

MEETING
STATE OF CALIFORNIA
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL

CLAREMONT RESORT
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LINDA KAY RIGEL, CSR
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison

Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT

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. Bruce Winder, Staff Toxicologist

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1 P R O C E E D I N G S

2 --o0o--

3 CHAIRPERSON FROINES: We will open the meeting
4 of the Scientific Review Panel for June 18, 2008.

5 And the first items on the agenda are the
6 continuation of the panel's review of the draft report,
7 Air Toxic Hot Spots Risk Assessment Guidelines, and
8 we're talking about the technical support document.

9 So Melanie, I think you're up.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Hi, good morning. Melanie Marty.

12 CHAIRPERSON FROINES: Melanie Marty.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Okay. There is a -- what we want to do today
15 is go over the revisions that were made to the main
16 body of the report, the technical support document,
17 pursuant to the last meeting and the comments that the
18 Panel made as well some comments from the Lead and a
19 few of the other Panel members. So we'll go over that.

20 Then we'll move on to the last three remaining
21 chemicals that we haven't given a presentation to you
22 yet but you have seen -- you've read the report. That
23 would be acrolein, formaldehyde, and manganese.

24 But before we begin, I did want to mention one
25 legal technical issue that happened when we noticed the

1 meeting. The meeting had the correct title of the
2 document, but it had April 2008 as the date rather than
3 June 2008.

4 What that does is it may have caused some
5 confusion on the part of the public looking on our
6 website to look at the latest version.

7 The public is allowed to provide comment to
8 the Panel, so the attorney for OEHHA and ARB thought
9 that it would be better for you all not to vote on
10 anything that was very substantive.

11 And the substantive issue is manganese. As
12 you'll recall, we had a public review draft of
13 manganese. We got a lot of comments, and we made
14 changes to the way we derive the REL. That was not in
15 the April draft. It was in the June draft.

16 So while we will make the presentation, and
17 you guys can ask us questions, you won't be able to
18 vote necessarily on that REL summary today. So that's
19 what our lawyers have told us.

20 CHAIRPERSON FROINES: So but we're going to
21 have a spirited discussion of the manganese issue.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: The spirited part is up to you.

24 PANEL MEMBER GLANTZ: But we can vote on the
25 rest of it, right?

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yes. None of the numbers -- none of the other
3 numbers changed between the two drafts. And as you'll
4 see in a moment, the revisions made were relatively
5 minor and didn't impact the bottom line.

6 CHAIRPERSON FROINES: Can I ask you a question
7 about manganese before we start?

8 There is all sorts of new manganese
9 nanomaterials, and they're being used as watt net --
10 manganese oxide wires. And clearly, manganese oxide
11 wires can act like fibers if they have the right length
12 and width.

13 And the question is: Are you folks in your --
14 in OEHHA, do you have a group that's looking at
15 nanomaterials for potential toxicity?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: We have a person who is acting as the point
18 person for OEHHA to look at nanomaterials and gather
19 available data that are out there, and it happens to be
20 Karen Riveles who is sitting here today.

21 So we're aware of the issue. We would like to
22 keep tabs on it and see what we can end up saying about
23 it.

24 It is interesting that you brought up the
25 fiber issue because there is a recent paper that looked

1 at carbon nanotube fibers in a rodent study and was
2 able to produce some of the early lesions that asbestos
3 produces in a rodent model.

4 CHAIRPERSON FROINES: Mesothelioma, in fact,
5 has been produced.

6 DR. MARTY: So that's -- yeah.

7 CHAIRPERSON FROINES: Well, see that's -- and
8 we were doing nano -- carbon nanotubes in my
9 laboratory. And we were not measuring the exposure to
10 the PhD student, and she was not fitted with a
11 classified respirator.

12 And if you say that we were bad, just think of
13 what it's like around the country. So this is a very,
14 very serious issue.

15 And you can't measure them. They float all
16 over the place. So it's quite serious.

17 Anyway, not to distract. It was the word
18 "manganese" that triggered me. So go ahead.

19 PANEL MEMBER GLANTZ: This is a symptom of
20 PTSD.

21 (Laughter)

22 CHAIRPERSON FROINES: What, the lights?

23 PANEL MEMBER GLANTZ: Random -- no, random
24 associations. That's a joke.

25 (Laughter)

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: First, we'll begin with an overview of the
3 revisions to the main body of the report.

4 We responded to the discussion by the Panel
5 from the May 16th meeting and also specific comments
6 sent to us by Panel members Friedman, Landolph and
7 Plopper and the Lead, Dr. Glantz.

8 There is a handout which delineates where the
9 changes were made, and also they were visible in
10 revisions made in the document we sent to the Panel.

11 We added a brief discussion of elderly --

12 CHAIRPERSON FROINES: Is this that -- is this?

13 DR. MARTY: Yes, that's the handout. And
14 also, you should have a copy of the slides.

15 We added a brief discussion of elderly as a
16 sensitive subpopulation. That came up at the last
17 meeting, since it's clear that that is the case from a
18 kinetic standpoint and other standpoints as well.

19 We clarified the summary of proposed changes.
20 So I had staff go back and look and make sure that
21 everything that was embedded in the document that was a
22 proposed change was actually in the summary.

23 We revised the weight of evidence discussion
24 per Panel comments from the last meeting and suggested
25 edits from Drs. Glantz and Blanc. These included

1 expanding the selected methodological issues that one
2 considers in looking at epidemiology data as well as
3 toxicology data.

4 We amended the discussion on strength of
5 association. Added a sentence on -- in the discussion
6 of biologic plausibility and coherence, and also
7 reworded a tiny bit on the issue of specificity.

8 Those changes were all in revisions made in
9 the document.

10 We modified Table 4.4.1 to improve the clarity
11 since there was some confusion at the Panel meeting
12 last time on that.

13 We added a brief discussion in a couple places
14 of uncertainty in PBPK modeling to hammer home the
15 point that PBPK modeling does not cure risk assessment
16 of all uncertainty.

17 (Laughter)

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
19 MARTY: We added to the summary of the modeling
20 approach that OEHHA had taken in the appendix regarding
21 the adequacy of earlier uncertainty factors for
22 intraspecies variability just to clarify the points,
23 really.

24 And we added a sentence summarizing the
25 implications of the information in Table 4.4.2.

1 We added examples of when application of the
2 database deficiency uncertainty factor might be
3 appropriate. That was in response to a lengthy
4 discussion at the last meeting.

5 So that pretty much was it for the changes
6 made to the actual technical support document. I don't
7 know if you wanted to have any discussion of those
8 changes now before we move on to the few changes made
9 in a couple of the REL summaries.

10 CHAIRPERSON FROINES: Well, just to ask Stan,
11 as the person with the overall picture of the document,
12 if he had looked at the changes and was comfortable
13 with them.

14 PANEL MEMBER GLANTZ: Yes.

15 I mean just to remind people, these are all
16 very minor changes, kind of nuanced issues that came
17 out of the last Panel discussion, and I think they've
18 all been -- I think they were -- they weren't big
19 changes. I think they made the document better.

20 Especially the issue about strength of
21 association and causality and the comments that Paul
22 made. But they've all been integrated. So I think the
23 thing's finished. I'm happy with it.

24 One other thing. We'll get on to the findings
25 that you'd asked us to draft, and I apologize; I

1 thought these had been sent out to the Panel, but they
2 hadn't.

3 But anyway, the original findings that Melanie
4 and her staff produced included the RELs for the
5 individual chemicals. And I suggested taking those out
6 so that the findings simply deal with the methodology
7 on the grounds that there can be a separate set of
8 findings adopted for each REL as they change, to kind
9 of disconnect them from the methods document which
10 should be more, you know, that's going to apply as more
11 chemicals are added.

12 CHAIRPERSON FROINES: Melanie, do you want a
13 vote on each chemical, or do you want a vote on the
14 collective chemicals? Or -- and within that context,
15 do you want findings on the chemicals?

16 Because in my view, it would be satisfactory
17 to vote on the chemicals without necessarily writing a
18 list of -- a document on Panel findings. Because they
19 speak for themselves for the most part.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
21 MARTY: In previous versions of the Reference Exposure
22 Levels, we did not have findings on every single
23 chemical.

24 CHAIRPERSON FROINES: Yeah. Like MTBE, we
25 never wrote a word, and that was a big one.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Right. So findings on the main body of the
3 report are fine, although I don't believe we did it the
4 first draft in 1999. But that's fine.

5 CHAIRPERSON FROINES: It is a strategic
6 question.

7 PANEL MEMBER GLANTZ: Well, no --

8 CHAIRPERSON FROINES: That is -- let me just
9 finish. It should be a strategic question. That is:
10 If we write findings for you on individual chemicals,
11 does that benefit you in some way? Or is it adequate
12 to simply have our vote?

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: Well, the way it might benefit us, if you'll
15 recall in the REL summaries, we do have whether we
16 believe the chemical should be listed as a TAC that
17 differentially impacts children. And that would be
18 beneficial to have a finding related to that.

19 And you folks did do findings when we
20 established the first list of five in 2001 related to
21 the TAC prioritization document which you all reviewed.

22 In those findings, you talked about how we'd
23 prioritized and then the evidence for each of those
24 five chemicals with respect to differential impacts on
25 kids.

1 So that would be useful.

2 CHAIRPERSON FROINES: Gary looks troubled.

3 PANEL MEMBER FRIEDMAN: About something else.

4 CHAIRPERSON FROINES: Okay.

5 So at the end of this, why don't you and me
6 and whoever else we -- Stan probably -- and if there is
7 a particularly controversial chemical, we could get a
8 small group and talk about findings, and then we could
9 write something up.

10 But I think we're talking about one or two
11 sentences, really.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: Right.

14 CHAIRPERSON FROINES: We're not talking about
15 something that's --

16 PANEL MEMBER GLANTZ: Right. I mean actually
17 the first draft of the findings that Melanie put
18 together that we then worked on to get the findings
19 that we're going to discuss, she actually had for each
20 of the -- except for manganese -- you know, a couple of
21 sentences on each one.

22 I agree; I think that's all that's necessary.

23 But it just seemed to me that it would be
24 better to separate the specific chemicals from the
25 overall methodology. Because over time, you're going

1 to be adding more chemicals.

2 CHAIRPERSON FROINES: Go ahead.

3 PANEL MEMBER GLANTZ: Did you want -- can we
4 like -- did you have anything else to say about the
5 main body of the document?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: No.

