The toxicodynamic variability, as we have
9 said, we seldom really have any particularly strong
10 information on what this is. So we're leaving the
11 defaults at root 10. But we are pointing out that some
12 specific organ systems and toxic endpoints have been
13 identified as of particular concern. And you may recall
14 the discussions we had on that point when we were working
15 on the SB 25 prioritization document back in 2001.

16 --o0o--

17 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

18 CHIEF SALMON: And with that in mind, we point out that
19 there are a number of types of toxicity which we basically
20 regard as red flags and that there may be a justification
21 in cases where these are seen, depending on what data we
22 have or might be looking at. In many, many of these case
23 we were thinking it appropriate to increase the value of
24 UFH-d because of the specific sensitivity in infants and
25 children to these endpoints.

1 44? Or have I just missed it?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: No, I think you're right. We have a very small
4 paragraph on it. It's really a --

5 PANEL MEMBER BYUS: But I'm not sure -- as I keep
6 reading it over and over again, it gradually sinks in.

7 But --

8 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

9 CHIEF SALMON: Well, it is --

10 PANEL MEMBER BYUS: But it's the softest
11 statement there. And I -- everything else, all the
12 uncertainty, the factors in my opinion are very nicely
13 backed up, models beautifully done, very nicely done.
14 Difficult to argue with, except for this one.

15 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

16 CHIEF SALMON: This one is just --

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: Page 64 on my printed copy, Section 449,
19 uncertainty associated with deficiencies in the overall
20 database, is where we have it. And what we did at the
21 last meeting, we said we will go back and look at how EPA
22 in their 2002 document describes it. So we literally put
23 that description in. And it essentially gives the risk
24 assessor a way to look at the totality of the database,
25 what is there, what is not there, and allows you -- if you

1 really think there's just not enough data for us to be
2 comfortable that that is a health protective value, it
3 allows you to add in another uncertainty factor. So
4 that's really what we're getting at.

5 I don't honestly know how often we will end up
6 using it.

7 PANEL MEMBER BYUS: It's that one sentence in the
8 middle there. It says, "In addition to identifying
9 toxicity information that is lacking, review of existing
10 data may also suggest that a lower reference value might
11 result if additional data were available."

12 Now, what you mean exactly by that sentence is
13 my -- that's what I don't -- if you gave me an example --

14 CHAIRPERSON FROINES: Where are you?

15 PANEL MEMBER BYUS: I'm on page 64.

16 CHAIRPERSON FROINES: So am I.

17 PANEL MEMBER BYUS: Okay. It's the --

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: It's the quote from the U.S. EPA document?

20 Right, it's up -- 449

21 CHAIRPERSON FROINES: Oh, yeah, oh, yeah. I got
22 it.

23 PANEL MEMBER BYUS: It's that one sentence. And
24 it just -- if you gave me an example.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: You know, I think -- it's hard to give examples,
2 and let me tell you why.

3 PANEL MEMBER BYUS: I know. And that's why
4 it's --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: I mean every single chemical that we run across --
7 you know, we're not dealing generally with pesticides or
8 drugs where there's a lot more toxicity information.
9 We're frequently dealing with something that, you know, no
10 one has really done full blown set of toxicity testing on.
11 So every situation that we end up looking at the database
12 is unique. And sometimes you will look at those data, or
13 if you have -- for example, you're looking at a chemical
14 that is structurally related to something that you know
15 has a lot more toxicity than is indicated by the very
16 minuscule database that you have working on. There is an
17 example where --

18 PANEL MEMBER BYUS: There's a good example.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: -- you might add in another database uncertainty
21 factor.

22 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

23 CHIEF SALMON: Or if you know that there's a metabolite
24 about which you have some suspicions.

25 PANEL MEMBER BYUS: If you could just put that

1 sentence --

2 PANEL MEMBER BLANC: That's an example of where
3 there's a data deficiency. What is an example of
4 something where the existing data suggests that there's a
5 data deficiency?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: Well, the existing data would be in this case on
8 the analog chemical, on an analogous chemical that's
9 structurally related. So, you know, if you're looking at
10 everything possible about that chemical or class of
11 compounds that you know about.

12 PANEL MEMBER BLANC: Well, how about an example
13 where there was an effect compared to controls but the
14 study size was so small that it was difficult to tease out
15 whether it was due to chance or not. And then you suspect
16 that if you had a larger study -- I mean wouldn't that be
17 an example where the data show the need for more data?

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
19 CHIEF SALMON: Yes. A good example of that might be, for
20 instance, a developmental study which only had one dose
21 which was fairly high. So you knew there was an effect,
22 but you didn't know what the dose response was. That
23 would be an example.

24 PANEL MEMBER BYUS: But you did a nice job of
25 examples all through here, really. And that made it to me

1 when I read it very clear. That's the -- so if you just
2 gave me one -- put one example -- I believe you, I just --
3 you need it. It's just too soft.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Okay.

6 PANEL MEMBER BLANC: But is there -- you
7 haven't --

8 PANEL MEMBER BYUS: I wanted to say something.

9 You don't want it to appear that it's arbitrary.
10 That's what I'm trying to tell you. And I know you're not
11 doing it in an arbitrary manner.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Yeah, we get it. I understand.

14 PANEL MEMBER BLANC: I think another potential
15 source of confusion could be a situation where you end up
16 even -- you have human toxicokinetic and toxicodynamic
17 data. And because of the multiplication factors you end
18 up with a greater uncertainty multiplication than you
19 would had you only had animal data. Is that

20 mathematically possible? Does the maximum uncertainty
21 that you could get with your factors for human data ever
22 multiply out to more than its -- it's 3 times 10 --

23 PANEL MEMBER BYUS: You said 3,000 was your max,
24 right?

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: I don't think we've ever had that problem. I mean
2 if it's done in humans, then your whole intraspecies
3 extrapolation you don't need to worry about.

4 PANEL MEMBER BLANC: So mathematically it can't
5 come out to be --

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: I don't think it would ever come out that way.

8 PANEL MEMBER BLANC: I mean I think you should
9 think of if there's a nice way of saying that in a
10 sentence, you know, or -- because the tables are separate,
11 aren't they, for -- there's no table that includes --
12 because it would be very bulky. But, you know, the human
13 extrapolation one is one table and the animal one is
14 another table. And then the uncertainty factors when you
15 don't have toxicokinetic data is another table, right?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: It's all on Table 441 on page 45. UFL, UFA,
18 UFA-k, A-d, H-k, H-d, and S. But I think it would be hard
19 to answer your question just looking at this table. You'd
20 really need examples. But, you know, having dealt with an
21 awful lot of reference exposure level development, we've
22 never had the issue that you're talking about.

23 CHAIRPERSON FROINES: I think this issue that
24 Craig's raising is really important. And it is
25 potentially a huge issue, because we're always dealing

1 with too little data.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Yeah, I think too it's safe to point out that if
4 we ever used the database deficiency factor, we would
5 justify it within the individual chemical summary. And so
6 it would be out there, "Why did you guys use this?" And
7 people would be able to say, "You shouldn't because of
8 this reason" or "here's some data you overlooked." So,
9 you know, it definitely would not be done just by us and
10 stick it out there.

11 PANEL MEMBER BYUS: Arbitrary.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Yeah.

14 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

15 CHIEF SALMON: Yeah. I think one of the --

16 PANEL MEMBER BYUS: So I mean if you want to use
17 the word -- I would use the word, not done in an arbitrary
18 manner and highly justified, for example, just as
19 a -- because, again, it's just -- you gave nice examples.
20 You really put in a lot of effort into trying to anchor
21 every statement with some example. And that came across
22 as a real strength to me when I read the document, because
23 it kept anchoring it back to why, why, why and an example.
24 And then I got to this one, it was like I still -- you
25 know.

1 PANEL MEMBER BLANC: But am I missing something,
2 that if we come back to this table on page 46, isn't the
3 maximum 30 for the intraspecies uncertainty and the
4 maximum is only 6 for the interspecies?

5 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
6 CHIEF SALMON: No, these are defaults, not maximum, by the
7 way. But just -- you know, these are default values which
8 we recommend in the absence of more specific information
9 to the contrary.

10 PANEL MEMBER BLANC: Right. But these defaults,
11 the possible default would only be 6 for interspecies but
12 it could be 30 for the intraspecies.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: If you're just looking at the default?

15 PANEL MEMBER BLANC: Yeah.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: And you're comparing the toxicokinetic UFs for
18 interspecies versus intraspecies.

19 PANEL MEMBER BLANC: Right.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Right.

22 PANEL MEMBER BLANC: Is there some other step I'm
23 forgetting? Let's say --

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: No.

1 PANEL MEMBER BLANC: Let's say you had the animal
2 toxicologic data and you needed to put in a default
3 uncertainty factor to --

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

5 CHIEF SALMON: But if you were using the uncertainty
6 factor defaults for both the kinetic and the dynamic
7 components, then you have an overall UFA of 10.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: And an overall UFH could be higher.

10 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

11 CHIEF SALMON: The overall UFH could be 30 by, you know,
12 using the defaults.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: But they would be layered one on top of the other
15 if you started with animal data.

16 CHAIRPERSON FROINES: I'm missing that. Could
17 you explain that.

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

19 CHIEF SALMON: If you were starting with an animal
20 experiment, you would take your NOEL or benchmark, you
21 would divide it by square root of 10 for the toxicokinetic
22 component of interspecies extrapolation. You would divide
23 it by a further square root of 10 for the toxicodynamic
24 component of that. In other words, an overall division by
25 10 for the interspecies extrapolation. You would then

1 take the result of that calculation and divide it by a
2 factor of most often 10 to represent the intraspecies
3 variability in the human species. And the further factor
4 of 3 for the toxicodynamic. In other words, the
5 factor -- the division factor overall to deal with the
6 diversity within the human species is, by default, 30.

7 PANEL MEMBER BLANC: Plus times 2 if there was --
8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Well, I see -- okay, Paul, I -- yeah, okay, I see
10 the confusion.

11 In the table, within a single box, we're saying
12 these are possible defaults, that you don't multiply those
13 together.

14 PANEL MEMBER BLANC: Oh, they're the most it
15 could be.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Right, exactly. And that --

18 PANEL MEMBER BLANC: Right, gotcha.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: The most it could be default. If there were other
21 things going on, you might actually have more -- we do
22 have a statement in there regarding that, but -- yeah, you
23 don't run down and multiply them all together in one box
24 and compare one box to the other.

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: It's the value chosen within the box in
2 each case.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Yeah. I think maybe we need to make this table a
5 little clearer, how we were using it.

6 CHAIRPERSON FROINES: You need to not have it at
7 the table. You need to have it as a dynamic process in
8 which you actually show going from step 1 to step 2 to
9 step 3.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Okay.

12 PANEL MEMBER BLANC: No, I think you could do it
13 with just another column which says "Maximum Possible
14 Uncertainty."

15 PANEL MEMBER GLANTZ: Well, no, the maximum
16 possible is 10 for each one of these. I think it's just a
17 question of labeling it better.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: Yeah, just labeling it. Okay.

20 CHAIRPERSON FROINES: The fact that --

21 PANEL MEMBER GLANTZ: Maybe you could change the
22 title to say, you know, value -- I mean this isn't the
23 best language, but to say, you know, value -- possible
24 values to be selected from or something like that. That's
25 not grammatically wonderful, but to make it clear that

1 it's one of -- one in each box.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Okay.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

5 CHIEF SALMON: We'll label --

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: The other thing you do is put in more lines.

8 PANEL MEMBER BLANC: Sub-lines, little dotted

9 lines?

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Yeah, little lines. Okay.

12 CHAIRPERSON FROINES: I'm still -- and I'll let

13 this go right away. But I'm still uncomfortable with this

14 square root of 10 business, because it's wholly dependent

15 on the fact that you're developing toxicokinetic and

16 toxicodynamic models that tests whether or not this square

17 root of 10 is adequate. I don't know if the

18 square -- dividing -- well I guess it's based on the fact

19 that you believe that you can develop clear pictures of

20 those parameters over time, huh?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Well, I think -- really what we're doing is saying

23 that the traditional safety factor of 10 or uncertainty

24 factor of 10 is a half log for kinetics and a half log for

25 dynamics. There are some studies out there that have

1 looked at using the traditional defaults of 10 for
2 interspecies and intraspecies and seeing are those really
3 adequate. And in general for many chemicals, they are.
4 But when you start digging, looking at the distributions
5 of kinetic factors in humans, you start to realize that,
6 well, there are a lot of chemicals they're not. So that's
7 really where the root 10 comes from, is just thinking
8 about it as these two separate contributions.

9 CHAIRPERSON FROINES: You know, we had a whole
10 day-long meeting on this topic some years ago.

11 PANEL MEMBER BLANC: I think, by the way...

12 PANEL MEMBER GLANTZ: He's saying give the
13 stenographer --

14 CHAIRPERSON FROINES: I understand what he's
15 saying.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Should we -- I think we're pretty close to finish,
18 because --

19 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

20 CHIEF SALMON: Yes, there's not very much left of this
21 part of the thing.

22 --o0o--

23 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

24 CHIEF SALMON: The LOAEL-to-NOAEL uncertainty factor is
25 something you'll recognize from the previous version of

1 the guidelines. And what we're saying is that it's --
2 actually we changed this a little bit from the public
3 review draft, and we've essentially gone back more to what
4 we had with the original proposal. The original proposal
5 was for the cute RELs that we had a table of effect
6 severity and that we would use a UFL out of 6 or 10,
7 depending on whether it counted as a severe or a mild
8 effect.

9 We had attempted to apply that this time around
10 with the chronic RELs as well. But the conclusion when
11 we've done that and we looked at it and we looked at the
12 comments we received, we essentially concluded that that
13 severity basis really doesn't work very well for chronic
14 LOAEL to NOAEL extrapolations.

15 So what we are basically saying is that we would
16 most usually be using a tenfold value for the -- for a
17 LOAEL-to-NOAEL uncertainty factor for chronic situations.
18 But we do -- we are prepared to consider some other
19 indications, which would be similar to what we had in the
20 previous chronic guidelines, where you have a low
21 incidence LOAEL or a weak statistical significance LOAEL.
22 We think about, you know, do we have a mild effect thing
23 in there. We come to the conclusion that very few things
24 which are actually chronic toxic effects would be
25 considered mild in that sense. So that's why we really

1 backed away from that.

2 But the other thing which is different in this
3 version of the guidelines from what we did previously is
4 we hope that we are relatively seldom going to be using
5 this. Because when we have reasonable data, even if there
6 isn't an actual NOEL identified in the data, we can
7 generally run a benchmark concentration analysis, which
8 does give us a firm point of departure, which has the same
9 properties as a NOEL. So in that case, we would not use
10 the UFL. We would use the point of departure calculated
11 from the data. And we would use the same uncertainty
12 factors as we'd apply to the NOELs for most data.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
14 MARTY: So just a reminder that that intermediate factor
15 of 6 was based on a derivation from acute studies and mild
16 effects. So that's where the intermediate factor of 6
17 came from in our last go-around with the document. So
18 we're pulling it forward, and we were going to try to use
19 it also in the repeated 8 hour or chronic. But it ends up
20 falling apart when you think about it, and this was
21 pointed out to us by some comments.

22 PANEL MEMBER FRIEDMAN: So I'm still not clear
23 why you picked 6.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
25 MARTY: Because it was actually the 95th percent of the

1 distribution for subset of chemicals for acute low LOAEL
2 to NOAEL ratios. So that's why we had picked 6 --

3 PANEL MEMBER FRIEDMAN: And That was just for --

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: -- in the '99 guidelines.

6 PANEL MEMBER FRIEDMAN: That was just for mild
7 effects?

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: It was for mild effects and it was acute
10 exposures. So, you know, when you start trying to think
11 about, well, we're actually trying to protect people from
12 essentially almost continuous exposures, it starts to fall
13 apart trying to apply that in a chronic or repeated
14 exposure scenario. So that's why we're ditching that now.

15 PANEL MEMBER GLANTZ: So you're just going to
16 stay with the 10?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: For the chronic, unless we have -- you know,
19 unless you can look at the dose response curve or have
20 other information that you're actually not very far from
21 the NOAEL, you're considerably less 10x, because its steep
22 dose response curve might be one thing to look at, you
23 know.

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

25 CHIEF SALMON: But having said that, it's less likely that

1 we would be using this factor in a situation where we had
2 dose response information. Because if we have dose
3 response information, unless there's something very
4 objectionable about the quality of the data, the chances
5 are that we could do a benchmark concentration analysis if
6 we had that sort of information. So hopefully we would
7 get away from this conundrum in that case.

8 --o0o--

9 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

10 CHIEF SALMON: Another thing which we have -- again, this
11 is a variation on what we did previously. But for acute
12 toxicants we have used a modified version of Haber's Law
13 to provide a time concentration adjustment, where we need
14 to take, for instance, a two-hour acute study and derive a
15 one-hour REL or something like that.

16 We're continuing to use the modified Haber's Law
17 approach. But we're recommending -- I mean in the cases
18 where we don't have actual measured values of the exponent
19 A -- which of course we do for quite a number of chemicals
20 which are listed in one of the appendices. But where we
21 don't have measured values for A, we're going to assume a
22 default N of 3 now rather than what we previously assumed
23 with 2. This is consistent with what U.S. EPA now does
24 and also consistent with some more recent data on
25 chemicals in general.

1 Further exceptions to this are that when we're
2 talking about a sensory irritant response, we have
3 evidence to show that in fact the time dependence of that
4 is rather different. The sensory response reaches a
5 plateau in a period of time something between a matter of
6 seconds and minutes, and is then essentially constant at
7 least over the sort of period of which we're interested
8 for an acute REL of one hour.

9 And therefore we're not going to be using Haber's
10 Law to adjust concentrations for sensory responses to
11 irritants. We're going to just use the concentration
12 dependence since that's the important dose metric in that
13 specific case.

14 --o0o--

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: I might add that the value the exponent 3 over 2
17 weights more heavily the concentration term than the time
18 term. So it's actually a little more health protective to
19 do it that way.

20 CHAIRPERSON FROINES: Andy, I think that you've
21 come to a place where we should break, because your next
22 slide, as I look at it, is on the reference levels for the
23 specific --

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

25 CHIEF SALMON: Yes. I was not going to talk about them

1 myself in detail. What I was going to do actually here
2 was say, well, this is -- you know, this is the next step
3 of the process.

4 And there are two things that we have to present
5 to you: One is the new RELs. And staff who are
6 responsible for those are available to present those to
7 you.

8 And the other thing which I have for you, which
9 you can consider now or at some other time, depending on
10 what you want to do, is that we have received a number of
11 comments. And I have I think sort of grouped and
12 paraphrased the comments that we've received and our
13 responses to them. So what I hope is a reasonably brief
14 coverage of the areas of comments that we've received.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: It's up to you. So it's up to you however.

17 CHAIRPERSON FROINES: Well, my question -- but
18 you've made much more complex the issue of a ten-minute
19 break. So --

20 PANEL MEMBER GLANTZ: Let's just take a
21 ten-minute break.

22 CHAIRPERSON FROINES: So Let me just ask one
23 question. When we come back, is that the appropriate time
24 to ask Stan to give his views of the process that he went
25 through, representing the Panel as the lead person, before

1 we go on to the RELs and the comments?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Yes.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

5 CHIEF SALMON: Yes, in fact it is. I mean my first slide

6 in discussing the comments, among other things,

7 essentially says we talked to Stan. So that would be a

8 very --

9 CHAIRPERSON FROINES: So we'll come back and put

10 Stan --

11 PANEL MEMBER BLANC: -- on the stand.

12 CHAIRPERSON FROINES: -- on the hot seat.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Yes.

15 CHAIRPERSON FROINES: And let's take a break.

16 (Thereupon a recess was taken.)

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: Just one clarification. We do have slides on

19 summarizing the comments received on just the TSD. I

20 don't know if the Panel is interested in hearing those

21 before Stan or not at all or after Stan.

22 CHAIRPERSON FROINES: You have commentary on --

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: -- the comments received, just on the methods

25 part. We have slides of those and our responses. But

1 you've all read the comments and responses. So I don't
2 know that it's necessary to go over them.

3 CHAIRPERSON FROINES: I think it would be
4 valuable. But I --

5 PANEL MEMBER GLANTZ: Yeah, I think I -- I mean
6 I'll tell you -- I mean basically what I have to say is
7 that I read through all of the stuff, made a lot of
8 comments. There were a bunch of inconsistencies, some of
9 which some of the other Panel members have pointed out.
10 And had two meetings with Melanie and Andy. And I
11 think -- and in the SRP revision they had I thought dealt
12 with most of the things I had raised. That was on the
13 previous draft.

14 Then when we met a few days ago, we went through
15 the current SRP draft. I think most of the things were
16 dealt with reasonably. I had some questions about how
17 they dealt with some of the public comments. And we also
18 had a big discussion about how they were going to discuss
19 the strength of association, which is the thing that was
20 handed out, which I was unhappy about.

21 And what you have is the result of sort of a
22 compromise. And Paul Blanc just edited this and made it
23 clearer.

24 So that -- I mean I think it would be better to
25 just let them go through the response to comments.

1 Because I think that just looking at the slides, some of
2 them are going to deal with my comments. Right?

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Yeah.

5 PANEL MEMBER GLANTZ: And they remember them
6 better than I do at this point.

7 CHAIRPERSON FROINES: Can we talk about this and
8 then go to the comments?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Oh, yeah.

11 CHAIRPERSON FROINES: And so in essence you've
12 just given your presentation?

13 PANEL MEMBER GLANTZ: I have. I've given -- I
14 think that what I would suggest we do is let them present
15 the response to comments about the technical support
16 document, and then stop and finish the discussion of that,
17 and then go on and talk about the individual RELs, which
18 is the application of the technical support document. I
19 mean that would be my suggestion.

20 But I think that what their report is going to
21 have, the main thrust of my more significant comments to
22 them. And as I said, there were a lot of inconsistencies
23 in the document that have been fixed.

24 I think overall it's a good piece of work.

25 And the other thing, which hasn't actually -- I

1 haven't talked to them since we met a few days ago. But
2 there were a few issues in the response to comments from
3 the public commenters that I also thought needed to be
4 better addressed, which I hope you're going to talk about.

5 No?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Well, no, I can't. I haven't stickied.

8 PANEL MEMBER GLANTZ: You have your stickies.

9 Okay.

10 Well, I have my notes from that if we need to.

11 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

12 CHIEF SALMON: So I'll just run through the public
13 comments received at this point.

14 PANEL MEMBER GLANTZ: Yeah.

15 CHAIRPERSON FROINES: No, no, no. I thought we
16 were going to talk about this issue here.

17 PANEL MEMBER GLANTZ: Okay. If you want to do
18 that, we can do that.

19 CHAIRPERSON FROINES: And then we can go to the
20 comments, because they are separate.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Okay. I think Peter handed everyone this revised
23 paragraph on strength of association.

24 As Stan mentioned, we went back and forth on it.
25 The earlier paragraph had explicit cutoffs for weak versus

1 strong association that really aren't found in a textbook
2 anywhere. They're sort of the way people thought about it
3 for a while.

4 Also our original paragraph really focused more
5 on the size or the magnitude of the effect estimate or
6 relative risk rather than other things that influenced the
7 strength of association, such as the statistical
8 significance and the study design and how well it dealt
9 with confounding and so forth.

10 So that reflects -- this new paragraph reflects
11 that discussion. And then Dr. Blanc has clarified it
12 further.

13 PANEL MEMBER GLANTZ: I mean basically the thing
14 that I was hot and bothered about was they had this thing
15 about a large effect being a factor of 2. And I don't
16 think there's anything magical about that. And there's
17 examples of studies that have found big effects that were
18 flawed. And there are also lots of examples of things
19 where you get a relative risk well below 2 where you have
20 very strong evidence that it's real. And so I wanted that
21 clarified, because I just think this 2 number has just
22 been pulled out of the air basically. Although Paul
23 explained to me there is some litigation context in which
24 it's important.

25 But to me what I'm -- I don't even like the term

1 "strength of association," although I think we're kind of
2 stuck with that because people are used to talking about
3 it. But I would almost call it like "quality of the
4 association" or "convincingness of the association." And
5 for that I think you need to look at the quality of the
6 study design, as we said, adjustment for confounding,
7 whether or not the result is statistically significant.
8 And to me the magnitude of the effect, which is detected
9 as less important -- I mean in fact it's harder to detect
10 a small effect than a big effect. So that's kind of built
11 in to whether or not it reaches statistical significance
12 in my view.

13 So this was the result of a lot of ping-pong
14 Emails back and forth where I was suggesting -- they
15 suggested one thing, I rewrote it, they sent it back, and
16 we kind of converged. And I think the net result of when
17 you write a paragraph by Email ping-pong is sometimes it
18 gets a little disjointed.

19 Paul made a few editorial suggestions, which I
20 think further clarify the points that I just made, which
21 Melanie has. I mean if you want, we can go through them.
22 But I think they're more editorial in nature and
23 clarifying.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
25 MARTY: So this would replace the paragraph on page 30 at

1 the bottom of the page under "Strength of Association."

2 CHAIRPERSON FROINES: I'm sorry. Peter asked me
3 a question. I didn't hear what you said. Sorry.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: This would replace the paragraph on page 30 at the
6 bottom of the page.

7 CHAIRPERSON FROINES: The first thing I would say
8 is you should -- Ken Rothman and Sander wrote another
9 causality paper that was published in the American Journal
10 of Public Health that's only about two years old. And I
11 will send you the paper. And it is basically their most
12 recent consideration of the issues of causality.

13 PANEL MEMBER FRIEDMAN: Would you send that to
14 all of us, please.

15 CHAIRPERSON FROINES: Oh, absolutely.

16 That's what I -- yeah.

17 And my only question is the -- I don't know what
18 you mean by the level of statistical significance.
19 Because we all know that there are people who, if
20 something's greater than .05 at 95 percent -- there are
21 people who make decisions in very rigid ways. And what I
22 think is we have to be very careful. And Toby Paige from
23 Brown University wrote a statistical paper some time ago
24 where he looked at different implications of different
25 statistical approaches defining causality. And he thought

1 that from a public health point of view one needed to have
2 a broader perspective.

3 PANEL MEMBER GLANTZ: Well, no, and I'm not -- I
4 certainly agree with that. What I was -- the way I
5 interpreted that is that if you have a very highly
6 significant result, okay, and a well designed study, you
7 can have a lot of -- I mean a lot of confidence in it.
8 But this did not mean to imply that .05 is the magic
9 number and that, you know, .050001 is no effect and
10 .049999 is. But I think -- you know, when I'm looking at
11 a study that's estimating a risk, if you have a very small
12 P value associated with that, that means you can have a
13 lot of confidence that it's not a chance finding. That
14 doesn't mean that if you -- that there's some magical
15 cutoff. And that you could have -- if you had -- if you
16 had an effect which was very severe, you know, it may be
17 that you'd have a P value of .1 and say, "Well, I don't
18 even want to take a 10 percent chance of this happening."

19 I mean maybe rather than saying statistical
20 significance, we could say -- and this is one of changes
21 that Paul was suggesting -- is to say the level of Type 1
22 error.

23 CHAIRPERSON FROINES: That's better.

24 PANEL MEMBER GLANTZ: Or the level of alpha
25 error, which is what he's saying. Or the risk of a false

1 positive.

2 CHAIRPERSON FROINES: My concern is that there's
3 a whole world of people out there who are very dismissive
4 if you don't reach a certain level.

5 PANEL MEMBER GLANTZ: Yes.

6 CHAIRPERSON FROINES: And they can take data for
7 which look like they're a clear risk that don't make it to
8 that level and they dismiss the study.

9 PANEL MEMBER GLANTZ: No, I mean I totally agree
10 with that.

11 PANEL MEMBER FRIEDMAN: Yeah, they say there's no
12 effect -- when like it's 1.2 but the lower confidence bond
13 is like .95, well, then it's no effect.

14 PANEL MEMBER GLANTZ: Yeah. No, I totally agree
15 with that. In fact, when I teach this stuff, I now
16 have -- and in this little book I wrote, Primer of
17 Biostatistics, that goes with Gary's epidemiology book --
18 I actually went back and found Fisher's original paper
19 where he suggested .05.

20 (Laughter.)

21 PANEL MEMBER GLANTZ: And you read it and it
22 said, "Well I thought about this and 1 percent seemed too
23 small and 10 percent seemed to big, so why don't we use 5
24 percent." I mean it basically says that. It just says,
25 "I thought this was a reasonable number."

1 I mean the point I make to the students is that
2 it's not -- .05 is not like Planck's constant or the speed
3 of light or pi, you know. It's just the numbers one guy
4 thought was a reasonable number. So we're all in
5 agreement about that.

6 The way I interpret --

7 CHAIRPERSON FROINES: I just think that the way
8 this is phrased though is that --

9 PANEL MEMBER GLANTZ: Well, no, we can fix that.

10 CHAIRPERSON FROINES: -- people can interpret --
11 people have biases. We all do. And people will interpret
12 it to fit their bias.