8 PANEL MEMBER GLANTZ: Well, could -- why don't
9 we talk about that and vote on that first?

10 CHAIRPERSON FROINES: The first thing to say
11 is, some people have had an opportunity to read the
12 findings that were prepared, and others have not. And
13 I don't even see mine here. But here are the findings.

14 Can we take five minutes and have -- because I
15 think Gary hasn't had a chance to read them, and I
16 suspect Paul hasn't. So let's take five minutes, and
17 you can read what --

18 PANEL MEMBER FRIEDMAN: May I just bring up a
19 minor point?

20 CHAIRPERSON FROINES: Please.

21 PANEL MEMBER FRIEDMAN: I really appreciated
22 all the responses to all my comments, but there's one
23 little residual nitpick that I have, and that relates
24 to Roman numeral page XII. This is of the executive
25 summary.

1 When you talk about trigeminal nerve mediated
2 irritation of the eyes, nose, and upper airway. It
3 seems to me that this sounds like something is
4 happening to the nerve and that therefore, as a
5 secondary effect, that affects the eyes, nose, and
6 upper airway, and it's really the reverse.

7 These things get irritated, and it's the
8 trigeminal nerve that transmits those to the brain.

9 So when you say trigeminal mediated, it just
10 doesn't make sense to me.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: We could change that wording. It's kind of the
13 language that people do use, but I see your point.

14 PANEL MEMBER FRIEDMAN: That's my only --

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: The trigeminal nerve is --

17 PANEL MEMBER HAMMOND: Transmitted.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: -- speaking to the brain.

20 PANEL MEMBER FRIEDMAN: Right.

21 PANEL MEMBER HAMMOND: It's being transmitted.

22 PANEL MEMBER FRIEDMAN: From the nose, et
23 cetera, so.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Transmitted. How about trigeminal nerve

1 transmitted?

2 PANEL MEMBER FRIEDMAN: Transmitted. That
3 would be excellent. Thank you.

4 CHAIRPERSON FROINES: So Gary, Paul, whoever
5 else hasn't read the findings: Could we take a minute
6 now and read them? And then I think we can finish them
7 because they're relatively brief.

8 (Recess)

9 CHAIRPERSON FROINES: We're back on the
10 record.

11 So we should go around the room and get
12 comments for Melanie and Andy on the findings, and I
13 mean for ourselves, rather.

14 Gary, did you have changes?

15 PANEL MEMBER FRIEDMAN: Well, the only thing
16 is I'd like to substitute Melanie's good word of
17 "transmitted" for mediated at the bottom of page 3 and
18 at the top of page 4.

19 CHAIRPERSON FROINES: Will you make sure that
20 you give that to -- all these changes to Peter, then he
21 can send them to me so I can make them?

22 PANEL MEMBER FRIEDMAN: Should I write it on
23 this?

24 CHAIRPERSON FROINES: Yeah.

25 PANEL MEMBER FRIEDMAN: That's all I have.

1 CHAIRPERSON FROINES: Joe?

2 PANEL MEMBER LANDOLPH: I don't have anything
3 substantive. Just these UFHKs, that nomenclature is so
4 turgid, I have to go back and retranslate it. But I
5 guess you can't do anything about that, so it's okay.

6 CHAIRPERSON FROINES: Are you going to give
7 comments to Peter?

8 PANEL MEMBER LANDOLPH: To?

9 CHAIRPERSON FROINES: Peter, so we can put
10 together a coherent complete document?

11 PANEL MEMBER LANDOLPH: Yeah. I could do
12 that, sure.

13 CHAIRPERSON FROINES: Stan?

14 PANEL MEMBER GLANTZ: I'm happy. I agree with
15 the changes that Gary suggested. And I'm all for
16 deturgidizing.

17 PANEL MEMBER BLANC: Deturgidizing. That's a
18 big help.

19 CHAIRPERSON FROINES: Kathy?

20 PANEL MEMBER HAMMOND: Fine.

21 CHAIRPERSON FROINES: Charlie?

22 PANEL MEMBER PLOPPER: Yeah, on number one
23 there, it talks about --

24 (Interruption by the reporter)

25 PANEL MEMBER PLOPPER: Number one, just a

1 comment about undeveloped metabolic and elimination
2 capabilities resulting in longer clearance half-times.

3 That's not always the case. So I wonder if
4 there's some way it could just be worded as an
5 imbalance, developmentally related imbalances?

6 Because sometimes the problem is the clearance
7 is the same; it's just that the metabolism is in a
8 different form, so it produces more reactive chemical.

9 And --

10 CHAIRPERSON FROINES: Where are you?

11 PANEL MEMBER PLOPPER: Page 2, number 1. I'm
12 just concerned that it would -- it limits. That's one
13 of the cases. And I would hate to get this tied into
14 that the clearance is the same, then it must be okay
15 for kids, and that's not the case at all.

16 PANEL MEMBER GLANTZ: What wording change did
17 you want?

18 PANEL MEMBER PLOPPER: Something that just
19 implies that there's an imbalance that increases
20 toxicity, and it's not necessarily imbalance of
21 metabolism and elimination. Rather than undeveloped
22 metabolic elimination capabilities resulting in longer
23 clearance half-times.

24 So what that -- to my interpretation, that
25 would mean that if the clearance is the same in

1 children as it is in adults, then there is no toxic
2 difference, and that's not going to be the case.

3 CHAIRPERSON FROINES: How would you change it?

4 PANEL MEMBER PLOPPER: Just to say there is a
5 metabolic -- developmentally related metabolic and
6 elimination imbalances.

7 That gives -- that makes leeway for
8 everything. Could be -- in some cases, chemicals are
9 actually more activated in children than they are in
10 adults, and they're eliminated the same. So there
11 still could be toxicity, but the elimination appearance
12 would be similar.

13 CHAIRPERSON FROINES: Do you need a second
14 sentence to give context?

15 PANEL MEMBER PLOPPER: Shall I work on
16 something like that?

17 CHAIRPERSON FROINES: If you would, because if
18 you just add in there are metabolically and
19 developmental imbalances, that sort of ends without
20 being clear.

21 PANEL MEMBER PLOPPER: Okay.

22 PANEL MEMBER GLANTZ: Maybe the thing to do,
23 because I actually -- that, the specific, you know,
24 underdeveloped metabolic and elimination capabilities
25 is what the report mostly talks about. So maybe we

1 should add another phrase. Keep that and add --

2 PANEL MEMBER BLANC: Comma, although other
3 imbalances could also occur.

4 PANEL MEMBER GLANTZ: Right.

5 PANEL MEMBER PLOPPER: Yes. Resulting in
6 heightened toxicity.

7 PANEL MEMBER GLANTZ: Because of -- why don't
8 we say underdeveloped metabolic and elimination
9 capabilities or other metabolic imbalances?

10 PANEL MEMBER PLOPPER: That sounds good.

11 CHAIRPERSON FROINES: Wait a second. I'm
12 trying to take notes, and I have: There are
13 metabolically developmental imbalances, although other
14 imbalances may occur.

15 PANEL MEMBER GLANTZ: No, no. Just leave it
16 as it is. Because of underdeveloped metabolic or
17 elimination capabilities. Leave that as it's written.
18 Then after that --

19 CHAIRPERSON FROINES: Wait. I have to find
20 it.

21 PANEL MEMBER BLANC: It's in the middle of the
22 paragraph.

23 PANEL MEMBER GLANTZ: Line 1, 2, 3, 4, 5, 6,
24 7, 8 -- it's the eighth line of Item 1.

25 CHAIRPERSON FROINES: Okay. Because of

1 underdeveloped --

2 PANEL MEMBER GLANTZ: Metabolic and
3 elimination capabilities. Leave that as it is.

4 And then just add after that: Or other
5 metabolic imbalances.

6 PANEL MEMBER BYUS: I actually don't like that
7 word, "imbalance."

8 PANEL MEMBER GLANTZ: Okay. Well --

9 PANEL MEMBER BYUS: And the reason is, I mean
10 you're all comparing these to adults. So if you say
11 compared to adults, it doesn't necessarily mean they're
12 balanced in any way.

13 PANEL MEMBER GLANTZ: That's true.

14 PANEL MEMBER BLANC: Other metabolic --

15 PANEL MEMBER BYUS: Just alterations from the
16 adult, which is the default assumption.

17 CHAIRPERSON FROINES: There are other
18 metabolic differences?

19 PANEL MEMBER BYUS: That's -- that is good.

20 PANEL MEMBER GLANTZ: Okay. Well, here,
21 Melanie has a suggestion. Is that okay? Am I allowed
22 to say that? Okay. That was a no.

23 Well -- no, this is a way to -- and here's the
24 wording she suggested which I thought was -- dealt with
25 this. To change it to say: Differentially affected by

1 some compounds because of developmentally related
2 differences in meta- -- instead of underdeveloped, and
3 elimination -- metabolic and elimination capabilities
4 resulting in longer clearance half-times.

5 I think that does what you want.

6 PANEL MEMBER PLOPPER: That -- that's great.

7 PANEL MEMBER GLANTZ: Okay. So the specific
8 change is to change the word "underdeveloped," delete
9 that word, and change it to developmentally related
10 differences in.

11 Okay. Are you happy with that?

12 PANEL MEMBER PLOPPER: All right.

13 PANEL MEMBER GLANTZ: Actually, that was my
14 idea, right? No.

15 CHAIRPERSON FROINES: These all come from the
16 Panel.

17 PANEL MEMBER GLANTZ: Yeah. But we are
18 allowed to accept good suggestions. That's a
19 clarification. So I think that gets at what you're
20 talking about.

21 PANEL MEMBER PLOPPER: That's fine.

22 PANEL MEMBER GLANTZ: So just again, to be
23 really clear: We're deleting the word "underdeveloped"
24 and changing it to say: Developmentally related
25 differences in.

1 CHAIRPERSON FROINES: Okay.

2 PANEL MEMBER PLOPPER: That's good.

3 PANEL MEMBER GLANTZ: That's better.

4 PANEL MEMBER PLOPPER: Good.

5 PANEL MEMBER BYUS: I have a question -- I

6 have --

7 CHAIRPERSON FROINES: Wait. Is Charlie

8 finished?

9 PANEL MEMBER PLOPPER: That was my main.

10 PANEL MEMBER BYUS: On the sentence above this

11 about the pharmacodynamic differences.

12 I might say in parentheses you have to account

13 for differences in interactions at the receptor by age.

14 I might say to account for the quantitative and

15 qualitative differences in interaction at the

16 receptors.

17 And I would make it parentheses S, because

18 there is more than one necessarily. I mean you don't

19 know what -- it isn't a classic receptor. Sometimes it

20 is for these things, and sometimes it isn't. It's just

21 a macromolecule that binds to it.

22 So I don't know what -- you might even put the

23 term receptor in parentheses -- I don't -- if you

24 wanted to. But I would certainly put a parentheses S

25 because there is oftentimes more than one.

1 CHAIRPERSON FROINES: Walk us through it.

2 PANEL MEMBER BYUS: Okay. I say -- I would
3 say: To account for quantitative and qualitative
4 differences in interactions at the receptors
5 parentheses S. So it could be single or plural.

6 CHAIRPERSON FROINES: For differences at the
7 receptor --

8 PANEL MEMBER BLANC: Qualitative and
9 quantitative differences in interactions at the
10 receptor(s).

11 PANEL MEMBER BYUS: That's it.

12 CHAIRPERSON FROINES: Write it up and give it
13 to us, so I don't have to try and figure out what was
14 said. Paul?

15 PANEL MEMBER BLANC: I'm completely confused
16 by the bolded italic'd statement between point 3 and
17 point 4 with a hanging parentheses. It seems like that
18 was something that was a parenthetical comment that was
19 then -- I don't know what that is supposed to be. It's
20 just hanging in space.

21 PANEL MEMBER GLANTZ: Well, what that was
22 trying to say, that's sort of a heading for what's
23 below it.

24 PANEL MEMBER BLANC: Well, I think that's
25 inappropriate.

1 PANEL MEMBER GLANTZ: Okay. We can delete it
2 if you want.

3 PANEL MEMBER BLANC: I would prefer that. I
4 think it's quite confusing.

5 PANEL MEMBER GLANTZ: Okay.

6 PANEL MEMBER BLANC: Also a substantive point,
7 I think that the issue of the pharmacokinetic
8 uncertainty factor, which is the second part of point
9 5, essentially the last sentence of point 5, where it
10 states the Panel also agrees that a pharmacokinetic
11 uncertainty factor could still be applied to account
12 for residual uncertainty when using a partial
13 dissymmetry model for either interspecies or
14 intraspecies extrapolation. Does everybody see that
15 sentence?

16 I think we might consider simply making that a
17 separate point. It would be the new point 6, and then
18 point 6 would be point 7, et cetera.

19 CHAIRPERSON FROINES: And what's point 6?

20 That --

21 PANEL MEMBER GLANTZ: No, he would just take
22 the last sentence of 5 and make it number 6.

23 PANEL MEMBER HAMMOND: Stand alone.

24 CHAIRPERSON FROINES: Is that correct?

25 PANEL MEMBER BLANC: Yeah, that was my

1 suggestion. If you believe it's important enough.

2 PANEL MEMBER GLANTZ: It doesn't matter to me.
3 I'm happy to do it.

4 PANEL MEMBER BLANC: And also --

5 PANEL MEMBER GLANTZ: So do people want to do
6 that? Any objection?

7 CHAIRPERSON FROINES: I think actually it's
8 good to do it because the sentence before it, you have
9 a little apples and oranges there.

10 You're making a statement about importance of
11 sensitivity analysis and PBPK modeling, and then you go
12 into really what is a separate subject.

13 PANEL MEMBER GLANTZ: Right. Okay.

14 PANEL MEMBER BLANC: Then is it clear to
15 everyone what a partial dissymmetry model is? Because
16 I wasn't -- that wasn't transparent to me.

17 Does that mean that, for example, there were
18 missing doses in the dose ranging? Or enough missing
19 doses in the dose range that more uncertainty was
20 called for? Or maybe --

21 CHAIRPERSON FROINES: Andy?

22 PANEL MEMBER BLANC: I think it's
23 jargonesque --

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
25 SALMON: The clearest specific example where we would

1 want to do this is in cases we are using what we
2 describe as the US EPA's effective concentration of the
3 HEC calculation which is a deposition model which has
4 data about the test species, but it isn't chemical
5 specific, if you have some particle size or something
6 like that.

7 It doesn't have the data about the specific
8 chemical that you're dealing with, so it doesn't deal
9 with metabolism, things like that. So it addresses
10 some of the issues but not all of them.

11 In another cases where we have -- there's an
12 example of this in the RELs. We don't have a PBPK
13 model for the actual chemical of interest, but we do
14 have a PBPK model for a chemical which we consider to
15 be a close analog, so we think we can use the
16 conclusions of the model, but there's some residual
17 uncertainty.

18 So it's -- that was the case in which this
19 proposal was framed in the guidelines.

20 PANEL MEMBER BLANC: Well, then I would
21 suggest simply deleting the words "when using a partial
22 dissymmetry model" and say the Panel also agrees that a
23 pharmacokinetic uncertainty factor could still be
24 applied to account for residual uncertainty for either
25 interspecies or intraspecies extrapolation.

1 PANEL MEMBER GLANTZ: All right. That's good,
2 yeah.

3 CHAIRPERSON FROINES: Help me here, Paul.
4 For --

5 PANEL MEMBER BLANC: It's the last line --

6 CHAIRPERSON FROINES: I understand all that.
7 You're taking out when using a partial dissymmetry
8 model from either --

9 PANEL MEMBER BLANC: No, no. When using a
10 partial dissymmetry model.

11 CHAIRPERSON FROINES: Okay. Good.

12 Andy, all due respect, you made the problem
13 escalate in your explanation.

14 (Laughter)

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
16 SALMON: I apologize. I was attempting to simplify. I
17 guess that says something adverse about the way my
18 brain works.

19 PANEL MEMBER BLANC: I would -- on point 6
20 which is now point 7, I would actually like to see
21 after the first usage of the term "Haber's law" to have
22 a parenthetic for dose times time equation or effects
23 or something.

24 Because again, it presumes a certain . . .

25 And also, similarly, a bit later in that point on the

1 very last page as we currently have it, OEHHA
2 recommends increasing the default exponent in the
3 modified Haber's law from 2 to 3.

4 I think it should be the default exponent for
5 concentration, just to make that clear, because that's
6 what you're talking about, right?

7 And John, I have a few other just grammatical
8 things, and I'll just pass that on. I think --

9 CHAIRPERSON FROINES: Pass it on to Jim.

10 PANEL MEMBER BLANC: -- Stan and I clearly
11 differ on our views on commas and where they should be
12 used, for example.

13 CHAIRPERSON FROINES: So --

14 PANEL MEMBER BLANC: I'll be happy to get you
15 a copy of Strunk & White at some point if you'd like to
16 revisit it.

17 PANEL MEMBER GLANTZ: I have one.

18 PANEL MEMBER BLANC: Do you.

19 (Laughter)

20 CHAIRPERSON FROINES: So everybody will give
21 their changes to Jim, and Jim will give all the changes
22 to me, and I'll make the changes. And I think what we
23 should do is to vote pending --

24 PANEL MEMBER BLANC: I only have one other
25 question for Stan, basically. And that is: Do you

1 feel that there's any need for a numeric point related
2 to the summary of causality, et cetera, in the document
3 or not?

4 We've spent a lot of time on it. Do you feel
5 that there would be any help to have that be one of the
6 bullets that we have, you know, reviewed and find
7 consistent? Or is it not necessary?

8 PANEL MEMBER GLANTZ: Well, actually, that's a
9 good idea, I think. What do other people think?

10 I mean what I could do while -- because I
11 would like to try to wrap this up today. What I could
12 do is while you go on to the other specific chemicals,
13 I could sit down and try to draft a brief statement
14 about the causality thing.

15 Because that's a good point. I think that is
16 important. Do other people agree? Okay, well, I can
17 just do that.

18 PANEL MEMBER BLANC: Where would you put that
19 in the report?

20 PANEL MEMBER GLANTZ: I would put it, well --

21 PANEL MEMBER BLANC: Would it be number 1?
22 The new number 1?

23 CHAIRPERSON FROINES: That would be a good
24 place for it.

25 PANEL MEMBER GLANTZ: Okay. All right. Well,

1 I will go do that.

2 PANEL MEMBER BLANC: I don't think it has to
3 be more than a couple sentences.

4 PANEL MEMBER GLANTZ: I agree, I agree. Let
5 me just find that and --

6 PANEL MEMBER BLANC: Oh, one other -- just one
7 other thing that's actually not completely grammatical.

8 Wait one second. I'm sorry to delay you.
9 Yeah, it's in the very first paragraph. There's a
10 parenthetic comment: The actual approved RELs for
11 these chemicals are addressed in a separate set of
12 findings.

13 I would remove the word "approved" for the
14 purposes of this, and this will be preceding any
15 approval of those so I don't want it to be presumed as
16 a foregone conclusion. Do you see what I'm talking
17 about?

18 PANEL MEMBER GLANTZ: Mm-hmm.

19 CHAIRPERSON FROINES: Are you going to go?

20 PANEL MEMBER GLANTZ: No, I'll stay here. Am
21 I going to what?

22 CHAIRPERSON FROINES: Are you going to go
23 write your section?

24 PANEL MEMBER GLANTZ: Yeah, I'll do that.
25 I'll just sit here and do it.

1 PANEL MEMBER BLANC: I think I have a question
2 for Melanie.

3 Do you find that having gone through all of
4 this with the generic blueprint for the RELs that as
5 you responded to individual -- comments on individual
6 chemicals that you received from the public that your
7 generic guidelines allowed you the flexibility to
8 address the points overall as they were coming in?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: Yes. And in fact, some of the public comments
11 actually made a difference in the generic guidelines
12 from the public review draft way back in November to
13 the next version.

14 PANEL MEMBER BLANC: So do you feel that going
15 forward if you took another five RELs that basically
16 you've covered the contingencies pretty well?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: I think so.

19 PANEL MEMBER BLANC: And is the feedback from
20 your staff that as they work on these things that they
21 feel that they have clear marching orders?

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: Yes.

24 PANEL MEMBER BLANC: Well then, I think it
25 serves its purposes in terms of consistency and

1 transparency.