13 PANEL MEMBER GLANTZ: Right. I mean the way that
14 what I tell people -- which is I think what they mean
15 here, but we can clarify this -- is that the P value is
16 the measure of the certainty you have in the conclusion
17 that you're drawing, and that that should be a guide in
18 making a decision where you consider the costs of false
19 positive or false negative solutions.

20 And it's not -- .05 is not, you know, as Gary
21 said, the dividing line between effects and no effects.
22 But we can clean this up.

23 This is certainly all in the spirit of what I was
24 trying to accomplish in asking that this one paragraph be
25 rewritten.

1 CHAIRPERSON FROINES: It's great work, Stan. If
2 they had walked in here with a 2 as -- that would have
3 caused the reaction.

4 PANEL MEMBER GLANTZ: Well, it already did. I
5 pre-reacted for the Panel.

6 (Laughter.)

7 PANEL MEMBER BLANC: Stan, I don't know if this a
8 question for you or for them. But in the section that
9 precedes that, where a list of the methodologic issues --
10 of selective methodologic issues --

11 PANEL MEMBER GLANTZ: What page is that on?

12 PANEL MEMBER BLANC: The same page.

13 PANEL MEMBER GLANTZ: Well, what page is it on?

14 PANEL MEMBER BLANC: Thirty. "Methodologic
15 issues that are considered in a review of the
16 epidemiologic literature include" -- and you have, you
17 know, four obvious examples.

18 I wonder if, with Stan's help, you might not want
19 to put a few more in there that would help you potentially
20 in terms of other outside commentary you might get,
21 because you --

22 CHAIRPERSON FROINES: Where are you, Paul?

23 PANEL MEMBER BLANC: It's the --

24 PANEL MEMBER GLANTZ: Page 30 on the top.

25 PANEL MEMBER BLANC: The top of the page.

1 You know, for example, I'm sure that in looking
2 at studies which have negative findings which you take
3 with a grain of salt that are based on occupational
4 cohorts, which is what you're forced to use, you take into
5 account survivor effects and the healthy worker effect.
6 And although you talk about selection bias, you don't say
7 the health -- you know, in particular, the healthy worker
8 effect, you don't talk about survivor bias and you don't
9 talk about over-adjustment for factors which are
10 intermediate in the causal pathway. And I think that
11 those are some things that you're doing all the time. And
12 since you're listing things here, I think --

13 PANEL MEMBER GLANTZ: Yeah, I think that's a good
14 idea.

15 CHAIRPERSON FROINES: I think that exposure
16 misclassification is a crucial issue.

17 PANEL MEMBER GLANTZ: Yeah, I agree with that
18 too.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Yeah, that was number 4.

21 PANEL MEMBER BLANC: What do you mean by bias?

22 PANEL MEMBER GLANTZ: Well, you know, actually as
23 I was sitting here listening to Paul, I was thinking we
24 should also have an exposure misclassification. That's
25 really different than exposure assessment, that's

1 different than bias in ascertaining --

2 PANEL MEMBER BLANC: Because then bias is towards
3 the null, isn't it?

4 PANEL MEMBER GLANTZ: Right. And bias and
5 ascertaining exposure could go either way.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: Right.

8 PANEL MEMBER FRIEDMAN: And there can be bias in
9 ascertaining the outcome too. I mean do we want them to
10 have to --

11 PANEL MEMBER BLANC: I think they should just
12 have enough things there that -- what I think they've done
13 is selected all the things that would be the -- sort of on
14 the side of saying, "I disbelieve this positive study."
15 But there's not very much here that is -- some of the
16 stuff that's very relevant to discounting negative studies
17 isn't as much here, except for the sample size, I suppose.
18 If you know what I mean.

19 PANEL MEMBER GLANTZ: Yeah, I think those are
20 good things to have.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: Yeah, I think we can add -- the over-correction
23 issue is a huge one. And we can have healthy worker
24 effect in there, you know. It is not meant to be
25 exhaustive, and we tried to be --

1 PANEL MEMBER BLANC: No, I know. And in fact you
2 need to put --

3 PANEL MEMBER GLANTZ: Melanie, I agree and I, you
4 know --

5 PANEL MEMBER BLANC: And I would put selective
6 methodologic issues just to underscore that.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Okay, sure.

9 PANEL MEMBER BLANC: But I would still loose it
10 up a little bit if you -- you know, it's not the be-all
11 and end-all. But if you have the energy and --

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Sure.

14 PANEL MEMBER BLANC: Because I think it
15 undersells what you actually do.

16 CHAIRPERSON FROINES: Yeah, I think -- I actually
17 think these issues are extremely important for the fact
18 that they get misused so often. I mean it's not -- this
19 is not a neutral issue.

20 PANEL MEMBER GLANTZ: Yeah, that's true, because
21 all of these items aren't reasons to discount a
22 significant finding -- a statistically significant
23 finding. I think that the -- that it would be good to
24 have other things where, you know, the presence of these
25 problems would make you discount a negative finding.

1 CHAIRPERSON FROINES: Well, I'm reviewing a paper
2 right now in which they have a statistically significant
3 finding, and then in the discussion they actually show all
4 the reasons why it may not be a causal relationship. I
5 mean it's going as far as they can --

6 PANEL MEMBER GLANTZ: -- these secondhand smoke
7 studies that come up positive, they do that. It's like,
8 "Well, we found this result but we don't believe it."
9 Because we're idiots. Anyway --

10 (Laughter.)

11 CHAIRPERSON FROINES: So I think we're set on
12 this and that we should move ahead with Andy.

13 --o0o--

14 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
15 CHIEF SALMON: Well, I'll --

16 PANEL MEMBER GLANTZ: Well, I just have to say
17 I'm glad that it was good that I made an issue of this,
18 because I actually had given them a hard time about this.
19 And they forgot to address it after the first meeting.
20 See, it was --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Which sat really well with Stan, let me tell you.

23 (Laughter.)

24 CHAIRPERSON FROINES: But the issue of the --
25 there's been so much debate about this value of 2 as, you

1 know, the gold standard, that it's good that you dealt
2 with it.

3 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

4 CHIEF SALMON: Well, we've had our discussion on the
5 comments from the Panel, so I'll move on to the public
6 comments here.

7 First comment, which we received from several
8 people, was that the increase of the UFH-k was unjustified
9 or that there was a sufficient safety margin provided by
10 overlap of other uncertainty factors.

11 PANEL MEMBER FRIEDMAN: Could you speak a little
12 louder.

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

14 CHIEF SALMON: Sorry. I'll try and get closer to the
15 microphone here.

16 Well, we disagree with these opinions. And we
17 provided what we think is a fairly detailed refutation
18 based on not only our own work but quite an extensive body
19 of recent studies from the scientific literature which we
20 think supports our proposal.

21 So that was the first comment.

22 --o0o--

23 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

24 CHIEF SALMON: The second comment was about the same
25 topic, but in the other direction. The suggestion was

1 instead of adjusting default values, that we should
2 actually include a specific tenfold uncertainty factor for
3 children's special sensitivities. These obviously would
4 be larger than what we proposed.

5 We considered the option of having a special
6 sensitivity factor of some size for children, but decided
7 that in fact modifying the existing default uncertainty
8 factors was easier to evaluate and to defend. And we also
9 note that OEHHA's actual proposal in the document you have
10 is similar in effect to the way U.S. EPA handles the
11 process of determining the need for and value of an FQPA
12 factor which they determine on a case-by-case basis.

13 --o0o--

14 CHAIRPERSON FROINES: That may not be a -- never
15 mind.

16 The fact that EPA does something these days
17 doesn't necessarily guaranty that we would agree with it.

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
19 CHIEF SALMON: No. Well, I think we're merely observing
20 in this particular case we're not so far apart as we
21 sometimes are.

22 The third class of comments were the concerns
23 which I think we've already talked about a little bit,
24 about how the LOAELs and NOAEL uncertainty factor was
25 defined and used. And as I said earlier, we have in fact

1 addressed this by confining the acute -- the mild and
2 severe consideration to the acute, which is where it
3 originally came from, and using basically for the most
4 part tenfold for chronic but with the possibility of other
5 factors where we think that would be appropriate.

6 --o0o--

7 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

8 CHIEF SALMON: A fourth comment. We had some suggestions
9 about the 8-hour REL. And in particular, as I mentioned,
10 that we should -- in addition to developing child
11 protective 8-hour RELs, that we should also develop 8-hour
12 RELs suitable for adult-only exposed populations.

13 We agree in principle this would be a reasonable
14 thing to do in certain cases and that we are saying that
15 we will consider doing that in the future.

16 There's a couple of points there. Firstly, that
17 we'll do that in specific cases rather than just across
18 the board. And the other clarification is that in fact
19 how these different versions of the 8-hour REL are going
20 to be used will be covered in the forthcoming revision of
21 the exposure assessment guidelines.

22 --o0o--

23 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

24 CHIEF SALMON: We received comments where the comparisons
25 were made between the values --

1 CHAIRPERSON FROINES: Are you comfortable
2 with -- I don't know whether -- are you comfortable with
3 the 8-hour REL?

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Well, it depends on -- you know, I mean -- the way
6 it would be used is for facilities that only emit eight
7 hours a day. They're only open eight hours a day, and
8 that's when they emit.

9 In the past what we did was take that and average
10 it out over 24 hours and apply the chronic REL. And so,
11 you know, we were concerned that we're not really taking
12 into account the effect of peak exposures and then zero
13 exposure. So that is why we thought it would be better if
14 we had an 8-hour REL useful for evaluating those kinds of
15 situations.

16 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

17 CHIEF SALMON: There are some -- well, there are many
18 cases where the 8-hour REL will be the same as the chronic
19 REL distributed over an 8-hour or a 24-hour period. But
20 there are some cases where it won't be for specific
21 reasons to do with the way the chemical toxicity goes and
22 what major defects --

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: -- and kinetics.

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: -- and the kinetics and so on.

2 PANEL MEMBER BLANC: Then do you provide -- in
3 your response, even if not in the document, wouldn't it
4 make sense to provide an example of that to be appropriate
5 critique? I mean, for example, a work site that's
6 emitting carbon monoxide, I can really see the rationale
7 for wanting to have an 8-hour REL as opposed to averaging
8 that out over 24 hours, which --

9 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

10 CHIEF SALMON: Most of the comments that we received in
11 relation to this generic topic actually have roots in the
12 manganese assessment. So --

13 PANEL MEMBER BLANC: I don't care what they have
14 roots in. But --

15 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

16 CHIEF SALMON: Yeah, so I think what I'm saying is that
17 you may see some compound-specific responses on that topic
18 when you get the manganese responses, which we're -- but
19 unfortunately we haven't got those because we're not done
20 with the assessment yet.

21 PANEL MEMBER BYUS: Yeah, I think you did a good
22 job describing the 8-hour, the rationale for it, providing
23 an example. I liked it.

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

25 CHIEF SALMON: As I say, the complexities come in later

1 when you get the exposure assessment.

2 PANEL MEMBER BYUS: Maybe I read some of those.

3 But I think it is of value to do it, potentially; that you
4 could really miss something if you didn't. So when you
5 can, it's good.

6 --o0o--

7 CHAIRPERSON FROINES: Does this mean you're going
8 to be doing permissible exposure limits for CalOSHA now?

9 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

10 CHIEF SALMON: Well, I don't think we're allowed to answer
11 that question.

12 (Laughter.)

13 CHAIRPERSON FROINES: Well, but do you understand
14 the implication of having an 8-hour REL for adults is
15 precisely that it's -- you're setting a standard. What
16 you're saying to CalOSHA, this should be your approach.
17 So it's not trivial. But it's really important because of
18 the problems of standard setting in general.

19 Are we going to hear that little George Alexeeff
20 comment?

21 OEHHA DEPUTY DIRECTOR ALEXEEFF: (Shakes head.)

22 CHAIRPERSON FROINES: No.

23 (Laughter.)

24 CHAIRPERSON FROINES: Let's move on.

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: Yes, the next one was that some people
2 presented comparisons between proposed RELs and measured
3 or calculated concentrations of the chemical in ambient
4 air, showing that some RELs approach existing
5 concentrations.

6 And our response is we note that these
7 comparisons may be of interest to risk managers dealing
8 with emissions or ambient levels, but they're not part of
9 the consideration that goes into the determination of a
10 REL.

11 PANEL MEMBER BLANC: Yeah. Was that the best
12 response you could make to that? I mean I think that's
13 part of the response. Isn't the inherent critique when
14 someone says your level's close to what the ambient levels
15 are, then what they're not saying is then why don't we see
16 the health effects that you're talking about generally in
17 the population?

18 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
19 CHIEF SALMON: I think we also say, firstly, that the REL
20 is a level of which we're reasonably confident that health
21 effects will not be observed. And, secondly, that if in
22 those cases where obviously ambient levels approach levels
23 that might be of concern, then one of the things that we
24 would be looking for is to see whether there are studies
25 of health effects from that chemical at those levels.

1 Now, one of the big problems is of course that
2 people say, "Oh, well, you're not seeing health effects at
3 this ambient level." But many of the times that assertion
4 is essentially based on hearsay rather than actual studies
5 anyway. So, you know, nobody really knows whether there's
6 an effect, because they haven't looked for a lot of these
7 things.

8 But in the cases where they have looked and where
9 there's a usable study, then that would have been part of
10 the database which goes -- you know, which goes into the
11 consideration of what the RELs would be.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: I think the other issue is, you know, when people
14 say that to me, I always think of PM and ozone. Well, if
15 we set the standards at the levels that we could achieve
16 in terms of a pollution, then, you know, we'd never have
17 any health protection, we'd never be cranking them down.
18 So to me looking at what is it out there and saying, "Oh,
19 well, your number is lower than what is out there," it's
20 really a red herring. It's a "so what?"

21 PANEL MEMBER GLANTZ: I think that what they -- I
22 mean I agree with the way that they presented it.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: We could strengthen the response to that a little
25 bit.

1 PANEL MEMBER BLANC: That was my point, is I
2 think you could say, perhaps not as explicitly as you just
3 have, but you could elucidate those points a little
4 more --

5 PANEL MEMBER GLANTZ: Well, what it actually says
6 in the response is pretty much what Melanie just said.
7 More -- I mean it's pretty strongly worded actually, and I
8 think it's correct. I mean the point is that what we're
9 setting here are levels that we think will be health
10 protective, not talking about what's in the air right now.
11 These are -- you know, could very well be goals.