2 CHAIRPERSON FROINES: I just had one -- a
3 little bit of an off-the-direct direction, point, and
4 it was one I made earlier.

5 That is, we need to think about educational
6 activities, and -- since we're all from universities --
7 and the question is: If I'm giving a course in risk
8 assessment, how do I take this document and within a
9 two-hour period make it -- make the information
10 available to students at the graduate level?

11 As of now, there is so much detail when you
12 are making decisions that it -- if I was a master's
13 degree student, I would find it very confusing.

14 It seems to me it would be worthwhile, if you
15 have the resources to do it, to think about how you
16 could give a 40-minute lecture on this topic. And that
17 means you need a 40-minute lecture on your cancer
18 methodology too so that a master's student or even an
19 undergraduate could come away saying oh, I know how the
20 State of California does its risk assessment for
21 carcinogens and noncarcinogens.

22 And right now, this document is not a document
23 one could be successful with because it would be
24 confusing when you get into the square root of 3 and
25 what have you.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: It's funny that you should say that because
3 next fall quarter we are teaching a risk assessment
4 class at UC Davis, and it will force us to do just that
5 for an entire quarter's worth of class.

6 PANEL MEMBER HAMMOND: How many lectures are
7 you doing?

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Two hour-and-a-half times ten weeks.

10 PANEL MEMBER HAMMOND: Oh, you're doing the
11 whole course?

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: OEHHA is doing the whole course.

14 CHAIRPERSON FROINES: So you'll make those --

15 PANEL MEMBER GLANTZ: Can we take it?

16 (Laughter)

17 CHAIRPERSON FROINES: You'll make those
18 PowerPoint slides available to all the rest of us
19 who --

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Sure.

22 CHAIRPERSON FROINES: -- teach a risk
23 assessment class?

24 I think it's important. I think that the
25 trouble is we live in this very enclosed world. And

1 obviously industry groups are interested in what is
2 happening because it affects them directly, but the --
3 it's very internalized. So the more explicit we can
4 make it, I think it's to everybody's advantage.

5 So shall we move on to the specific chemicals,
6 Melanie?

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Yes.

9 CHAIRPERSON FROINES: Gary?

10 PANEL MEMBER FRIEDMAN: I have a request. I
11 have to leave at 12:30 so I just want to make sure that
12 arsenic, which is what I was responsible for, gets
13 discussed before then. It doesn't necessarily have to
14 be first but --

15 CHAIRPERSON FROINES: Can we do arsenic first?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Absolutely.

18 CHAIRPERSON FROINES: I have a question that
19 relates to arsenic.

20 I'm assuming that this is an apples and
21 oranges issue, and that is that you have a PHG which
22 shows a very high degree of potency for arsenic in
23 drinking water, and yet today we're talking about
24 noncancer risk assessment, so that PHG is not germane
25 to this discussion; is that correct?

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Right, right. We also have a potency factor
3 for inhalation exposure to arsenic as well.

4 So in a risk assessment, if a chemical causes
5 more than just cancer, then those other endpoints are
6 also evaluated. And that's why we have RELs for things
7 that are also carcinogens. Okay.

8 These slides are towards the back of the
9 handout you had on changes to the TSD. So I'm going to
10 ask Joe to go through the revisions he made on the
11 arsenic REL.

12 OEHHA STAFF TOXICOLOGIST BROWN: Joe Brown,
13 OEHHA.

14 Based on the comments we had last meeting,
15 basically went back and took another look at the, both
16 bronchiectasis data and the lung function data.

17 Next slide, please.

18 And recall the bronchiectasis data is the
19 study Smith, et al., 2006. What I did, I went back and
20 I tried to do a benchmark dose analysis based on the
21 data here.

22 I had to construct a control based on the
23 reference value, and I assumed a value of .04 percent,
24 and I gave a quantal value of 1 over 2500. And I used
25 a 10-year exposure, and the treated level in arsenic of

1 40 micrograms of arsenic per liter.

2 You'll recall the response levels were 4 out
3 of 651 for 90 micrograms per liter times 10 years, and
4 9 out of 488 or -- at 870 micrograms arsenic per liter
5 for 13 years.

6 So fitting the data, we really didn't get very
7 good fits. But the best fitting model was log probit,
8 and it gave a P value of .026 and a 1 percent benchmark
9 dose level of 2.77 milligrams per liter times years, so
10 a cumulative dose metric.

11 Next slide, please.

12 PANEL MEMBER FRIEDMAN: Could I interrupt
13 there?

14 OEHHA STAFF TOXICOLOGIST BROWN: Sure.

15 PANEL MEMBER FRIEDMAN: When you say the P
16 value is .026, does that mean that's the degree that it
17 doesn't fit, that it significantly departs from that
18 model?

19 OEHHA STAFF TOXICOLOGIST BROWN: The criteria
20 for fit is .1 or greater, so.

21 PANEL MEMBER FRIEDMAN: So it really didn't
22 fit then.

23 OEHHA STAFF TOXICOLOGIST BROWN: It didn't
24 fit, but if you look at the graph, it doesn't look that
25 bad. It's one of these, if you want to -- it's one of

1 these statistical versus biological significance
2 questions.

3 PANEL MEMBER FRIEDMAN: So compared to other
4 models --

5 OEHHA STAFF TOXICOLOGIST BROWN: Yeah. It
6 wasn't that bad, actually.

7 Okay. So the model fit was not adequate by
8 our definition. It did not rate .1. But for the
9 purposes of comparison, I went ahead and calculated the
10 value anyway based on this.

11 If you look at the bottom, it's 2.77 with the
12 correction for micrograms to milligrams divided by 13
13 years, 10 cubic meters per day, 30 UF for child, and
14 50 percent absorption, and the final value is 1.42.

15 And this is similar to some other values in
16 Table 8.3.1, so I just added 1.4 to this table so --
17 and I noted there that it wasn't an adequate fit, and
18 it was for comparative purposes only.

19 And the second thing we did, this really isn't
20 really so much an analysis as a calculation based on
21 reported slopes in this paper by von Ehrenstein, et al.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: If I could just interrupt, this is in response
24 to Panel comments from the last meeting.

25 OEHHA STAFF TOXICOLOGIST BROWN: This is --

1 Dr. Blanc suggested that we ought to take a look at the
2 loss of lung function as a function of intake of
3 arsenic.

4 The reported slopes were minus 45 milliliters
5 per hundred micrograms of arsenic per liter increase in
6 drinking water and a loss of forced vital capacity of
7 minus 41.1 milliliters per 100 micrograms per liter
8 increase.

9 Next slide, please.

10 And if you assume low-dose linearities, these
11 values can be converted to inhalation values of .044
12 micrograms per meter cubed for FEV1 and .048 micrograms
13 per meter cubed for FVC.

14 And each of these values corresponds to a 1
15 milliliter loss in lung function, and the calculation
16 is shown there.

17 Both of these values were added to Table
18 8.3.2. This is an adult human table. So the
19 calculation is slightly different than for the child.

20 That's basically the main changes we made,
21 substantive numerical changes to the document. There
22 are some minor additions to the text in terms of
23 references that we used, but that's about it.

24 We did not change the REL. So these are
25 basically additional values trying to put things in

1 perspective, but did not change the bottom line values
2 that we had.

3 PANEL MEMBER BLANC: Did you find that the
4 exercise was reassuring in terms --

5 OEHHA STAFF TOXICOLOGIST BROWN: Yes.

6 PANEL MEMBER BLANC: -- of the value --

7 OEHHA STAFF TOXICOLOGIST BROWN: The values
8 were similar to some of the other values we had so it
9 was -- we didn't find any that were surprising.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: It also showed that the choice of the study for
12 the reference exposure level was the most sensitive
13 human study.

14 So that's it for the additions to the arsenic
15 REL summary document. Any further questions?

16 CHAIRPERSON FROINES: I have slides. Did I
17 miss . . .

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: We skipped to arsenic first, so they're --

20 OEHHA STAFF TOXICOLOGIST BROWN: They're at
21 the back.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: -- towards the back.

24 OEHHA STAFF TOXICOLOGIST BROWN: Toward the
25 back.

1 CHAIRPERSON FROINES: I got it. We're okay.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: We jumped over acetaldehyde. We're going to go
4 to that now.

5 PANEL MEMBER BLANC: Well, just for the
6 record, on 4.1.4 on the PBPK model section where
7 there's track changes text referring to the Leo, et al
8 study, that's in addition?

9 OEHHA STAFF TOXICOLOGIST BROWN: That's in
10 addition. I added that. I took a look at this paper
11 again. I thought since it relates to children,
12 although the study leaves something to be desired in
13 terms of how much it explains, it was an interesting
14 study, and I decided to beef up the discussion of
15 relevant PBPK as it applies to arsenic.

16 PANEL MEMBER BLANC: I commend you for doing
17 that.

18 OEHHA STAFF TOXICOLOGIST BROWN: Yeah. It's
19 an interesting approach, and some of the actual
20 pharmacokinetic models they used are very similar to
21 the models that we used in the past that were, you
22 know, developed by Dr. Yu at UCLA so.

23 PANEL MEMBER BLANC: I also think it's an
24 extremely thoroughly referenced REL, and I'm going to
25 come back to that topic later in our meeting today.

1 OEHHA STAFF TOXICOLOGIST BROWN: We could add
2 more references because they keep growing.

3 PANEL MEMBER BLANC: I understand, but this is
4 comparatively rather well-referenced.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: There is a huge amount of data on our side.

7 PANEL MEMBER BLANC: I understand.

8 CHAIRPERSON FROINES: There is a very good
9 review on arsenic in the Annual Review of Pharmacology
10 and Technology by Yoshito Kumagai which you might take
11 a look at.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: We have that.

14 OEHHA STAFF TOXICOLOGIST BROWN: Do we have
15 it? Okay.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Shall we continue with --

18 CHAIRPERSON FROINES: Please.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: -- changes made to --

21 PANEL MEMBER FRIEDMAN: Do we want to discuss
22 this at all?

23 CHAIRPERSON FROINES: Oh, sorry. My fault.

24 PANEL MEMBER FRIEDMAN: Well, I just want to
25 thank you. You made a lot of changes according my

1 recommendations. They were mostly minor
2 clarifications.

3 But there is one that I still am not sure
4 about, and that's on the top of page 27 where you say
5 the estimated SMRs were not elevated in all groups.

6 The values for subsequent 10-year age groups
7 are 5.9, 4.9, 2.0, 4.0, 2.8, and 3.8 with a total, with
8 a 90 percent confidence interval of 3.5 to 4.1.

9 And those all sound elevated to me, so I
10 didn't understand saying that they weren't elevated. I
11 mean they weren't as high as the first one that you
12 quoted which was 11.7 for the age 30 to 39, but in all
13 the other age groups that you quote, they all seem to
14 be well above 1, so I didn't understand that.

15 OEHHA STAFF TOXICOLOGIST BROWN: I'll have to
16 go back and look at it I guess. I --

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: This is the Smith '98 paper. We'll have to go
19 back and look at what we missed.

20 PANEL MEMBER BLANC: I think there is a word
21 "as" missing. Not as elevated.

22 PANEL MEMBER FRIEDMAN: That would solve it.

23 PANEL MEMBER HAMMOND: Or one could say they
24 were not equally elevated in all groups.

25 PANEL MEMBER FRIEDMAN: That was my only

1 comment.

2 CHAIRPERSON FROINES: Do we want to vote on an
3 individual chemical basis? Yes?

4 PANEL MEMBER BLANC: I think if you do that,
5 you're going to lock yourself into findings, separate
6 findings for each chemical.

7 And as little things come up today with the
8 presentations, rather than putting ourselves into the
9 position of having to say we would approve it
10 contingent on the minor changes that we've discussed,
11 we'll be able -- since we know we can't approve all
12 five of them today, it will allow us to avoid any
13 confusion about this issue with the dates and all that.
14 So I wouldn't at this point vote on any of the specific
15 RELs.

16 CHAIRPERSON FROINES: Okay. So you would vote
17 at the next meeting on all the RELs at one time?

18 PANEL MEMBER BLANC: Yep.

19 CHAIRPERSON FROINES: Is that a problem for
20 you, Melanie?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: No. That's not a problem.

23 CHAIRPERSON FROINES: Joe?

24 PANEL MEMBER LANDOLPH: Melanie, I had to
25 apologize. I sent in my comments late, and I think

1 they were too late to get into this document.

2 But when you have time, could you look at them
3 and find if they're appropriate?

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Yes.

6 PANEL MEMBER LANDOLPH: My apologies for being
7 late.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: We actually did take most of your comments and
10 get them in. I think there were a few that we didn't.

11 CHAIRPERSON FROINES: So we should come to
12 that when we get to acrolein.

13 So does everybody agree with Paul that we
14 should defer overall approval until we have a complete
15 package?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: Okay.

18 CHAIRPERSON FROINES: I'm getting nods, so I
19 think I'll go with the nods.

20 Melanie?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Yes. Okay. Back to the center of that
23 handout, acetaldehyde.

24 Karen Riveles is going to go over the changes
25 made in response to the last Panel meeting to the

1 acetaldehyde REL summary.

2 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Hello.

3 I'm Karen Riveles, OEHHA.

4 CHAIRPERSON FROINES: Before you start, I have
5 a curiosity question. Do you folks interact with ARB
6 to the degree that you're aware of what's happening
7 with acetaldehyde as we move into ethanol and biodiesel
8 fuel?

9 I mean there is the issue of the toxicology
10 and the risk assessment; but there is, it seems to me,
11 a major exposure assessment issue because if we're
12 using as much ethanol as I think we are, the levels of
13 acetaldehyde should be going up, and that's
14 problematic, I think.

15 So what's the connection between the two
16 agencies?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: Well, there's actually several with regard to
19 fuels.

20 The first connection was a document we
21 produced back in 2000, I think it was, Andy and I
22 worked on with Research Division looking at the impact
23 of ethanol as a fuel additive on overall air quality.

24 And the ARB did model the concentrations of
25 acetaldehyde in the air, and they did find that they

1 were elevated. But if you take all of the carcinogens
2 together that were modeled, some went up, some went
3 down so that there wasn't a change in the cancer risk
4 from the gasoline-related carcinogens that were
5 modeled. So that's one thing.

6 The other thing is that OEHHA does sit on a
7 Panel to review fuel additives under -- I forget the
8 statute number. But it's when ARB introduces a fuel
9 additive for or okays a fuel additive, they have to do
10 multimedia exposure and risk assessment.

11 It's not my group. It's another group. But
12 we do have interactions with that group. So that's
13 another way we have been looking at it.

14 CHAIRPERSON FROINES: Because there is
15 literature showing increased levels of acetaldehyde so
16 that those -- that stuff from earlier I'm aware of.
17 But seems to me this is an issue that deserves more
18 attention, perhaps, by the ARB.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: They're pretty well aware of it, particularly
21 given the carbon -- the low carbon fuel standards that
22 they're looking at which may involve using more
23 bio-based ethanol. So we -- and we are plugged in.

24 PANEL MEMBER FRIEDMAN: John, could you
25 elaborate a little? It sounded like you said we're

1 using a lot of ethanol now here, and I don't know where
2 I can get it for a car. Where is it being used?

3 CHAIRPERSON FROINES: As an additive to
4 gasoline.

5 PANEL MEMBER FRIEDMAN: Is that -- I was not
6 aware that was being done in California.

7 CHAIRPERSON FROINES: You're getting it. It's
8 not just -- MTBE has been replaced. I think, ARCO
9 stations use ethanol, for example.

10 PANEL MEMBER FRIEDMAN: What percentage of
11 the --

12 CHAIRPERSON FROINES: I don't remember off
13 hand. But it varies because I was at a gas pump the
14 other day, and it was still using MTBE. So there's a
15 crazy-quilt quality to it, but some companies are using
16 ethanol, what, around ten percent perhaps?

17 PANEL MEMBER HAMMOND: I've seen ten percent.

18 PANEL MEMBER FRIEDMAN: And that's being
19 imported from the midwest corn states, or is that grown
20 here or --

21 CHAIRPERSON FROINES: And from the developing
22 countries.

23 PANEL MEMBER BLANC: Perhaps we can proceed.

24 CHAIRPERSON FROINES: We can proceed. But I
25 want to raise it as an issue, even with Paul's

1 hesitation, because I think this is a quite significant
2 issue which is going to grow over time.

3 So you're on your own.

4 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Thank
5 you. I'm Karen Riveles, and I'm going to go over the
6 changes that were made in response to the Panel
7 discussion at the previous SRP meeting.

8 This first slide is just an overview of those
9 changes. So I added additional information on the
10 human studies where aerosolized acetaldehyde solutions
11 were used.

12 We did some extrapolation calculations from
13 the aerosolized dose to what the approximate
14 concentration in the air would be, and we also added
15 information on the sensitivity analysis that was done
16 as part of the PBPK model for acetaldehyde.

17 These changes and additions are seen in the
18 revisions made in the document that was sent to the
19 Panel.

20 So first of all, I went back over all of the
21 studies that used aerosolized acetaldehyde, and the one
22 thing that needed to be cleared up was who the subjects
23 were in the studies.

24 So in the studies, there were four studies
25 that used Japanese subjects and two studies that used

1 Caucasian subjects. In the studies that used Japanese
2 subjects, these subjects were either asthmatic or
3 nonasthmatic.

4 In one study, they stated that the Japanese
5 asthmatic volunteers either had prior sensitivity to
6 alcohol or prior to the study showed nonsensitivity to
7 alcohol.

8 However, that's all that was said. Therefore,
9 we don't know exactly what their ALDH-2 status was.
10 All we know is that they had a nonsensitivity to
11 alcohol.

12 So these studies were either asthmatic
13 volunteers versus nonasthmatic. And then there was one
14 study that looked at asthmatic volunteers that had
15 prior sensitivity versus nonsensitivity.

16 And the one that's of particular interest to
17 us in our REL calculation was the study done by Myou,
18 et al. in 1994. This was using Japanese subjects. And
19 they looked at aerosolized acetaldehyde that
20 potentiated bronchial hyper-responsiveness when
21 followed by provocation by methacholine.

22 And the concentrations that they saw this at
23 in the air doing the extrapolation calculation were
24 approximately 12.5 ppm.

25 This is indeed in the similar concentration

1 range as our key study for our REL determination which
2 we used a concentration of 25 ppm in human volunteers
3 according to the Silverman study.

4 This response is of concern because it's an
5 experimental analog to asthma, so this may be
6 indicative of a similar chemosensory response triggered
7 both by reactivity in the airways and eye irritation.

8 So the potentiation of methacholine-induced
9 bronchoconstriction shows the potential of acetaldehyde
10 in concentrations of 12.5 ppm or higher to exacerbate
11 asthma. So adult asthmatics that inhaled these
12 aerosolized solutions of acetaldehyde showed increased
13 irritation and bronchoconstriction.

14 In our calculations of calculating from these
15 aerosolized solutions to concentrations in the air, we
16 took known values of the nebulizer that was operated at
17 5 liters of air per minute, the acetaldehyde solution
18 output of .14 ml per minute, and then the
19 concentration of acetaldehyde that was known to be put
20 in the solution. This example is .8 milligrams of
21 acetaldehyde per ml.

22 When doing the extrapolation then, we came up
23 with a concentration in the air of 22.4 milligrams per
24 meter cubed which is about 12.5 ppm.

25 The aerosolized acetaldehyde solutions could

1 not be used to determine the acute REL because it only
2 demonstrated the effect of that one concentration, and
3 there was no information on dose response. As well as
4 they were using subthreshold concentrations in the
5 provocation studies, and the exposures were very
6 short-term, of two to four minutes.

7 The extrapolated concentrations in the air for
8 the other studies, all of the other studies except the
9 one I mentioned, were between 300 and 700 ppm; however,
10 they were studying different endpoints. The one that I
11 mentioned was the only one that studied the
12 potentiation of bronchoconstriction.

13 The other major revision after our discussion
14 at the last meeting was inclusion of information on the
15 sensitivity analysis that was performed by Teeguarden,
16 et al in their PBPK analysis of acetaldehyde.

17 This was a nose -- upper respiratory tract
18 nose model specifically for acetaldehyde, and the
19 sensitivity analysis was performed to incorporate
20 humans with ALDH-2 polymorphisms into the model.

21 The respiratory and olfactory epithelial
22 tissue acetaldehyde concentrations were determined to
23 be largely linear functions in both species, and
24 therefore the impacted ALDH-2 polymorphisms was shown
25 to have a negligible contribution to acetaldehyde

1 concentration in nasal tissue.