12 So I think it's stated pretty clearly already. I
13 mean you could look at it -- if you want to suggest
14 there's specific rewording, you can. But I think if you
15 read what's actually in the document, it's pretty strong.

16 CHAIRPERSON FROINES: It also is -- I mean what
17 we've learned in the last ten years with respect to
18 particulate matter is that we now know that there are
19 multiple endpoints that we had not known in the past and
20 PM is beginning to look like ETS in terms of the number of
21 endpoints and that they're occurring at levels that are
22 not -- that are ambient levels and that there is in fact
23 adverse health effects -- quite significant adverse health
24 effects going on precisely at levels that would
25 be -- which we regulate. So it says that if -- we may not

1 be -- one has to assume that as you learn more, you may
2 find more and therefore your values are -- that's part of
3 a dynamic process.

4 PANEL MEMBER GLANTZ: Right. But even given
5 that, that's really disconnected from what levels happen
6 to be out there in the air right now.

7 CHAIRPERSON FROINES: Yeah. This is a silica
8 problem. This is the silica problem.

9 --o0o--

10 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

11 CHIEF SALMON: Okay. Next comment -- we received comments
12 from a couple of interested parties basically saying that
13 they wanted us to include a risk assessment on non-cancer
14 effects of diesel exhaust along with the other sample
15 RELs.

16 And our response to that is that we're aware that
17 this is a big issue and we are in fact working on it. But
18 we've got -- you know, it wasn't going to fit within what
19 we're doing here, but it is something which we're
20 currently looking at.

21 --o0o--

22 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

23 CHIEF SALMON: Another comment which we received --

24 CHAIRPERSON FROINES: You did say -- what did you
25 say? Because obviously for me this is a crucial --

1 PANEL MEMBER GLANTZ: They said they're working
2 on that.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
4 MARTY: We're working on the non-cancer risk assessment
5 for diesel exhaust.

6 PANEL MEMBER GLANTZ: It's just not in this
7 document.

8 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
9 CHIEF SALMON: It wouldn't fit physically or temporally.

10 CHAIRPERSON FROINES: I'm glad you used the word
11 "diesel exhaust," because in my view we erred in some
12 respects when we adopted what -- when we did what we did
13 for diesel particulate, which oversimpli -- all our data
14 suggest that the vapor phase co-pollutants are very
15 important.

16 --o0o--

17 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
18 CHIEF SALMON: We received a number of comments, both for
19 and against, or a mention of the general principle, which
20 has been in place for awhile, that a cumulative
21 uncertainty factor of 3,000 should be regarded as
22 practical upper limit.

23 And our response to these is basically that we
24 tend to agree with the interpretation that has come out of
25 U.S. EPA's guidelines. It's not that we're saying this is

1 a hard limit of 3,000 which we will never exceed. We're
2 saying that if an indication of the cumulative uncertainty
3 factor exceeds 3,000, it probably indicates that there's a
4 pretty poor supporting data. And that may be insufficient
5 for derivation of a reasonably reliable health protective
6 level. But that doesn't mean that we wouldn't be prepared
7 to go with it in specific cases if we felt that was
8 justified. But we see this essentially as a warning --
9 you know, this is a warning light on the dashboard, if it
10 goes higher than 3,000, to ask ourselves whether the
11 underlying data are of sufficient quality.

12 --o0o--

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

14 CHIEF SALMON: We have received a number of both
15 supporting and dissenting comments on the UFD. I think
16 we've probably covered that in discussion already. But
17 our response is in line with what we said earlier. And we
18 have in fact amended the wording of the technical support
19 document a little bit to reflect some of those concerns to
20 make it a little clearer. And we're obviously --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: We will amend it further.

23 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

24 CHIEF SALMON: We will amend further in response to the
25 discussion today.

1 --o0o--

2 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

3 CHIEF SALMON: I think this is the last one.

4 The comment was made that there are significant
5 problems in developing RELs for chemicals, such as some of
6 the metals, which are essential nutrients. And one
7 commenter suggested that since there are homeostatic
8 controls for such elements, the use of an interspecies
9 toxicokinetic uncertainty factor was unnecessary.

10 We agree that there are certainly problems with
11 developing health protective RELs for essential nutrients.
12 But the details in fact did vary considerably between
13 specific cases. And we didn't see any particular merit in
14 the suggestion to reduce the UFA-K to 1 across all such
15 cases. We thought that we would need to in fact look at
16 the individual cases, try and decide what was most
17 appropriate in each case.

18 So that's the end of my presentation.

19 CHAIRPERSON FROINES: What time is it?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: 11:35.

22 CHAIRPERSON FROINES: Shall we move ahead to the
23 RELs?

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Sure.

1 So I think we have staff coming forward to give
2 presentations. We'll start with the --

3 PANEL MEMBER GLANTZ: Can I just say one thing
4 before we do that?

5 CHAIRPERSON FROINES: Please. You should say as
6 much as you want.

7 PANEL MEMBER GLANTZ: Oh, okay.

8 PANEL MEMBER BYUS: Well, let's not get carried
9 away now.

10 (Laughter.)

11 PANEL MEMBER GLANTZ: Well, I was going to
12 suggest -- when I came into today I was going to suggest
13 that we adopt -- we approve this part of the document.
14 But I think since we're meeting in less than a month or
15 about a month, I'm going to assume that, except for the
16 specific fairly minor tweaks that got discussed here,
17 people are happy with what this part of the document says.
18 Is that a fair...

19 Okay. And so I'll work with Melanie and Andy,
20 and we'll get all these other things fixed up for next
21 time and some findings written. So hopefully at the next
22 meeting we can just approve the technical support
23 document.

24 CHAIRPERSON FROINES: So you're actually
25 proposing not to move today?

1 PANEL MEMBER GLANTZ: Well, if you -- or we could
2 vote today, or alternatively since -- actually let me
3 propose we do vote and just subject to, you know, the
4 comments that we can pick up on in the transcript in
5 cleaning things up. I guess why don't I move that we
6 approve the technical support document. And then I'll
7 work with the staff to get these corrections done, and we
8 can then run them by the Chair.

9 Are people -- would you rather do that?

10 PANEL MEMBER BLANC: I think what I would suggest
11 as a middle ground is that we make it clear that we are
12 quite supportive of the technical document to the extent
13 that it certainly should continue to be used as the basis
14 for finalizing the individual substance-by-substance
15 estimations that you're doing, and that we'll finalize --
16 give final approval -- we'll approve of a final text, you
17 know, at the next meeting.

18 PANEL MEMBER GLANTZ: Okay.

19 PANEL MEMBER BLANC: Because I think that's what
20 you're worried about. If we don't approve it, how can
21 they continue to use this to go ahead and refine that.

22 PANEL MEMBER GLANTZ: Okay, that's fine. Why
23 don't we do that. I mean we're not talking --

24 PANEL MEMBER BYUS: I think that, you know, as we
25 discuss these chemicals, it will even make our --

1 theoretically the value of this document, it will even be
2 greater. And maybe we will say something different or
3 something even stronger than we might now. So I mean I
4 think you are right. I would agree with you, Paul.

5 PANEL MEMBER GLANTZ: Okay. Well, so in the
6 meantime I'll work with them to take care of everything
7 that's identified; and with the idea that when we come
8 back to the next meeting, it will be approved. I don't
9 see any great huge controversial issues outstanding at
10 this point.

11 CHAIRPERSON FROINES: Now, the issues I think
12 that need to be worked on, it's interesting, are -- I
13 think are minor with respect to what needs to be done.
14 But they do reflect major issues, so that there -- it's
15 sort of --

16 PANEL MEMBER GLANTZ: Right. But what I meant
17 was I don't see any tremendous criticism of the document.

18 CHAIRPERSON FROINES: No. I think Paul said it.

19 PANEL MEMBER GLANTZ: These are all matters of
20 clarification, nuance, making the presentation better.
21 And then we'll draft some findings that we'll circulate
22 before the meeting.

23 CHAIRPERSON FROINES: I think Paul said it. I
24 don't --

25 PANEL MEMBER GLANTZ: Okay. So there's no need

1 for a motion or anything.

2 CHAIRPERSON FROINES: I think Craig or Gary would
3 have disagreed if they didn't share that view.

4 PANEL MEMBER GLANTZ: Okay. That's fine with me.

5 CHAIRPERSON FROINES: Okay. Unless Melanie
6 has -- unless there's some time issue that you absolutely
7 need a different approach.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: No, it's fine.

10 CHAIRPERSON FROINES: So just to -- so the Panel
11 thinks this is a fine document that needs some minor
12 tweaking and that we'll approve the final version next
13 month. But in the interim, it does stand as a standard
14 around which to approach the REL determination.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Okay. We'll start the chemical by chemical with
17 acetaldehyde first.

18 This is Dr. Karen Riveles, who is in Andy's
19 group. And she will make the presentation on the
20 acetaldehyde REL.

21 So first we'll present what we did. And then if
22 you want to hear a summary of the comments, we'll do that.

23 CHAIRPERSON FROINES: I should just say that I
24 think acetaldehyde is going to become a major issue in the
25 future. As long as we keep using ethanol and biodiesel,

1 this issue is going to just keep growing, in my view. So
2 you got a good one.

3 --o0o--

4 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Thank you.

5 Just by way of overview on the first slide, I've
6 indicated what the final calculations for the acute 8-hour
7 and chronic REL are.

8 The acute REL is based on eye irritation in human
9 volunteers, was determined to be 750 micrograms per meter
10 cubed or 420 parts per billion.

11 And I'm going to go into more detail on each one
12 of these in the next slides.

13 The 8-hour REL and the chronic REL are both based
14 on an animal study in rats on nasal degeneration of
15 olfactory epithelium. And the 8 hour was determined to be
16 270 micrograms per meter cubed, and the chronic to be 140
17 micrograms per meter cubed.

18 --o0o--

19 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The key
20 study for the acute REL determination was by Silverman, et
21 al., 1946. It used human volunteers, an average of 12
22 subjects of both sexes per dose group, for a 15-minute
23 exposure of 0, 25, 50, or 200 parts per million.

24 Motion pictures were shown to occupy the
25 subject's attention during the exposure.

1 And may I note, it was 1946.

2 --o0o--

3 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The
4 results of this study were that the 200 ppm's resulted in
5 responses of bloodshot eyes and reddened eyelids in all
6 subjects.

7 The majority, in quotes, of subjects experienced
8 some degree of eye irritation as 50 parts per million and
9 several subjects did at 25 parts per million.

10 Therefore, the lowest observable adverse effect
11 level for a severe effect was determined to be 50 ppm and
12 for a mild effect to be 25 ppm. No NOAEL was determined
13 for this study.

14 And while words like "majority" and "several" are
15 vague, that was all that was provided in the results of
16 the study. But the strength of the study is that it was
17 done in humans.

18 --o0o--

19 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So to
20 review our REL derivation. Again there was a total of 24
21 adult human volunteers. The exposure method was
22 inhalation. The endpoint or critical effect that was
23 looked at was eye irritation. And a LOAEL for a minor
24 effect -- mild -- excuse me -- was 25 ppm, while a NOAEL
25 was not observed.

1 The exposure duration was 15 minutes. And this
2 was not time adjusted due to what was mentioned earlier
3 about Haber's Law not applying to sensory irritation.

4 --o0o--

5 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: A LOAEL
6 uncertainty factor for a mild effect was applied of 6 due
7 to the fact a NOAEL was not determined.

8 Since it was done in human volunteers, the
9 interspecies factor was 1.

10 Once again, we've divided the intraspecies
11 uncertainty factor into two components, with the
12 toxicokinetic component being 1 because it occurred at the
13 site of contact in mainly a localized effect.

14 Whereas the toxicodynamic uncertainty factor was
15 10 due to the potential asthma exacerbation in children.

16 PANEL MEMBER BLANC: Because it's an irritant?
17 Because it's a water soluble irritant? Would that be the
18 rationale?

19 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Yes.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: There are also data indicating that there are
22 people who react with hypersensitive airways in the
23 presence of acetaldehyde. So it's a little bit more than
24 just assuming --

25 PANEL MEMBER BLANC: There is?

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yeah.

3 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: There are
4 four or five studies that look at human volunteer adults
5 that inhaled aerosolized solutions of acetaldehyde and
6 were measured for SEV values for asthma exacerbation. And
7 it was found that asthmatics are particularly more
8 sensitive to the effects of acetaldehyde. But no studies
9 were done in children.

10 CHAIRPERSON FROINES: Are there studies looking
11 at inflammatory processes?

12 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: There are
13 a few studies looking at inflammation, but not in human
14 volunteers.

15 I don't have any further information on that.

16 PANEL MEMBER FRIEDMAN: This is a very minor
17 nitpick, but on an earlier slide when you talked about
18 method of exposure being inhalation, since it was hitting
19 the eyes directly it didn't involve inhaling and then
20 getting there, say, through the blood stream. So I was
21 wondering if a better term might be airborne or --
22 airborne or something like that or atmospheric or
23 something like that rather than inhalation. Very minor
24 point, but relevant to the eye irritation I think.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Yeah, it is a little bit kind of a confusing term
2 in that case.

3 CHAIRPERSON FROINES: Can I just say one thing.

4 If you take two molecules of acetaldehyde and you
5 condense them chemically and you lose water in the
6 process -- a molecule of water, you form an unsaturated --
7 and alpha-beta unsaturated aldehyde. And alpha-beta
8 unsaturated aldehydes form irreversible inhibition of a
9 wide range of proteins, and that can result in
10 inflammatory processes because it affects signal
11 transduction pathways. And alternately you have the
12 potential for cytokines, what have you, coming out of
13 being activated by genes. And that can result in
14 inflammatory responses.

15 So there's a potential for the chemistry that
16 goes on with acetaldehyde to have quite significant asthma
17 effects theoretically. And that's why I asked the
18 question then. And it's going to -- that's an issue in
19 terms of the chronic issues as well. Because if you're
20 breathing it on a daily basis 24 hours a day, that
21 chemistry is going on.

22 Anyway, go ahead.

23 --o0o--

24 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So that
25 leads to a cumulative uncertainty factor of 60. And

1 dividing the 25 ppm LOAEL for a mild effect divided by 60
2 is what gives us the 750 micrograms per meter cubed, or
3 420 parts per billion.

4 While there are many acute animal studies that
5 I've mentioned in the REL summary, most are done at much
6 higher doses. And then you have animal to human
7 extrapolation issues to deal with. So although this study
8 was limited, it was the best available study because it
9 was done in humans.

10 PANEL MEMBER BLANC: So can we come back to this
11 issue of acetaldehyde as an inducer of airway -- of
12 bronchial constriction. So you're review of the data is
13 that basically you could use it instead of a methacholine
14 challenge if you wanted?