2 And those are the revisions that were made.

3 And so for each study of aerosolized acetaldehyde, I
4 did the extrapolation of what would be an approximate
5 concentration in the air, and those are shown in
6 revision mode.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
8 MARTY: I think we can say those were useful exercises
9 to do and that they let us know that we were on the
10 right track for using the studies we had used.

11 I also want to add that those extrapolations
12 to concentration are a little uncertain, and the
13 deposition pattern from an aerosolized solution may not
14 be the same as from a vapor phase inhalation, so that's
15 why people hesitate to use instillation studies in risk
16 assessment.

17 CHAIRPERSON FROINES: Joe?

18 PANEL MEMBER LANDOLPH: I have a question.

19 In that Myou study, was that bronchial
20 hyper-responsiveness potentiated by methacholine, was
21 that a permanent or semi-permanent event? Did it
22 persist in the human volunteers for a long period of
23 time, or did they address that all in the study?

24 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That
25 was not addressed in the study.

1 PANEL MEMBER LANDOLPH: Thank you.

2 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: And
3 once again, these were extremely short exposure periods
4 of two to four minutes.

5 CHAIRPERSON FROINES: Other comments? Paul.

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

8 PANEL MEMBER BLANC: Yeah. I want to go back
9 to your acute REL which still uses the 1946 study.

10 There doesn't seem to have been any change in
11 your uncertainty factors based on the observation that
12 at a half-an-order-of-magnitude-lower dose there was an
13 effect which was not the mild eye irritation effect of
14 your reference study but rather a not-mild effect which
15 would be bronchoconstriction.

16 So I want you to walk through for us how the
17 rationale of the various values you used might not have
18 changed, and in particular, I think the LOAEL
19 uncertainty factor of 6 rather than 10 in this
20 particular case. Because we already could say that
21 maybe the LOAEL should have been not 25 but 12.5.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: Well, again, this goes back to the certainty
24 with extrapolating from intratracheal instillation.

25 I think what we felt was in doing so we were

1 actually in -- it supported use of the toxicodynamic
2 factor of 10 for potential asthma exacerbation in
3 children. So --

4 PANEL MEMBER BLANC: I agree with that part.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
6 MARTY: In this REL, the 25 ppm was the LOAEL for eye
7 and upper respiratory irritation, and that doesn't
8 address potential bronchoconstriction from
9 acetaldehyde, so we had put in that toxicodynamic
10 uncertainty factor of 10.

11 So we still think that the eye irritation does
12 fall under the default for a mild effect, so we used
13 that LOAEL to NOAEL factor of 6 there.

14 But then on top of that to help account for
15 potential bronchoconstriction, we used another
16 uncertainty factor of 10. So that's what we're doing.

17 CHAIRPERSON FROINES: That's how you get to
18 60?

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: That's how we get to 60.

21 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The use
22 of the aerosolized acetaldehyde provocation was to
23 support the use of the 10. So it's used as a
24 supporting study.

25 PANEL MEMBER BLANC: For that.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Right.

3 PANEL MEMBER BLANC: And the fact that the
4 effect occurred at a lower level than the LOAEL study
5 in question doesn't otherwise come into play? Just --
6 I'm just asking a methodologic question.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Well, you're referring to the 12 and a half ppm
9 which was the estimated airborne concentration?

10 PANEL MEMBER BLANC: Yeah.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Yeah. Again, to me, there's a fair amount of
13 uncertainty in estimating that concentration from an
14 instillation.

15 So, you know, my guess is that you actually
16 get better deposition by instilling an aerosol than you
17 do from inhalation of a vapor. So there's that issue.
18 It's very hard to make that direct extrapolation.

19 So that 12 and a half is relatively uncertain.
20 A factor of 2 in risk assessment is actually pretty
21 small. So we didn't think that it was, you know, that
22 we needed to then change anything about the rest of the
23 REL calculation but rather use it to support the
24 additional tenfold --

25 CHAIRPERSON FROINES: What's your particle

1 size in your aerosol?

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: I don't think that they have that information.

4 PANEL MEMBER BLANC: Well, they said what kind
5 of nebulizer it was. Wasn't it DeVilbiss or something?

6 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: It's a,
7 yeah, DeBliss.

8 PANEL MEMBER BLANC: DeVilbiss?

9 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Yes.

10 PANEL MEMBER BLANC: And DeVilbiss does have a
11 standard, characterized particle size. And in fact,
12 there is a wealth of information on delivered dose with
13 an aerosol which is not the same thing as instillation.

14 PANEL MEMBER PLOPPER: So did they install it
15 -- or was it instillation or was it by inhalation? I
16 don't understand.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: It's an aerosolized inhale. So to me, that's a
19 little closer than breathing a vapor in air. And I
20 just, you know, there's a enough uncertainty in that
21 calculation that I don't think we should hang our hat
22 on that calculation.

23 PANEL MEMBER PLOPPER: I know, but what he's
24 saying is you could -- you can get a fairly accurate
25 measure of the concentration because those nebulizers

1 are very well characterized.

2 PANEL MEMBER HAMMOND: The other part --

3 PANEL MEMBER PLOPPER: If they know the amount
4 of inhalation that was done, you can get a pretty good
5 accurate -- get an actual dose.

6 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The
7 studies themselves make it very clear they did not
8 calculate the concentrations in air or the delivered
9 concentration. Those were extrapolations done with the
10 information that was provided.

11 PANEL MEMBER BLANC: I understand that. I
12 mean that would be typical of -- it would be very
13 atypical, let's say, for these kinds of aerosolized
14 research studies to measure the delivered dose in some
15 manner other than how they did the nebulization and
16 what the standard particle sizes are of the DeVilbiss
17 nebulizer, either.

18 I don't think that's what's giving me some
19 pause for thought here. Also I think there's a
20 question when -- they only used one dose, is that
21 right? Just refresh --

22 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: For
23 that part of the study --

24 PANEL MEMBER BLANC: Right.

25 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: -- that

1 determined the hyper-responsiveness to provocation by
2 methacholine, yes, it was one dose.

3 PANEL MEMBER BLANC: Right, and then they saw
4 this effect.

5 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: And it
6 was a subthreshold dose. They'd previously done a dose
7 response to measure PC20.

8 PANEL MEMBER BLANC: Right.

9 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: But
10 then they picked a subthreshold dose to use for the
11 potentiation of methacholine.

12 PANEL MEMBER BLANC: Right, and the doses that
13 they used to develop -- to determine the PC20 to
14 acetaldehyde used higher -- the average dose that
15 induced to PC20 was higher, but did they provide the
16 actual data, since I didn't review the papers, at which
17 some people began to respond and drop their FEV1, or
18 they just presented it as a mean?

19 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Just as
20 a geometric mean.

21 PANEL MEMBER BLANC: Without the data.

22 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Without
23 the individual responses, correct.

24 PANEL MEMBER BLANC: Well, one thing that -- I
25 actually think this is a rather critical issue. And as

1 I stated the last time, it partly draws from my
2 discomfort at having to use a 1946 study, certainly.

3 But also we're talking about a much more
4 critical acute endpoint which has public health
5 relevance and where public health-protective standards
6 are quite important coupled, of course, with John's
7 relevant comments about the likely growing importance
8 of this as an air pollutant.

9 So since we have the luxury of not approving
10 this necessarily today -- and although I do appreciate
11 the effort which you have gone into so far in doing
12 some of these extrapolations -- I would suggest two
13 things, one which can be accomplished easily, and that
14 is clarifying the outstanding issues that you may have
15 about delivered dose from an aerosol inhalation and how
16 that relates to a vapor phase inhalation versus an
17 instillation.

18 And secondly, I think I would try to contact
19 the authors in terms of getting the raw data for the
20 challenge study for the individual responses so that
21 you can look at what the five percent confidence
22 interval would be for responses of bronchospasm.

23 Because what -- as I understood it from your
24 previous presentation, basically what they've shown
25 with this chemical is that it can be used like a

1 methacholine test. If that is -- which is unusual.

2 This is not a typical effect. It's really
3 only been shown for sulphur dioxide in terms of air
4 pollutants previously. And as much as people have
5 looked at ozone and nitrogen dioxide, they have not
6 been able to show that it acts in this manner.

7 There are subsets of people who may be
8 hyper-responsive in weird ways, but it's not -- it
9 doesn't correlate with methacholine responsiveness.

10 The implications of that is that there is a
11 bimodal distribution where there is a large group of
12 asthmatic or hyper-responsive people who will respond
13 to lower levels of acetaldehyde.

14 And just having the mean value for what the
15 mean PC20 equivalent response is completely misses the
16 boat in terms of what people responded to at the lowest
17 level.

18 So even if the mean PC20 dose of acetaldehyde
19 was much higher than the estimated 25 parts per million
20 from this other study, in fact you may see that five
21 percent of the people responded in that other study at
22 ten parts per million equivalent.

23 And I think it's worth doing extra legwork, if
24 possible, to try to get those data since this is a
25 fairly critical issue and goes to the heart of the

1 whole intent of children as a high-risk subpopulation
2 from the point of view of asthma.

3 CHAIRPERSON FROINES: I may be -- I'm sorry,
4 Kathy; go ahead.

5 PANEL MEMBER HAMMOND: Just a small comment,
6 that this acetaldehyde has a high vapor pressure. So
7 it's quite possible that even with the nebulizer that
8 what people are breathing is a mixture of aerosol and
9 vapor phase.

10 So we want to, I think, be aware of that issue
11 as we look at that issue.

12 But I totally concur with Paul's comment that
13 it's important to look at the actual individual data
14 for all the reasons he outlined.

15 CHAIRPERSON FROINES: I think that's
16 particularly true because the vapor is presumably going
17 to be taken up by passive diffusion. So you may have
18 greater intracellular concentration from the vapor.

19 PANEL MEMBER HAMMOND: Well, it depends on
20 where you're looking because it's highly water soluble.
21 It could be taken up in the upper airways.

22 CHAIRPERSON FROINES: Yeah. So I'm a little
23 confused at this stage. The Appleman study, you're not
24 using as your final determination?

25 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: It's

1 the eye irritation study. We're using the asthma study
2 for the acute REL. And we were using the asthma study
3 to support the tenfold uncertainty factor in
4 toxicodynamics, to support the increased sensitivity of
5 the asthmatics.

6 PANEL MEMBER BLANC: John, the Appleman is for
7 the 8-hour. We're talking about the acute. They're
8 using the Silverman 1946 study.

9 CHAIRPERSON FROINES: Well, that's partially
10 what bothers me.

11 So does anybody else have comments? Because I
12 think Paul's given OEHHA work to do in the interim.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
14 MARTY: I have a concern about -- again, this is the --
15 well, it's a concern about dose rate.

16 This aerosol is given pretty rapidly over a
17 space of a few minutes. So when calculating to
18 concentration in air, I don't know that you could, you
19 know, would get that much in that short period of time.

20 So that's why I'm asking Andy to go back and
21 check on that. Because that's -- I've always had that
22 issue with trying to use these sorts of instillations
23 and then translate it to an inhalation.

24 PANEL MEMBER HAMMOND: This is not an
25 instillation. Nebulizer --

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Well, to my mind, it's a lot closer to an
3 instillation than it is to inhalation.

4 PANEL MEMBER HAMMOND: I don't -- I mean --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: It's a nebulizer.

7 PANEL MEMBER HAMMOND: It's a nebulizer going
8 into a space though that is then breathed. It's not
9 going directly into --

10 PANEL MEMBER BLANC: No, it is. It is.

11 PANEL MEMBER HAMMOND: Into a mask? But the
12 mask is still into the air that's breathed as opposed
13 to --

14 PANEL MEMBER BLANC: Yeah, yeah.

15 PANEL MEMBER HAMMOND: So it's not
16 instillation.

17 PANEL MEMBER BLANC: I think that respiratory
18 physiologists would just not take your view that this
19 is -- if someone held a gun to their head and said is
20 this closer to an instillation or inhalation, they
21 would view it as inhalation.

22 I think at our last meeting I suggested that
23 you might want to consult with Dr. Homer Boushet, in
24 particular. Was that done?

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: We tried, but we didn't get a response.

2 PANEL MEMBER BLANC: So you e-mailed him and
3 he didn't respond.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Yeah.

6 PANEL MEMBER BLANC: Melanie, why don't you
7 copy me on the e-mail to Homer, and then I can respond.

8 I think the other person who might have some
9 rather interesting comments for you would be Dr. Jay
10 Nadel, if you don't get a response.

11 But copy me, and I can prod a little bit.
12 Because, you know, you've got these world experts at
13 your, you know, a few miles away. And I think that
14 for -- in particular, for Dr. Nadel who did the
15 pioneering work with sulphur dioxide, this would be
16 particularly interesting, this question.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: So also remember it's potentiating the
19 bronchoconstriction of methacholine.

20 PANEL MEMBER BLANC: That's in this study.
21 But in the study I suggested you get the raw data from
22 it was actually using, if I recall correctly from your
23 previous summary of it, it was actually using
24 acetaldehyde as a bronchoprovocateur,
25 bronchoconstriction provocation chemical. Isn't that

1 correct?

2 THE WITNESS: Yes, but it was also found that
3 the acetaldehyde was 265 times less sensitive than
4 methacholine.

5 PANEL MEMBER BLANC: Well, no one's proposing
6 distributing methacholine into the general air of
7 California either on that, on the other hand.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
9 MARTY: I think that the point is that you would have
10 to have a provocation as strong as methacholine to see
11 the potentiation of acetaldehyde at 12 and a half parts
12 per million. So where that dose response is, below
13 that, we can't know.

14 PANEL MEMBER BLANC: But I want to see the
15 other data. I mean if you can find the other data.

16 Because again, we're not talking about the
17 mean response. After all, if you look at the mean
18 methacholine response for the general population, for
19 PC20, it would be very, very high. But if you look,
20 you know, order of magnitude higher than for
21 asthmatic -- the mean for asthmatics, I guess.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: Well, that -- the mean concentration of PC20
24 was about thirtyfold more than the subthreshold
25 concentration given. So I don't know if that tells you

1 anything.

2 PANEL MEMBER BLANC: That makes me suspicious.

3 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: In this
4 Myou 1994 paper under subject characteristics, there is
5 nine subjects, and they do have mean PC20 values for
6 each individual.

7 And they range from 30.5 mgs per mil to the
8 lowest I see here is 20 -- or 18.6 mgs per mil.

9 Can we go back a slide?

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Sure.

12 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That
13 will just put us into the --

14 22.4. So 22.4 was the mean. And it looked
15 like one subject at 18.6 mgs per mil, so you only have
16 nine subjects, so you basically have an N of 1. And in
17 terms of -- but these are mean values, once again.
18 These aren't this many subjects at this concentration
19 responded.

20 PANEL MEMBER BLANC: Right.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Is there a suggestion that we should be adding
23 an additional uncertainty factor or?

24 PANEL MEMBER BLANC: I think the first
25 suggestion is to go back and try to figure out these

1 other things, and that may help you determine whether
2 you need either to add an additional uncertainty factor
3 or whether you in fact would be in a position to use
4 the acute inhalation -- the acute nebulized inhalation
5 data to generate your acute REL and then support that
6 with the 1946 data as a corollary, perhaps.

7 That -- I mean that remains to be seen. But
8 I'm -- and you may come back and say listen, we did our
9 homework, and we still feel that although these data
10 support the uncertainty factor of ten based on the
11 toxicodynamics we would still continue to use the
12 Silverman study, and we wouldn't change anything else,
13 and unfortunately we can't exploit these other data any
14 more than we have.

15 And that may be your final determination. I'm
16 just not completely convinced yet. And it's such an
17 important potential issue that I wouldn't want to not
18 go the extra mile on this one, recognizing that you've
19 already put considerable extra effort into clarifying
20 this situation.

21 CHAIRPERSON FROINES: Kathy?

22 PANEL MEMBER HAMMOND: I'm sorry, I haven't
23 read the underlying papers here, but it's also
24 important to recall that acetaldehyde is highly
25 reactive.

1 So the actual concentration, especially if
2 there's a mask which would be a high surface-to-volume
3 ratio, if this was with a mask and tubing, you actually
4 might have a much lower concentration.

5 This may be a high overestimate of the
6 concentration that the subjects actually experienced.
7 Is that clear?

8 OEHHA ASSOCIATE TOXICOLOGIST RIVELES: I
9 understand your comment.

10 PANEL MEMBER HAMMOND: I'm not sure what to do
11 with that, but that would raise more concerns then,
12 that this responsiveness might be in response to a much
13 lower concentration.

14 CHAIRPERSON FROINES: So are we set with
15 respect to -- Melanie, are we set with what needs to be
16 done between now and the next meeting?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: I think so.

19 PANEL MEMBER HAMMOND: I guess I would like to
20 reiterate Paul's comment that -- this is clearly
21 difficult to interpret some of the studies as we raise
22 more issues on this.

23 On the other hand, it's particularly important
24 as with such an important issue in California. And
25 since we are talking about a chemical that is being

1 released in general, especially with some of the new
2 fuel additives, we need to be pretty careful about
3 this.

4 PANEL MEMBER PLOPPER: I would just say I want
5 to reiterate that. Nebulization is not instillation.
6 It's inhalation. So don't just, I mean --

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
8 MARTY: Okay.

9 PANEL MEMBER PLOPPER: There's a whole
10 literature that pretty much defines that.

11 So don't -- I mean my interpretation when I
12 read through this was it was -- like Paul said, this
13 current one that you have for the cubic exposure is too
14 high.

15 I thought that's what this document was
16 leading up to, and then you say that it's not. So I
17 think you need to get a way to calculate exactly what
18 those -- closer to what those concentrations are.

19 Because nebulization, part of the idea, it's
20 going to be small enough, even if they did something
21 wrong with their nebulizer, it's going to be small
22 enough that it's going to be very well inhaled and very
23 widely distributed. So it will have lots of contact.
24 May even react less than the gas particle till it gets
25 to the tissue.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Okay.

3 CHAIRPERSON FROINES: I wanted to make two
4 sort of side comments sort of on a general point.

5 One of the things we do here is we do
6 acetaldehyde. But clearly, one of the major toxic
7 issues of acetaldehyde is its chemistry that creates
8 peroxyacetaldehyde. And we don't talk about that, even
9 though that's probably a hundred times more toxic than
10 acetaldehyde.

11 The second thing that's important is when you
12 take two molecules of acetaldehyde, and if you lose a
13 molecule of water, you get an alpha,beta-unsaturated
14 carbonyl which is going to undergo Michael addition
15 reaction. And so those are going to be electrophilic,
16 and they're going to be irreversible, and they're going
17 to have quite significant toxicity.

18 So it seems to me that around the issue of the
19 peroxides that get formed, and around the issue of the
20 aldo condensations that can occur, we're talking about
21 a chemical, but we're sort of missing the forest for
22 the trees.

23 Because there are really quite significant
24 toxicities from products of acetaldehyde. And the
25 question is, as a policy question: How can we get at

1 those matters?

2 Because they're -- you know, we wrote about
3 the peroxyxynitrites in the MTBE document in the '90s and
4 the condensations of enol forms of acetaldehyde, you
5 know, every good chemist knows that chemistry.

6 And so we're missing things that really may
7 have significant toxicity, and we're focusing on
8 acetaldehyde, which we should. But it's just not as
9 simple as the way the picture is drawn.

10 So the ARB needs to consider what is it --
11 what are the other issues that may be more toxic than
12 acetaldehyde that we need to be concerned about within
13 the context of dealing with air pollution?

14 PANEL MEMBER HAMMOND: John, does that --
15 would that imply that a REL should actually be based on
16 the expected chemical reactions?

17 CHAIRPERSON FROINES: I don't know. Because I
18 don't think anybody is measuring the products of aldo
19 condensations, enol condensations.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
21 MARTY: I mean to address that concern, we would have
22 to do a REL based on toxicological studies of the
23 product of the reactions.

24 CHAIRPERSON FROINES: Right.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: And the --

2 CHAIRPERSON FROINES: For which there is very
3 little.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: -- Air Board would have to do regulation to
6 reduce the reactants. So, you know, that's, in the
7 regulatory scheme how --

8 PANEL MEMBER HAMMOND: I guess the example
9 would be ozone where the REL is based on ozone itself,
10 but you look at the precursors to it, and that's how
11 you do the regulation to prevent the exposure.