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: It wasn't nearly as sensitive as a methacholine
17 challenge.

18 PANEL MEMBER BLANC: But it will invoke bronchial
19 constriction in asthmatic and normal subjects and will
20 differentiate between asthmatics and normal subjects?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: I think that the asthmatic subjects were more
23 sensitive and -- Karen, you can correct me -- put I also
24 remember that the acetaldehyde itself increased the
25 sensitivity to methacholine challenge.

1 PANEL MEMBER BLANC: Right. So I guess my
2 question is, was it the problem that these studies
3 delivered an aerosolized dose that prevented you from
4 extrapolating to an airborne concentration?

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Yes.

7 PANEL MEMBER BLANC: But couldn't you extrapolate
8 based on the nebulizer delivery system as to what the
9 parts per million equivalent would be or the milligrams
10 per cubic meter concentration?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: They were -- if you tried -- and I'm not sure that
13 it's actually a valid way to do it. These were very
14 large, very high concentrations if you tried to make that
15 extrapolation. So in terms of a looking at a more
16 sensitive endpoint, we already had that in our in ocular
17 irritation.

18 PANEL MEMBER BLANC: Okay. But the ocular -- I
19 mean two things about your ocular study. One, is not so
20 thrilled to be using a 1946 study in 2008 just on general
21 principles. Secondly, because your main extrapolation
22 then to childhood exposure is based on increased bronchial
23 responsiveness in asthmatic children, if you thought that
24 the benchmark exposure for causing bronchial constriction
25 was far above what your endpoint concentrations were for

1 the eye irritation, it wouldn't actually make sense then
2 to put in the uncertainty -- the sixfold uncertainty
3 factor, would it?

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Well, we did talk about that a little bit. And
6 part of the issue is how do you extrapolate from the
7 studies they did in terms of the aerosol.

8 And then the other issue is that we have
9 previously identified asthma as a disease that
10 differentially impacts kids. And we don't have really
11 very good information on whether the concentrations to
12 which you would be exposed in the ambient air are adequate
13 to actually trigger bronchial reaction. We decided to go
14 ahead and apply that uncertainty factor for toxicodynamics
15 anyway.

16 So the point you're making is definitely it's an
17 uncertainty. And, you know, it's a question we thought
18 about but went ahead and applied it anyway.

19 PANEL MEMBER BLANC: And when you said that when
20 you did the conversion from the nebulized concentration to
21 some kind of airborne milligram per micrograms per cubic
22 meter, what kinds of -- what kinds of parts per million
23 were you coming up with, as opposed to 25 -- 25 parts per
24 million was how much in micrograms per -- milligrams per
25 cubic meter? I'm sorry.

1 OEHHA ASSOCIATE TOXICOLOGIST RIVELES:

2 Forty-five.

3 PANEL MEMBER BLANC: Forty-five milligrams per
4 cubic meter.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Yeah, my back of the envelope was about five grams
7 per cubic meter if it was -- even if it's, you know,
8 doable to take an aerosolized spritz and try to figure out
9 what that would be in milligrams per cubic meter.

10 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

11 CHIEF SALMON: The big trouble this that extrapolation is
12 that you don't know how the deposition is going to be
13 working between a vapor phase exposure versus an
14 aerosolized exposure. One suspects a lot of the aerosol
15 would be depositing in the upper respiratory tract, for
16 instance.

17 PANEL MEMBER BLANC: I don't -- I mean if De
18 Vilbiss nebulizer gets pretty fine particles that get into
19 the airway, that's why you use it for a test of bronchial
20 constriction.

21 Who is the primary reviewer for this? I don't
22 want to step on someone's toes.

23 PANEL MEMBER GLANTZ: You don't?

24 (Laughter.)

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: I believe -- according to my -- Dr. Froines was
2 the lead on acetaldehyde.

3 CHAIRPERSON FROINES: I didn't remember that.

4 PANEL MEMBER GLANTZ: But you can particularly
5 step on his toes.

6 PANEL MEMBER BLANC: Thank you.

7 Well, I think it's a challenge because here
8 you've got this sort of very large data set of human
9 exposure with a relevant endpoint from a public health
10 context and an interesting biological effect, which I
11 actually wasn't aware of this sort of -- that you could
12 use it, you know, as a poor man's methacholine. I know
13 that you could use sulfur dioxide as methacholine if you
14 wanted. And that's how much more responsive asthmatics
15 are to sulfur dioxide.

16 You know, you may want to just consult informally
17 with Warren Gold or someone else who -- or Homer Boushey
18 on how you're doing the conversion given how De Vilbiss
19 nebulizers work and what the delivered dose is. Because
20 the delivery dose is actually pretty small, and so maybe
21 you're not as many orders of magnitude higher than you
22 think. I don't know.

23 PANEL MEMBER GLANTZ: They're both at UCSF.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Okay. We could take a closer look at that. I

1 realize that we didn't actually even explain why we didn't
2 use these, I don't think. Karen, did we?

3 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: No.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Yeah. So we could describe that.

6 PANEL MEMBER BLANC: So that at a minimum --

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: At a minimum we could do that. And, you know, I'm

9 happy to call Homer Boushey and talk about that.

10 PANEL MEMBER BLANC: Because in fact the

11 chemistry of acetaldehyde is that it would be in water

12 droplets, wouldn't it? I mean in reality when you --

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: I know we've had this issue many times. I mean

15 there is a whole bunch of installation studies with diesel

16 exhaust particulate, for example. And it's very hard to

17 say what does that mean in terms of meters -- you know,

18 micrograms per meter cubed? So it's always an issue

19 trying to do that jump -- make that jump.

20 CHAIRPERSON FROINES: Let's go ahead, unless Paul

21 has more.

22 PANEL MEMBER BLANC: No, I just -- I think this

23 is something you really should explore and see if it

24 changes -- they may actually just be a great justification

25 for sticking with your eye study. But that sixfold

1 factor, you may be better able to justify it.

2 PANEL MEMBER GLANTZ: You know, there's also -- I
3 wasn't going to bring this up. But I will since you're
4 going to be revisiting this event.

5 There's a fair amount of evidence that
6 acetaldehyde has very strong oxidizing effects that affect
7 platelets and cardiovascular risk too. And Neal Benowitz
8 at San Francisco General has done a bunch of stuff with
9 that. So you might want to just talk to him too. I don't
10 know if the magnitude of the effect -- or the doses are
11 above or below what you're talking about. But it's very
12 long-lived in blood. And, you know, he thinks a lot of
13 the cardiovascular effects of secondhand smoke are due to
14 the acetaldehyde in the secondhand smoke. And he's
15 written some stuff about acetaldehyde and cardiovascular
16 effects or reviews of it or something. But I would also
17 talk to him.

18 CHAIRPERSON FROINES: But --

19 PANEL MEMBER GLANTZ: If it turns out that it's
20 no where near as sensitive an endpoint as what you have in
21 there, I wouldn't bother with it. But it might be worth
22 at least checking.

23 CHAIRPERSON FROINES: But I would argue that --
24 we're talking right now about a specific issue associated
25 with the acute effects.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yes.

3 CHAIRPERSON FROINES: I don't think there's any
4 question but that acetaldehyde is an important chemical in
5 terms of chronic effects.

6 PANEL MEMBER GLANTZ: No, but these acute effects
7 could be platelet activation and triggering acute coronary
8 effects.

9 CHAIRPERSON FROINES: Yeah, but that may occur
10 also as a result of the inflammatory processes in the lung
11 that produce immunologic responses that affect the
12 cardiovascular system. So the mechanism is actually
13 complicated.

14 PANEL MEMBER GLANTZ: Well, they're probably
15 direct ended. And both of those things are probably going
16 on actually.

17 I just think since you're going to be looking
18 into this a little more, it's worth checking. And it may
19 be that the acute effects aren't that important or it may
20 be that the levels of exposure required are higher than
21 what you're talking about here, in which case there's
22 nothing to pursue. But I think it's worth just checking.

23 CHAIRPERSON FROINES: We in our studies have
24 shown the compounds like this produce lung remodeling,
25 produce mucosecretion that produce esophageal contraction.

1 I mean there are a lot of effects that we've shown from
2 these kinds of compounds that are very relevant to
3 acetaldehyde.

4 --o0o--

5 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Okay. The
6 key studies for the 8-hour and chronic REL determinations
7 that were used are two studies done by Appelman. The
8 first one was done in 1982 and it was a four-week
9 inhalation study where ten male and ten female rats were
10 used per dose group. They were exposed to 0, 400, 1,000,
11 2,200, or 5,000 ppm for six hours a day, five days a week.

12 --o0o--

13 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: A
14 follow-up study done by the same group in 1986, also
15 four-week inhalation study on rats, used male only Wistar,
16 rats ten per dose group, and exposed them to 0, 150 or 500
17 ppm for six hours per day, five days per week.

18 --o0o--

19 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this is
20 a concurrent derivation of both the 8-hour and chronic
21 RELs, since they were based on the same key studies in
22 rats. And the critical effects was nasal degeneration of
23 olfactory epithelium being the most sensitive endpoint. A
24 LOAEL was determined as 400 ppm and a NOAEL was determined
25 at 150 ppm.

1 using a dichotomous incidence data analysis.

2 And just a note, the blank spots are
3 representative of where the one study only used male
4 animals instead of female animals for those 2 dose groups.

5 --o0o--

6 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this
7 table shows the results of benchmark dose modeling for
8 numerous continuous models. And they're all in quite good
9 agreement for the benchmark concentration of 100, 101, and
10 97. And so a mean was taken of those values.

11 --o0o--

12 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: And 99 was
13 then -- which is what the mean is, 99 ppm was used as the
14 benchmark dose.

15 A time adjustment was necessary for a REL
16 determination. And for the 8-hour we used a time
17 adjustment that assumed the 8 hours includes the active
18 waking period when an adult inhales 10 meters cubed of
19 air, which is half the daily total intake of 20 meters
20 cubed.

21 And it was ingested for the 6 hours to 24 hours
22 and the 5 days a week to 7 days a week. Whereas the
23 chronic time adjustment was only 6 hours per 24 and 5 days
24 per 7.

25 We used a PBPK model that's recently been

1 of 48.3 ppm using the probit model. However,
2 statistically these models were not reliable due to the
3 small sample size and the dose spacing. If you look at
4 the table below, you'll see the 150 ppm that was the
5 determined LOAEL for the study versus the 50 ppm of the
6 NOAEL for the study. It jumped from 0 response to 100
7 percent response.

8 --o0o--

9 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this
10 was -- we went ahead and determined what a REL would look
11 like using this study anyway. So, again, it's Dorman, et
12 al., 2008, which was published in February of '08, using
13 12 animals per group of rats that were exposed to, again,
14 0, 50, 150, 500, or 1500 ppm for six hours per day, five
15 days per week, for 13 weeks, with the same endpoint of
16 nasal degeneration of olfactory epithelium. The LOAEL
17 determined was 150 and the NOAEL was 50. We used the
18 dosimetric factor from the Teeguarden PBPK model of 1.36.
19 The time adjustment for exposure was adjusted similarly to
20 the previous derivations, 6 out of 24 hours and 5 out of 7
21 days.

22 A LOAEL uncertainty factor of 1 because a NOAEL
23 was given. A subchronic uncertainty factor of radical 10.
24 The exposure was right on the border line of 12 percent
25 lifetime of the animal. A toxicokinetic factor of 1

1 750, 1500, or 3,000 ppm six hours a day, five days a week,
2 for up to 28 months. And while this was the chronic study
3 that we saw and we did see nasal olfactory degeneration,
4 we were not able to use this because 1) a NOAEL was not
5 determined for this study, and 750 ppm was the lowest dose
6 used. So we would have needed to see lower doses for that
7 one. But it is in support of our key study that we did
8 use.

9 --o0o--

10 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: We did
11 only receive one public comment for acetaldehyde, and that
12 was that we should take a look at the Dorman and
13 Teeguarden studies. They weren't published at the time of
14 our initial public review draft in November. They were
15 released in February in inhalation toxicology. So we did
16 review those and I did incorporate them, both as using the
17 Teeguarden PBPK as a more specific measure of what's going
18 on with toxicokinetics with acetaldehyde, and as well as
19 looking thoroughly at the Dorman data, doing benchmark
20 dose modeling. And it turns out that these are in good
21 agreement with the Appelman data. We felt that the
22 Appelman data was a better -- we were better able to model
23 using benchmark dose modeling. And it was statistically
24 more significant.

25 That's all.

1 PANEL MEMBER FRIEDMAN: I have a question.

2 What are your thoughts about the fact that in the
3 Appelman study there were a couple of animals with nasal
4 degeneration with 0 dose?

5 And second question related to that is, what do
6 you do with your benchmark model? Do you include those or
7 not?

8 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Yes, those
9 were included in the benchmark modeling. And we didn't
10 treat it in any particular different way

11 PANEL MEMBER FRIEDMAN: You know, what do you
12 think -- does that mean that the study is not accurate
13 or --

14 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Well, it
15 was 2 out of 40 animals.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: So I think it just means that, you know, like many
18 other disease processes, there is a background rate. It's
19 not 0.

20 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

21 CHIEF SALMON: It might be a viral infection of --

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: That's right.

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

25 CHIEF SALMON: All sorts of reasons why --

1 CHAIRPERSON FROINES: Say that again. Peter was
2 just giving me something.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Oh, it just indicates there's a -- as with most
5 disease processes, there is a background rate, a
6 background incidence of in this case. And Andy pointed
7 out that if the animals got a viral infection, you might
8 see impacts on the nasal epithelium.

9 PANEL MEMBER BLANC: And since acetaldehyde is a
10 very specific example of a chemical for which we know that
11 there's human genetic variation in its metabolism, how
12 does the uncertainty -- or the square root of 10
13 adjustment for variation or even the animal to human
14 factor of 10 take into account that -- would we anticipate
15 that someone who was acetaldehyde dehydrogenase deficient
16 would have more of a response?

17 OEHHA ASSOCIATE TOXICOLOGIST RIVELES:

18 Teegarden -- the Teegarden, et al., study did
19 look at ADLH2 deficient humans and incorporated that into
20 the dosimetric adjustment factor.

21 PANEL MEMBER BLANC: Which you said was about 3
22 or something along --

23 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: 1.36.

24 PANEL MEMBER BLANC: Is that 1.36, is that a
25 function? Is there a square function or something? It

1 doesn't sound like very much of an adjustment for a
2 genetic deficiency in metabolizing something.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: Well, it's actually -- the model does not just
5 look at that. It includes other things like flux across
6 the nasal epithelium. So, you know, it's actually a
7 little more complicated than just looking at kinetic
8 aspects.

9 PANEL MEMBER BLANC: I mean does it -- I guess
10 what I'm asking is mechanistically or mathematically does
11 it just smooth, assuming that some percent would be
12 genetically deficient? Is that what it does? Because
13 that maybe is not exactly the point that --

14 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

15 CHIEF SALMON: I think they were doing analysis of
16 various, you know, example model parameters in effect.
17 You know, I don't think it was a population-based model or
18 anything fancy like that. I think they were just using
19 specific parameter values.

20 One of the things about this is of course that
21 although obviously metabolism does have an influence --
22 probably, you know, quite a significant influence at one
23 level, we're basically here looking at a point of first
24 contact, impact. So the opportunities for systemic
25 metabolism at least and all these other distributional

1 processes are considerably reduced. So you're not going
2 to see quite the same range of variability due to
3 metabolic factors that you would be seeing for a systemic
4 effect. The fact of the matter is that, you know, we have
5 allowed for the fact that there is a potential variability
6 there, both in terms of looking at the dosimetric
7 adjustment factor and what the model tells us. And also
8 in incorporating -- can we go back to your table here.

9 The uncertainty factors we used.

10 In this particular case we have an intraspecies
11 uncertainty factor toxicokinetic component of square root
12 of 10 here, which is in fact more than we've used in some
13 other cases where we would have a strict point of contact
14 effect with no metabolic contribution.

15 CHAIRPERSON FROINES: Andy, where's your square
16 root of 10?

17 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

18 CHIEF SALMON: On slide number 14, the intraspecies
19 toxicokinetic uncertainty factor, square root of 10 for
20 inter-individual variation.

21 PANEL MEMBER BLANC: So people who are
22 acetaldehyde dehydrogenase deficient, relatively speaking,
23 are only three times less efficient -- one-third as
24 efficient. They're not one-tenth as efficient, they're
25 not one-twentieth as efficient at metabolizing?

1 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

2 CHIEF SALMON: The supposition is that we've had one-third
3 the impact on the nasal epithelium. We're not talking
4 about how much acetaldehyde --

5 PANEL MEMBER BLANC: Yeah, but what is the basis
6 of that? I understand that that's what you're doing by
7 default. But what is your biological basis in this
8 particular example?

9 I'm harping on this a little bit because here we
10 have a very clear example of a very common genetic variant
11 in humans, which I'm sure it wasn't in the test animals
12 that they studied. And it's fine if you tell me that
13 acetaldehyde doesn't exist in nasal epithelium and
14 therefore the metabolism of the chemical doesn't occur in
15 the nose anyway and therefore the effect is -- it's broken
16 down by other effects. Or if you said that there would be
17 mechanistically no reason to expect a greater epithelial
18 irritation with or without acetaldehyde -- I mean I would
19 accept all of those things. But what I'm trying to
20 understand is the rationale --

21 CHAIRPERSON FROINES: I wouldn't -- I think to
22 assume that in epithelial cells that there is no
23 metabolism is wrong.

24 PANEL MEMBER BLANC: Well, I --

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: That isn't assumed. But what the
2 Teeguarden model is saying is that in terms of the
3 localized concentrations reached, the primary driver is
4 the rate of delivery, you know, by atmospheric deposition.
5 And the local metabolism has some influence but not a huge
6 amount. Is that --

7 CHAIRPERSON FROINES: Yeah, but I think that's
8 the problem that Paul's raised, precisely. It's like --
9 it's saying, we know that there's very wide variability
10 with respect to that population. I mean that is the
11 ability to handle acetaldehyde so that --

12 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

13 CHIEF SALMON: If the primary determinant is the rate of
14 deposition rather than rate of metabolism, then that
15 variation in metabolism would have a somewhat limited
16 effect.

17 PANEL MEMBER BLANC: Yes, but -- you know, I know
18 you made that clear from his model. But was there a basis
19 for that presumption in his model? I mean a convincing
20 basis.

21 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

22 CHIEF SALMON: Well, it's asserted to be, you know, a
23 reasonably factual model of what goes on.

24 PANEL MEMBER BLANC: And by the same token, even
25 if you accepted that, you have a factor of 10 because you

1 feel that children have more asthma and this is going to
2 therefore be preferentially an issue for exposure in
3 children, right? That's the basis of the 10?

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
5 CHIEF SALMON: Yes. I mean there's an issue here in terms
6 of looking at the nasal deposition -- you know, based on
7 the rat study obviously, it's deposition in the upper
8 respiratory tract which is driving the critical response
9 here. But when you go to the human situation, we're also
10 concerned about responses further down the respiratory
11 tract for two reasons: One is that the human nose is a
12 notably less efficient scrubber than the rodent nose. So
13 the fact that you're seeing upper respiratory tract
14 lesions in the rodent fairly exclusively doesn't mean that
15 there won't in addition be lower respiratory tract
16 responses in the human.

17 CHAIRPERSON FROINES: Andy, that was a question I
18 was going to ask you and Paul, because -- what was done,
19 if anything, in terms of looking at lower respiratory
20 tract?

21 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
22 CHIEF SALMON: Well, the Teeguarden model is a nose model.
23 So the answer is that doesn't accommodate that, which is
24 one of the reasons why we have an extra concern about
25 lower respiratory tract responses.

1 The other issue is that even if your exposure and
2 human response is -- you know, if you can confine your
3 attention to what's going on in the upper respiratory
4 tract. The sensory response is to irritants in humans,
5 include things driven by the central nervous system which
6 affect the lower respiratory tract. I mean in rodents you
7 have this rather simplistic, you know, the RD-50 type
8 response. And that's a fairly simple, you know, effect on
9 the control system.

10 In the human case your response isn't simple like
11 that. It involves a whole range of things, including -- I
12 think we -- hearing earlier, you know, you do see things
13 like -- secretion and bronchiole responses and coughing
14 and, you know, various other things which actually
15 potentially interact with the kind of problems that you're
16 having as an asthmatic. So the human situation -- and I
17 think what we're saying is it's a lot more complicated and
18 it does include at least notionally the possibility for
19 lower respiratory tract responses. So that's one of the
20 reasons why that uncertainty factor was increased.

21 PANEL MEMBER BLANC: Well, let me finish with my
22 thought. Actually this is for me to see if I understand
23 how you're doing all these things.

24 So you have these other studies in humans where
25 it looked at acetaldehyde dehydrogenase and bronchial

1 hyper-responsiveness with inhalation of acetaldehyde. And
2 those studies showed that there was a different response,
3 or didn't, with acetaldehyde dehydrogenase deficiency?

4 I mean it says acute -- on page 8 it says,
5 "Another acute human study showed increased sensitivity to
6 acetaldehyde by alcohol sensitive subjects." So I'm
7 assuming -- and then it goes on to detail that. Right?

8 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That is
9 correct, whether they were actually diagnosed as being
10 ADLH2 deficient, I'm not sure of that detail, but I can
11 look at the paper.

12 PANEL MEMBER BLANC: Okay. I mean we could
13 assume that they must have decided that, determined that.

14 So let's take the hypothetical scenario of a
15 child who happens to be alcohol dehydrogenase sensitive --
16 deficient. So wouldn't that child -- and on general
17 principles you're saying children are ten times -- we have
18 to be ten times lower to be protective of children with
19 asthma. But that's not being protective of children with
20 asthma who are alcohol dehydrogenase deficient, is it?

21 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
22 CHIEF SALMON: No. That's where the UFH-k comes in where
23 we've got a root 10 --

24 PANEL MEMBER BLANC: Oh, for the square root of
25 10.

1 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

2 CHIEF SALMON: Yes.

3 PANEL MEMBER BLANC: What is your basis? Was the
4 curve suggestive that the difference was threefold in this
5 study of -- for example, in the study of asthma in the
6 bronchial constriction in the alcohol dehydrogenase
7 sensitive versus non-sensitive subjects?

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: I don't think it was threefold.

10 PANEL MEMBER BLANC: Was it less than threefold?

11 I mean I'm hoping it's less than threefold, because --

12 CHAIRPERSON FROINES: That would be very
13 surprising, don't you think?

14 PANEL MEMBER BLANC: What?

15 CHAIRPERSON FROINES: That would be surprising.

16 PANEL MEMBER BLANC: Well, I don't know. I don't
17 know the study.

18 CHAIRPERSON FROINES: No, no, I'm saying in terms
19 of that issue, the fact that it would be that limited, it
20 would be surprising.

21 PANEL MEMBER BLANC: I don't know. I mean you
22 can see where I'm going with this. If it was sixfold,
23 then obviously you --

24 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

25 CHIEF SALMON: You'd need a bigger factor.

1 PANEL MEMBER BLANC: -- you'd need a bigger
2 factor. This would be one of those examples where in
3 certain cases, you know, we use a bigger number.

4 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
5 CHIEF SALMON: Yeah. No, I see where you're going.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: Well, we're looking at a couple of different ways
8 of looking at this. In the papers, it looked like the
9 mean causing a 20 percent decrease in Epi D1 ranged from
10 18 to 45 depending on the group. So that's within
11 threefold.

12 We should put that in here if it's in here.

13 PANEL MEMBER BLANC: Anyway, I don't think you
14 need to -- what I would say is one of two things: Either
15 review the data and say it was about threefold and this
16 supports their use and say that explicitly. Or if it's
17 not and you need to change your number, change your
18 number, I mean, to be consistent.

19 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
20 CHIEF SALMON: It sounds like the threefold is in fact
21 in -- you know, a reasonable ballpark. But we'll tighten
22 up on that, make sure we believe what we see in the paper
23 here.

24 PANEL MEMBER BLANC: And then say it.

25 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

1 CHIEF SALMON: Yes.

2 PANEL MEMBER BLANC: Mr. Chair?

3 CHAIRPERSON FROINES: What?

4 PANEL MEMBER BLANC: When we finish this
5 chemical, can we have our lunch break?

6 CHAIRPERSON FROINES: Yeah.

7 I will spend some time on this, because I didn't
8 spend time on it, between now and June.

9 How do you feel about your -- I mean if you ask
10 yourself where are the concentrations of acetaldehyde in
11 the air, what do you get? What's the ARB data on
12 acetaldehyde?

13 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

14 CHIEF SALMON: I think they're a few parts per billion
15 typically. I'm not sure whether -- do we have --

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: It's in the -- in the South Coast, the annual
18 average was 1.4 parts per billion in '02. But
19 interestingly enough, you get probably more exposure
20 indoors, because there's a lot of indoor sources.

21 There's been some measurements of U.S. homes and
22 it ranged from 8 to 20 parts per billion. So it's higher
23 in and out.

24 CHAIRPERSON FROINES: This is one of those issues
25 where we know that -- well, this is one of these issues

1 that the overall concentration of various types of
2 carbonyls becomes an important issue, because the
3 cumulative exposure to carbonyls is -- if you look at one
4 chemical with the 1.2 part per billion versus a REL of 76,
5 that's -- you want it to be dismissive if you're not
6 careful. But the issue of the carbonyl concentrations in
7 the mix and the potential for chronic effects via number
8 of mechanisms which are becoming clearer as we speak, it
9 raises an important question of how are we going to
10 address that issue in the future.

11 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
12 CHIEF SALMON: One of the things which we commented on in,
13 you know, the ethanol report that we did some years ago
14 was the facts that if you added up the risks -- well, not
15 the risks -- but, you know, the hazard indices for, you
16 know, for the various eye and respiratory irritants, you
17 came up with, you know, a significantly elevated hazard
18 index. So I think it was about three point something for
19 eye irritants and not far short of that for respiratory
20 irritants. And that wasn't looking at the whole range of
21 it, but it was certainly including, say, formaldehyde,
22 acetaldehyde, and acrolein or something like that. So
23 definitely there is a cumulative impact of these
24 carbonyls.

25 CHAIRPERSON FROINES: You don't think --

1 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

2 CHIEF SALMON: No, there is -- there definitely is a
3 cumulative impact of these carbonyls.

4 CHAIRPERSON FROINES: Yeah. So I think we should
5 table this and finish this next month. And go take a
6 lunch break, as Paul is my conscience on breaks.

7 PANEL MEMBER BLANC: And what time do you want to
8 reconvene?

9 CHAIRPERSON FROINES: I don't have a watch.

10 PANEL MEMBER BLANC: It's 12:35.

11 CHAIRPERSON FROINES: We have -- Craig and I have
12 planes at 3:30. So we're going to have to stop about
13 what, 2 o'clock?

14 MR. MATHEWS: 2:15, 2:20.

15 So it's 12:35 --

16 PANEL MEMBER BLANC: 1:15?

17 CHAIRPERSON FROINES: It's 12:35 now?

18 1:15 would be fine.

19 (Thereupon a lunch break was taken.)

20

21

22

23

24

25

1 arsenic per liter, or one point decrement. And at one
2 liter a day, this is also 2.27 micrograms of arsenic per
3 day.

4 And then I converted that to an inhalation-based
5 value, assuming 9.9 cubic meters per day inhalation rate,
6 a 50 percent absorption by the inhalation route for
7 arsenic. And --

8 PANEL MEMBER FRIEDMAN: May I interrupt with a
9 question?

10 OEHHA STAFF TOXICOLOGIST BROWN: Sure.

11 PANEL MEMBER FRIEDMAN: On the previous slide
12 where you have the decreasing intellectual function, minus
13 0.443 points per microgram, you have R squared equals 1.0.
14 I've never seen an R squared like that. Are you saying
15 that things fit perfectly on that regression line?

16 OEHHA STAFF TOXICOLOGIST BROWN: That's exactly
17 what I'm saying.

18 PANEL MEMBER FRIEDMAN: Wow. Okay. I just had
19 never seen that before.

20 OEHHA STAFF TOXICOLOGIST BROWN: We're using a UF
21 of 30 here. It's 3 --

22 CHAIRPERSON FROINES: The one liter per day?

23 OEHHA STAFF TOXICOLOGIST BROWN: Yes, one liter
24 per day in children.

25 CHAIRPERSON FROINES: Oh, in children.

1 OEHHA STAFF TOXICOLOGIST BROWN: And if you look
2 at the document, we have some different values in there,
3 slightly higher for children -- drinking water in
4 California children. But this is sort of a default, and
5 we thought it would probably be better -- it's probably
6 actually more health protective to stick with the one
7 liter per day per children in this particular age group.

8 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
9 CHIEF SALMON: The children in question are 10-year old
10 children?

11 OEHHA STAFF TOXICOLOGIST BROWN: Yeah, they're
12 10-year old children. They're in Bangladesh obviously,
13 and it's pretty hot there.

14 As I said, we're using UF age of 30. It's 3 for
15 pharmacodynamic and 10 for pharmacokinetic differences.
16 And we could calculate the cREL based on this particular
17 study by dividing the 2.27 per day by 9.9 cubic meters per
18 day, 30 for UF and .5 for absorption.

19 Now the absorption figure of 50 percent is a
20 default. But actually there's some data to support this.
21 In children, we looked at the ICRP, a lung model for
22 children for respirable particles. And they give values
23 depending on inhalation rate of 42 to 52 percent deposited
24 for respirable particles. And there's also a study cited
25 in the document by Votter, et al., on occupational

1 exposure, where she looked at urinary excretion and
2 calculated a value of 42 percent excreted. And that
3 similarly was absorbed through the inhalation pathway.

4 I estimated 52 percent by my own calculations on
5 her data set. So, you know, 42 to 54 percent, the 50
6 percent default that we think is reasonable.

7 --o0o--

8 OEHHA STAFF TOXICOLOGIST BROWN: Now, there's
9 also a key supporting study here, Tsai, et al., 2003. And
10 these are different endpoints but related. A study of
11 cognitive development in 49 13-year old children, also
12 exposed to arsenic through drink water root.

13 They did four developmental tests. These are
14 computer-based studies based on how long they could study
15 the children. These were school children they were
16 looking at. Now, there were three groups identified less
17 than .15 parts per billion, arsenic and water as a
18 control, 131 and 185 as the two dose groups. And they
19 found significant dose responses on three of the four
20 tests - the continuous performance test, the pattern
21 memory test, and the switching attention test. The most
22 sensitive of these was the switching attention. And we
23 were able to analyze the data and getting benchmark dose
24 at the 5 percent level of 19.7 parts per billion. Or if
25 you looked at it in terms of cumulative arsenic intake

1 the range of human sensitivity to arsenic metabolism,
2 essentially affecting the methylation capacity, which
3 seems to be related to some of the endpoints, although not
4 specifically the endpoint we're studying here. We don't
5 have data for that yet.

6 --o0o--

7 OEHHA STAFF TOXICOLOGIST BROWN: Another comment
8 we received was that the key studies for the 8-hour and
9 the cREL are based on drinking water studies and not
10 inhalation.

11 Well, inorganic arsenic is known to act similarly
12 by the oral or inhalation exposure. An example is lung
13 cancer, which is caused by both inhalation and ingestion
14 of inorganic arsenic.

15 We believe oral studies are relevant, and we have
16 no suitable inhalation study for a quantitative analysis
17 of these neural developmental endpoints.

18 Inhalation of our airborne arsenic is probably
19 going to occur in a particulate form. And it's always
20 going to involve some swallowing of these particles
21 through mechanical removal into the upper airways and then
22 swallowing. So there's going to be some oral component
23 even to inhalation of airborne arsenic particles.

24 --o0o--

25 OEHHA STAFF TOXICOLOGIST BROWN: Another comment.

1 Why was the Wasserman study used when others gave higher
2 values.

3 Well, the Wasserman study gives a value of .015
4 micrograms per cubic meter. And it's supported by the
5 Tsai study, as we said, a .046. That's a difference of
6 threefold. And we felt that rather than derive a mean of
7 two or more studies, we chose to use the most health
8 protective study of the most serious and adverse effects
9 seen in children.

10 You know, on occasion we have used means in the
11 past. But there are four things that we thought were
12 comparable. And, you know, currently I think more
13 recently we've tried to focus on the most sensitive --

14 CHAIRPERSON FROINES: Can I ask you a question,
15 Joe?

16 OEHHA STAFF TOXICOLOGIST BROWN: Sure.

17 CHAIRPERSON FROINES: Going back to this issue of
18 oral versus inhalation. Are there any studies in the
19 literature that looked at the relative systemic uptake of
20 inhalation versus oral ingestion?

21 OEHHA STAFF TOXICOLOGIST BROWN: Well, I
22 mentioned the study with water, which was in smelter
23 workers. And they calculated the value -- or estimated
24 value at 42 percent. Higher values are seen by the oral
25 route. We generally assume complete absorption of --

1 CHAIRPERSON FROINES: I can't hear you.

2 OEHHA STAFF TOXICOLOGIST BROWN: I said we
3 generally assume complete absorption of oral inorganic
4 arsenic. In animals it's -- I think it's well over 70
5 percent, depending upon the form and, you know, what it's
6 given with.

7 Certainly there would be less taken up by the
8 inhalation route than the oral route. The question is,
9 how much less? You know, our defaults are 50 and 100
10 percent respectively according to inhalation and oral.

11 Does that answer your question?

12 You know, the data is not that great. I mean, as
13 I said -- and I made my own estimate on Fawer's data. I
14 took four of her subjects and assumed ten cubic meters per
15 day during the workday, one liter per day of urinary
16 excretion, and I got 52 percent on four subjects. This
17 was their -- she followed the workers through the week,
18 measured airborne arsenic. It wasn't specified as to
19 particle distribution, so we don't know about that. But
20 we know it was in the air, it was measured. And she
21 followed it the year and it was more or less study, study,
22 looking at the grass -- over the week. So she was more or
23 less a sort of study, study situation where they were
24 breathing it in every day and it was coming out every day
25 in the urine.

1 So those are the --

2 CHAIRPERSON FROINES: She's a good scientist. So
3 it's --

4 OEHHA STAFF TOXICOLOGIST BROWN: It would be
5 great to have more data. But, you know, it's difficult to
6 get volunteers to take this stuff.

7 Okay. We had another comment here.

8 You know, comparing our values with other values,
9 that the Netherlands' Public Health & Environment, they
10 developed a level, a tolerable concentration in air of one
11 microgram per cubic meter for cancer and non-cancer
12 effects. And this was, as the commenter said, nearly two
13 orders of magnitude higher than our value.

14 And I guess -- you know, I guess we would say we
15 just don't agree with -- I don't know how old this
16 particular assessment is anyway. But I think in our view
17 the risks of arsenic exposure have been historically
18 underestimated for both cancer and non-cancer endpoints;
19 one reason being the lack of suitable animal models for
20 arsenic-related disease.

21 I don't think EPA has a comparable value for
22 non-cancer for arsenic.

23 CHAIRPERSON FROINES: Well, OSHA standard is ten
24 micrograms per cubic meter.

25 OEHHA STAFF TOXICOLOGIST BROWN: It's difficult

1 to say. You know, there's so much new stuff coming out on
2 arsenic. As I said before, it's like a growth industry,
3 arsenic research, right now. And, you know, I've got a
4 database of over 1400 articles on my computer at home.

5 CHAIRPERSON FROINES: I was at a meeting last
6 week with Allen Smith, and he has all sorts of work coming
7 out. And there's a very good review of arsenic toxicology
8 and -- by a fella named Yoshito Kumigai, who wrote a
9 review in the annual review of -- is it Pharmacology and
10 Tox -- it's Toxicology and Pharmacology -- in the last
11 couple years. You might not have found it. It's quite
12 good.

13 OEHHA STAFF TOXICOLOGIST BROWN: I'm updating my
14 database all the time. But it's possible I missed
15 something. People are sending me things all the time, but
16 I catch some, I miss others.

17 That's the final slide I have. I didn't want to
18 overdo this. The document is quite lengthy. I basically
19 wanted to hit the highlights of this.

20 And we took comments from Gary Friedman and
21 adopted most of his suggestions and responded point by
22 point. So I think you got that to --

23 PANEL MEMBER FRIEDMAN: I didn't see the response
24 point by point. You're just saying that it's just in the
25 document?

1 OEHHA STAFF TOXICOLOGIST BROWN: No. I
2 actually -- I don't know why you didn't receive it.

3 PANEL MEMBER FRIEDMAN: I never got it.

4 OEHHA STAFF TOXICOLOGIST BROWN: I assume -- I
5 made point-by-point responses and I passed them up the
6 line.

7 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
8 CHIEF SALMON: I'll have to check on that. I thought we
9 sent those.

10 PANEL MEMBER FRIEDMAN: Well, this document that
11 we received on April 2008 with I guess is a modified -- is
12 this your final report, this report?

13 OEHHA STAFF TOXICOLOGIST BROWN: Not necessarily
14 final. But it should include responses I made to your
15 comments and any others I received that --

16 PANEL MEMBER FRIEDMAN: Oh, okay. So that's the
17 next thing I should be reviewing?

18 OEHHA STAFF TOXICOLOGIST BROWN: Yeah, you should
19 take a look at that. And also you should get my
20 point-by-point responses to your comments. But I did go
21 through them. I spent a lot of time answering them.

22 PANEL MEMBER FRIEDMAN: One thing I just today
23 was flipping through looking for my suggestion that there
24 be a glossary of all these abbreviations. Did that ever
25 show up in anything --

1 OEHHA STAFF TOXICOLOGIST BROWN: That's in the
2 appendix.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: We have a glossary in the appendix.

5 OEHHA STAFF TOXICOLOGIST BROWN: One of the
6 answers was that you should look at the appendix because
7 that's our glossary. But we did go through and add more
8 explanations and tried to dejargonize as much as possible.

9 PANEL MEMBER FRIEDMAN: Oh, thank you.

10 OEHHA STAFF TOXICOLOGIST BROWN: So that was
11 done.

12 PANEL MEMBER FRIEDMAN: Overall I thought it was,
13 you know, a well done report. But most of my concerns
14 were about clarification and what critiques of some of the
15 studies quoted as to whether, you know, you --

16 OEHHA STAFF TOXICOLOGIST BROWN: But you had a
17 couple of numerical comments in there which I responded
18 to.

19 PANEL MEMBER FRIEDMAN: Oh, good.

20 OEHHA STAFF TOXICOLOGIST BROWN: So you'll need
21 to look at those. But I also clarified one in the text.
22 So as you go through the -- as you go through that, you
23 shouldn't see the same sort of questions jumping up at you
24 because I actually did make an effort to respond to your
25 questions.

1 PANEL MEMBER FRIEDMAN: Okay. And, Andy, will
2 you forward to me the responses?

3 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

4 CHIEF SALMON: Sure.

5 CHAIRPERSON FROINES: So, Melanie, did -- I don't
6 want to take up more than a minute or two on this. But if
7 I remember correctly, the cancer number is .007 parts per
8 billion, and this is clearly quite different. So that in
9 terms of looking at arsenic, what's the sort of
10 relationship between that very, very conservative value
11 for cancer relative to the non-cancer RELs?

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: Well, I think it --

14 CHAIRPERSON FROINES: I'm not sure the question
15 I'm asking --

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Well, when somebody does a risk assessment of a
18 source of arsenic, they're going to have to look at both
19 non-cancer and cancer. So they would use the universal
20 factor for arsenic. And we will actually talk a little
21 bit about arsenic in our upcoming revision of the cancer
22 risk methodology, because it's an example where recent
23 data from Allen Smith actually shows that in utero, in
24 early childhood exposure results in higher relative risks
25 for lung cancer in actually relatively young adults. So

1 it's a great example of a chemical that's a carcinogen,
2 and the carcinogenicity -- the carcinogenic potency is
3 worse from early life exposure.

4 PANEL MEMBER BLANC: Can you clarify again for
5 the key dose response that you used, which was the drop-in
6 IQ per water concentration? Can you go back to what the
7 water concentration was.

8 OEHHA STAFF TOXICOLOGIST BROWN: 2.27 micrograms
9 of arsenic per liter.

10 PANEL MEMBER BLANC: Would lead to a --

11 OEHHA STAFF TOXICOLOGIST BROWN: -- to a
12 decrement of one point.

13 PANEL MEMBER BLANC: So one thing you might want
14 to do by analogy -- going to your study of lung function
15 decrement that's on page 24. You show that there is a 45
16 ML decrement per 100 micrograms per liter or a 4.5 ML per
17 10 or a 1 ML for 2.3 or something. So --

18 OEHHA STAFF TOXICOLOGIST BROWN: And what are you
19 driving at? What's the point of comparing --

20 PANEL MEMBER BLANC: Well, you're saying that
21 there is this -- I would say that there's a supportive
22 similar health effect to the similar dose response. I
23 mean I don't know what -- I suppose I'd rather lose an ML
24 of lung function --

25 OEHHA STAFF TOXICOLOGIST BROWN: It's hard to

1 look at a one point loss in a small study. But if you
2 look at a population, a one point loss could be
3 significant.

4 PANEL MEMBER BLANC: Well, If you look at a
5 population of 1 ML loss per year -- I mean I don't know
6 what it would be, you know, but --

7 OEHHA STAFF TOXICOLOGIST BROWN: Yeah, that's an
8 interesting point. I'll have to look at the --

9 PANEL MEMBER BLANC: So that's just a -- I
10 mean just -- in fact, it's not -- one from an occupational
11 point of view wouldn't have thought that central nervous
12 system toxicity would necessarily have been your target
13 organ of toxicity -- your non-cancer target organ of
14 toxicity for arsenic. So I think it would be nice to back
15 it up with something else.

16 I'm quite confused as to why section 6.2.3
17 is -- what it is, where it is. Can you explain that?

18 On page 27, lung effects. I wonder if this was
19 left over from something else.

20 OEHHA STAFF TOXICOLOGIST BROWN: You know, the
21 document was rearranged a few times and -- if you have a
22 suggestion --

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
24 MARTY: It's because it's in infants and children.

25 PANEL MEMBER BLANC: But this is studies of

1 adults and cancer risk and mortality. I mean --

2 OEHHA STAFF TOXICOLOGIST BROWN: Lung effects

3 and --

4 PANEL MEMBER BLANC: And it's cancer and it's --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: I don't know what you guys are looking at. The

7 one I'm looking at it says chronic toxicity, infants and

8 children, 6.2 and 6. --

9 PANEL MEMBER BLANC: Yeah, I know. And then in
10 that if you go to page 27, the section on lung effects --

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Oh, that's a good style. Allen Smith talks about

13 bronchiectasis as well as lung cancer. So did we not put

14 the bronchiectasis in here?

15 PANEL MEMBER BLANC: No, bronchi -- and that was
16 going to be another point -- is I didn't see the
17 bronchiectasis studies. Maybe I missed it.

18 Oh, there's the bronchiectasis. And that wasn't
19 a childhood effect.

20 CHAIRPERSON FROINES: It's on page 28.

21 PANEL MEMBER BLANC: That was an adult's, wasn't
22 it

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Well, yeah, the bronchi -- well, actually what

25 they did was look at -- they were able to separate out

1 people who had been exposed to very high amounts in utero
2 in early childhood from those who were not exposed to
3 those same high amounts and looked at the risk of
4 bronchiectasis in young adults.

5 PANEL MEMBER BLANC: But they both had it.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Well, the in utero and early childhood exposures
8 had higher SMRs for bronchiectasis than the -- if that
9 exposure had not occurred.

10 PANEL MEMBER BLANC: I see.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: So it was sort of -- he was looking at the period
13 of exposure. Because they had very high concentrations of
14 arsenic in their drinking water and then they actually did
15 something about it and it dropped.

16 PANEL MEMBER BLANC: This is the chili thing.

17 But then what about the -- but he's also co-published on
18 bronchiectasis from Bangladesh. So then at least that
19 should have been in the other section on lung disease.
20 And I don't see why the lung cancer part that precedes it
21 is so relevant then.

22 OEHHA STAFF TOXICOLOGIST BROWN: Well, only
23 because it was part of the same study, think --

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Yeah, it was part -- I mean we can, you know,

1 de-emphasize that.

2 OEHHA STAFF TOXICOLOGIST BROWN: If you'd just
3 match it, it would seem like it's coming out of blue.
4 It's sort of an introduction to --

5 PANEL MEMBER BLANC: All I did was I read it.

6 OEHHA STAFF TOXICOLOGIST BROWN: Okay. So we
7 need to think about --

8 PANEL MEMBER BLANC: And I think that the first
9 author on the Bangladesh bronchiectasis was Steinmass.

10 I mean you should ask Craig. Has Craig looked at
11 this section for you?

12 OEHHA STAFF TOXICOLOGIST BROWN: I don't know.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Well, we sent it to his branch. Whether they
15 asked Craig to look at it or not, I don't know. But he
16 can ask him to look at it.

17 OEHHA STAFF TOXICOLOGIST BROWN: It might be
18 bureaucratically impossible.

19 OEHHA DEPUTY DIRECTOR ALEXEEFF: We can have him
20 look at it.

21 OEHHA STAFF TOXICOLOGIST BROWN: I know he's
22 sympathetic to it.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Okay. I know that there are some new studies
25 poised to come out in animals, looking at lung development

1 and arsenic exposure. So if it comes out soon enough,
2 we'll add that too.

3 OEHHA STAFF TOXICOLOGIST BROWN: That's almost
4 like a moving target.

5 PANEL MEMBER BLANC: No, I know. But this other
6 thing I mean you could do right away in terms of just the
7 lung that --

8 OEHHA STAFF TOXICOLOGIST BROWN: If it's already
9 out there, we can look at it and do it.

10 PANEL MEMBER BLANC: Yeah.

11 PANEL MEMBER GLANTZ: Are we going to do mercury
12 now?

13 CHAIRPERSON FROINES: Unless there are other
14 questions on arsenic.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
16 MARTY: Okay. If the Panel's ready, we can move on to
17 mercury. And we thought we would do mercury today because
18 Dr. Byus was the lead. So if that makes sense.

19 PANEL MEMBER BYUS: As long as we get Dr. Byus on
20 his airplane.

21 (Laughter.)

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: That would leave acrolein, formaldehyde and
24 manganese for the next meeting.

25 CHAIRPERSON FROINES: We've got about 20 minutes.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Twenty minutes. Okay.

3 OEHHA STAFF TOXICOLOGIST WINDER: Okay. I'm
4 Bruce Winder with OEHHA.

5 Again, I'll present the overview slides here.

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

8 OEHHA STAFF TOXICOLOGIST WINDER: The acute REL
9 for the mercury study was based on central nervous system
10 disturbances in pups of rats that were exposed during
11 pregnancy. The 8-hour REL is -- and that acute REL is .6
12 micrograms per meter cubed. The 8-hour REL is .06
13 micrograms. And the chronic REL is .03. Now, both the
14 8-hour and the chronic RELs are based on neurotoxicity in
15 adult humans.

16 --o0o--

17 OEHHA STAFF TOXICOLOGIST WINDER: The acute REL
18 is an animal study. I could find no acute studies in
19 humans.

20 In this case, as I mentioned, the rats were
21 exposed through the mother in utero. And this was to a
22 mercury vapor level of 1.8 mg per meter cubed for one or
23 three hours per day during gestation days 11 through 14
24 and 17 through 20.

25 Then the endpoint here are neurobehavior in the

1 it's chronic or 8-hour study there would be very little
2 clearance here.

3 --o0o--

4 OEHHA STAFF TOXICOLOGIST WINDER: Now, we use an
5 interspecies uncertainty factor of 1 since this is a human
6 study. The toxicokinetic intraspecies, this is square
7 root of 10. We don't expect a substantial difference
8 among individuals there.

9 But the toxicodynamic effect we go for the full
10 because again we're expecting a higher level of
11 susceptibility for neurodevelopmental exposures.

12 So for our 8-hour study, a cumulative UF of 300,
13 for an 8-hour REL of .06 micrograms per meter cubed

14 --o0o--

15 OEHHA STAFF TOXICOLOGIST WINDER: So same set of
16 studies when it's applied for the chronic REL. Again, the
17 same neurotoxicity endpoint. LOAEL is the same.

18 And the time adjustment here involves this
19 breathing rate that was introduced to some of the others
20 of 10 cubic meters during a workday for a full day.

21 So this gives us an adjusted value of 9
22 micrograms per meter cubed.

23 --o0o--

24 OEHHA STAFF TOXICOLOGIST WINDER: Again, it's an
25 interspecies. You have 1 because it's a UF study.

1 the similarity between both elemental and methyl mercury
2 effects, we didn't think an additional database deficiency
3 factor was necessary

4 --o0o--

5 PANEL MEMBER BLANC: I'm sorry, if I caught that
6 correctly. So what you're saying is that the methyl
7 mercury database, which is more robust, suggests that
8 developing -- that the developing human or developing
9 mammals are three times as sensitive as adult
10 experimentally exposed? Is that what you're saying?

11 OEHHA STAFF TOXICOLOGIST WINDER: I think that's
12 a fair assertion, yes. And that based on the similarity
13 between the two, using that methyl mercury, the database,
14 you'd say that we expect in this circumstance to have a
15 similar kind of --

16 PANEL MEMBER BLANC: Is that what the data from
17 Minamata suggests in terms of human methyl mercury? I
18 would have characterized the gap as being more than
19 threefold.

20 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, that's a
21 point. I would guess somewhere in the neighborhood of 3
22 to 10.

23 PANEL MEMBER BLANC: Well, 3 to 10 is not 3.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Except for when we use a 10 on the chronic. We

1 use a 10 for intraspecies toxicodynamics on the chronic.

2 PANEL MEMBER BLANC: I thought you used human
3 data for the chronic, not animal data.

4 OEHHA STAFF TOXICOLOGIST WINDER: That's true.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Yes, adult human data. So we did -- I'm just
7 responding to your thinking about what the difference in
8 toxicity was if there was congenital Minamata versus what
9 happened to the adults in that setting.

10 PANEL MEMBER BLANC: Yeah.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Yeah. So, you know, the factor we used here
13 was --

14 PANEL MEMBER BLANC: Not for the acute. I'm
15 talking about neurologic effects generically. It's a
16 neurologic endpoint if you're using for everything, right?

17 OEHHA STAFF TOXICOLOGIST WINDER: That's right.

18 PANEL MEMBER BLANC: You've got a neurologic
19 effect for the chronic. You're using chloralkali worker
20 data from Finland.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Right.

23 PANEL MEMBER BLANC: And you're using the square
24 root of 3 and square root of 3 for the pharmacodynamic and
25 pharmacokinetic adjustments.

1 OEHHA STAFF TOXICOLOGIST WINDER: Now, you're
2 talking about for the acute?

3 PANEL MEMBER BLANC: No, the chronic.

4 OEHHA STAFF TOXICOLOGIST WINDER: For the
5 chronic. Okay.

6 PANEL MEMBER BLANC: Craig, am I on target with
7 this?

8 PANEL MEMBER BYUS: I think so.

9 OEHHA STAFF TOXICOLOGIST WINDER: We've got the
10 square root of 10 for the toxicokinetic -- a full 10 for
11 the toxicokinetic.

12 PANEL MEMBER BLANC: You are using for the
13 chronic?

14 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

15 PANEL MEMBER BLANC: Okay, good.

16 Okay. I missed that. Sorry.

17 So you're assuming that the 10 -- but then let me
18 ask the same question. Does the Minamata data, for
19 example, say that it's 10 or is it worth more than 10? Is
20 it a hundredfold? What do the data --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Yeah, I'm not sure we have a good quantitative
23 handle on the Minamata data. You'd have to have pretty
24 good exposure estimates for in utero, perinatal, and
25 adults.

1 comments suggesting that our RELs were lower than
2 so-called comparable values from ATSDR and U.S. EPA for MR
3 RELs, the reference concentrations in the AEGLs.

4 Well, now AEGLs are values that are derived for
5 typically once-in-a-life-time emergency and short-term
6 exposures. We're trying to develop RELs here to protect
7 health after potentially repeated or long-term exposures.

8 So these two numbers are really not comparable
9 enough designed to treat the same sort or exposure
10 scenarios.

11 And the MR RELs and the RfCs are also developed
12 without a particular consideration of children or other,
13 you know, specifically susceptible populations. And these
14 things have been developed and they don't -- the stories
15 won't reflect their most recent science receiving this.

16 --o0o--

17 OEHHA STAFF TOXICOLOGIST WINDER: It's also
18 mentioned that the acute REL is only two, threefold higher
19 than the U.S. EPA's ATSDR chronic values. And the
20 commentators expected that our short-term values would be
21 much higher than the chronic. Well, what's happening here
22 is they're trying to compare our values with what the U.S.
23 EPA has derived for their chronic And as we've mentioned
24 previously, it's not appropriate to try and compare this
25 to AEGLs or RfCs. However, we agree that you would expect

1 the acute exposures to be higher. And when you compare
2 our proposed acute REL, it is twentyfold higher than the
3 proposed chronic REL. So we don't see a conflict there.

4 --o0o--

5 OEHHA STAFF TOXICOLOGIST WINDER: It says the
6 cumulative certainty factor of 300 seems far too high for
7 an 8-hour REL since the critical study is in humans.

8 Well, the reason for this is that, as I
9 mentioned, there's the LOAEL to NOAEL uncertainty factor
10 of 10 because of the severity of the effect, the
11 intraspecies toxicokinetic factor of square root of 10.
12 This is default for inter-individual variability. We
13 didn't expect this to be particularly high in terms of
14 toxicokinetics between adults and -- populations.

15 The intraspecies toxicodynamic factor of 10, this
16 again because of the developmental susceptibility. So
17 when this is all put together, this comes to the three --
18 totals.

19 And that's the end of those.

20 CHAIRPERSON FROINES: Craig, do have any
21 comments?

22 PANEL MEMBER BYUS: I thought it was very well
23 written. I mean really did a nice job pulling all the
24 different data together in a nice easy to, you know, read
25 form. You laid out your arguments very nicely. It was

1 nice. I had a few minor little comments here and there.

2 I'll just -- one of them is, what is the parallelogram

3 approach to doing --

4 OEHHA STAFF TOXICOLOGIST WINDER: Oh, that --

5 PANEL MEMBER BYUS: On page 14. Lowendowski, et

6 al., used a parallelogram approach to analyze in vivo/in

7 vitro data and responses of rats, mice, and humans, methyl

8 mercury. I have no idea what that is.

9 OEHHA STAFF TOXICOLOGIST WINDER: It's a -- let
10 me see if I can dig out the paper here.

11 It's a method of examining the LOAELs and NOAELs
12 for, in effect -- again, this was done -- this is an in
13 vitro study of human cell, rat cells, mice cells -- to
14 look at the effect where they're seeing the NOAEL and
15 LOAEL for each of those species. And they're finding that
16 the -- for the humans this effect was that it seemed a
17 tenfold lower approximately than in the rats and mice.

18 PANEL MEMBER BYUS: Where does the parallelogram
19 come in?

20 OEHHA STAFF TOXICOLOGIST WINDER: It's a way of
21 presenting the data.

22 PANEL MEMBER BYUS: Okay. I have a few other
23 minor little things like that.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: We should explain that better.

1 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So
2 perhaps some explanation of that.

3 PANEL MEMBER GLANTZ: That's as opposed to the
4 trapezoid.

5 (Laughter.)

6 PANEL MEMBER BYUS: Yeah, that's what I'm
7 thinking. There's a square or the triangle approach. I
8 couldn't understand why it was a parallelogram.

9 PANEL MEMBER GLANTZ: At least it wasn't
10 circular.

11 (Laughter.)

12 PANEL MEMBER BYUS: Yeah, that's good.

13 PANEL MEMBER BLANC: So the problem with using
14 NHANES data, the mercury values or the equivalent national
15 data is because you can't tease out what is methyl mercury
16 versus what is elemental mercury, is that the problem with
17 that?

18 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I don't
19 think NHANES's going to discriminate the speciation there.

20 And there's only blood; there isn't blood and
21 urine available?

22 OEHHA STAFF TOXICOLOGIST WINDER: On NHANES'
23 mercury? I'm not sure about that.

24 There's definitely blood, but I don't know if
25 there's any mercury --

1 PANEL MEMBER BLANC: Because isn't one of them
2 reflective of inorganic mercury more than --

3 OEHHA STAFF TOXICOLOGIST WINDER: That I'm not
4 sure.

5 OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
6 CHIEF SALMON: I think that all depends on what the time
7 scale is that you're looking at. I think the long term it
8 will come out in the urine. But, you know, there's a
9 definite time scale issue as to when you're looking at
10 urine versus blood levels.

11 But in the very long term obviously everything
12 gets -- you know, gets oxidized and winds up in the urine.
13 But that's -- you know, that's in the long term, anything
14 up to 30 years sort of thing.

15 CHAIRPERSON FROINES: Is somebody driving?

16 PANEL MEMBER BYUS: Will somebody drive us?

17 CHAIRPERSON FROINES: We have to stop.

18 PANEL MEMBER BLANC: Okay. Bye.

19 PANEL MEMBER GLANTZ: I thought you had to go.

20 PANEL MEMBER BLANC: I move that we adjourn.

21 CHAIRPERSON FROINES: Thank you.

22 Second?

23 PANEL MEMBER GLANTZ: Second.

24 CHAIRPERSON FROINES: All in favor?

25 (Ayes.)

1 CHAIRPERSON FROINES: Thank you.
2 (Thereupon the California Air Resources Board,
3 Scientific Review Panel adjourned at 2:14 p.m.)

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2 I, JAMES F. PETERS, a Certified Shorthand
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13 way interested in the outcome of said meeting.

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