12 So I guess to that degree the REL is the
13 compounds. So I think John's right. We should be
14 aware of the reaction products and their toxicity.

15 CHAIRPERSON FROINES: Well, the nitrites
16 are -- people have been measuring those in Brazil for a
17 long time.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: Yeah.

20 CHAIRPERSON FROINES: Anyway, why don't we
21 take a five-minute break, give you a break. We will
22 take a five-minute break.

23 (Recess)

24 CHAIRPERSON FROINES: Can we get started?

25 Okay. First item is the document that Stan wrote. And

1 do people have comments?

2 PANEL MEMBER GLANTZ: So this is the new
3 number 1. This should be inserted before the current
4 number 1. Nothing would be deleted.

5 PANEL MEMBER HAMMOND: We'll just read it.

6 PANEL MEMBER GLANTZ: And I have corrected all
7 the commas per Dr. Blanc.

8 PANEL MEMBER HAMMOND: Here's one that
9 shouldn't be there.

10 CHAIRPERSON FROINES: Gary?

11 PANEL MEMBER FRIEDMAN: I have a few suggested
12 changes in wording. Good otherwise.

13 You know you talk about level of statistical
14 significance, i.e., the ability to exclude a false
15 positive error.

16 PANEL MEMBER GLANTZ: Yeah.

17 PANEL MEMBER FRIEDMAN: I think you should use
18 the same wording for power, that is the ability to
19 exclude a false negative error, rather than just saying
20 risk of false negative error. Because power is not
21 risk, it's the ability to exclude it. Just like
22 significance was on the other.

23 PANEL MEMBER GLANTZ: Yeah.

24 PANEL MEMBER FRIEDMAN: Then near the end
25 where you say: If the outcome is serious and the study

1 small, i.e., low power --

2 PANEL MEMBER GLANTZ: Wait, wait. Yeah.

3 PANEL MEMBER FRIEDMAN: The outcome is serious
4 and the study small, a larger P value such as P less
5 than .10 may be an adequate -- may be adequate evidence
6 for identifying.

7 I don't think that's really good evidence. I
8 think I would rather see you say may be an adequate
9 criterion for suspecting an effect.

10 Because it isn't adequate evidence. It's a
11 small study. And you've got a P value of .10. That is
12 one chance in ten you're wrong. So it isn't really
13 good evidence. It may be a good criterion, a better
14 criterion.

15 PANEL MEMBER BLANC: Why not simply say may be
16 adequate as an alpha value? Because you've already
17 explained what an alpha value is above.

18 PANEL MEMBER FRIEDMAN: Well, it doesn't have
19 more ability to exclude a false positive error. It
20 doesn't have much ability to do that.

21 PANEL MEMBER GLANTZ: No, but the point that
22 this is making is that if it's a serious outcome,
23 okay -- well, maybe the thing to do is just to say if
24 the outcome is serious, a larger P value may be
25 adequate evidence for identifying an effect.

1 PANEL MEMBER FRIEDMAN: Well, and may be --

2 PANEL MEMBER GLANTZ: Or maybe identify is the
3 wrong word.

4 PANEL MEMBER FRIEDMAN: Yeah, I mean it's too
5 strong. It may be for health protective reasons an
6 adequate criterion, but it isn't any better evidence,
7 you know.

8 PANEL MEMBER BYUS: Correct.

9 PANEL MEMBER GLANTZ: We could take adequate
10 out, take the word evidence out I mean.

11 PANEL MEMBER FRIEDMAN: I would say adequate
12 value -- it's a criterion. It's a criterion.

13 PANEL MEMBER GLANTZ: Okay. Why don't we just
14 say if the outcome is serious, a larger P value may be
15 acceptable for identifying an effect? Or may be used
16 to identify an effect?

17 PANEL MEMBER BLANC: I would say it may be an
18 acceptable threshold for excluding a --

19 PANEL MEMBER GLANTZ: Well, except that the
20 point we're trying to make here is that if you have a
21 very serious endpoint.

22 PANEL MEMBER BLANC: I understand what you're
23 saying, but what's basically the function of what
24 you're saying is I'm going to have a different
25 threshold for the point at which I'm unwilling to

1 accept a false positive.

2 PANEL MEMBER GLANTZ: Why don't we just --

3 PANEL MEMBER BLANC: False negative, whatever
4 the right word is.

5 PANEL MEMBER GLANTZ: Why don't we say --
6 fitting with John's trying to write this in English --

7 PANEL MEMBER BLANC: Right.

8 PANEL MEMBER GLANTZ: Why don't we say if the
9 outcome is serious, a larger P value may be acceptable
10 for identifying an effect?

11 PANEL MEMBER BLANC: Well, you want to keep
12 the study small there because that's part of your
13 point. If you had a serious effect but, you know, a
14 very powerful study, you still wouldn't --

15 PANEL MEMBER GLANTZ: That's true.

16 CHAIRPERSON FROINES: I think that you are --
17 I think there needs to be something about what we are
18 measuring. In other words, the measurement itself is
19 an end in itself.

20 It's a little bit like saying: If this
21 outcome is serious, the magnitude of the effect needs
22 to be given serious consideration.

23 PANEL MEMBER FRIEDMAN: That's a whole
24 separate issue.

25 PANEL MEMBER GLANTZ: Yeah.

1 Why don't we do this? Why don't we say: If
2 the outcome is serious and the study small, a larger P
3 value may be used to identify an effect.

4 PANEL MEMBER FRIEDMAN: Okay. That's --

5 PANEL MEMBER BYUS: That's better.

6 PANEL MEMBER FRIEDMAN: Yeah.

7 PANEL MEMBER GLANTZ: So put it up there on
8 the screen. That helps. Are there any other changes
9 people want?

10 PANEL MEMBER LANDOLPH: I'll let you do it
11 however you want, but the sentences -- lines 8 to 14,
12 it's just one long sentence. It runs on awful long.
13 If you could just figure out a way to chop it into two
14 short sentences.

15 PANEL MEMBER BYUS: Put some commas in.

16 PANEL MEMBER GLANTZ: The other thing is to
17 delete all the parenthetical statements inside the
18 parenthetical statements.

19 But the reason I kept those is because that
20 was something that was the subject of a lot of
21 discussion.

22 CHAIRPERSON FROINES: But we'd like to read
23 this into the record so it's in the record.

24 PANEL MEMBER GLANTZ: No, we will. You want
25 to let me -- so people just want me to --

1 CHAIRPERSON FROINES: Take a second.

2 PANEL MEMBER GLANTZ: -- break it up into two
3 sentences. Okay, give me a second.

4 PANEL MEMBER FRIEDMAN: How about: For
5 epidemiological studies, it's important to consider the
6 following aspects. And then colon, then you can list
7 all these things.

8 PANEL MEMBER BYUS: That's better.

9 PANEL MEMBER FRIEDMAN: Would that do it?

10 PANEL MEMBER LANDOLPH: Or even just say it's
11 important to consider the strength of the study design
12 period, and it's particularly important to consider the
13 rest of those things.

14 PANEL MEMBER BLANC: No -- oh, I see.

15 PANEL MEMBER LANDOLPH: Just so it doesn't run
16 on into a long thing too long.

17 PANEL MEMBER BLANC: All of those things are
18 study design things, right?

19 PANEL MEMBER GLANTZ: Right.

20 PANEL MEMBER BLANC: Yeah, so I think if you
21 just put a period after study design and then say this
22 includes colon. Get rid of particularly, you know,
23 controlling for study. And then you also don't have to
24 put parentheses within the parentheses.

25 PANEL MEMBER LANDOLPH: That's right.

1 CHAIRPERSON FROINES: Stan, will you make
2 those changes, and when we break --

3 PANEL MEMBER GLANTZ: Here, I'll just --

4 CHAIRPERSON FROINES: Wait. When we break,
5 talk with the stenographer and read into the record the
6 document?

7 PANEL MEMBER GLANTZ: Okay. Well, are there
8 any other changes people want?

9 CHAIRPERSON FROINES: So we don't take time
10 here?

11 Melanie, let's go.

12 PANEL MEMBER GLANTZ: Well, no. Are there any
13 other changes people want?

14 CHAIRPERSON FROINES: Hearing none. If we
15 have them, somebody will speak up.

16 PANEL MEMBER GLANTZ: Do you want me to just
17 read this into the record real quickly now, and then
18 we'll be done?

19 PANEL MEMBER BLANC: Sure.

20 PANEL MEMBER GLANTZ: Okay. This would be the
21 new -- this would be the new finding number 1 which
22 would go before the current finding number 1 which
23 would be renumbered 2 and then subsequently. So it
24 would be:

25 OEHHA uses a weight of evidence approach

1 to determine whether or not exposure to
2 a chemical causes a particular effect
3 including the number and quantity --

4 Or, pardon me.

5 -- the number and quality of toxicology
6 and epidemiological studies and data on
7 biological plausibility.

8 In analyzing animal studies, the nature
9 and extent of the exposure and the
10 characteristics of the exposed animals
11 are generally well-controlled.

12 Issues such as observation of the
13 dose-response relationship,
14 reproducibility of findings, and
15 mechanism of action, including
16 consideration of its relevance to
17 humans, are key elements of the weight
18 of evidence.

19 For epidemiological studies, it is
20 important to consider the strength of
21 the study design. These strengths
22 include controlling for confounding
23 variables, including overadjustments for
24 potential confounders which could lead
25 to underestimating the effects of the

1 toxin; 2) obtaining an unbiased sample;
2 3) the potential for bias in
3 ascertaining exposure, in particular
4 nondifferential exposure
5 misclassification which biases the
6 sample --

7 Pardon me.

8 -- biases the effect size estimates
9 toward the null; and 4) the level of
10 statistical significance, i.e., the
11 ability to exclude a false positive
12 error.

13 The power of the study to detect
14 biologically meaningful effects, i.e.,
15 the risk of excluding a false --

16 PANEL MEMBER FRIEDMAN: No, the ability to
17 exclude, I thought we agreed.

18 PANEL MEMBER GLANTZ: I'm sorry. The ability
19 to exclude. Sorry. You're right.

20 -- to exclude a false negative error is
21 important in considering studies that do
22 not reach traditional statistical
23 significance, particularly if the
24 biological endpoint is serious.

25 If the outcome is serious and the study

1 small, i.e. low power, a larger P value,
2 e.g., P less than .10, may be used to
3 identify an effect.

4 The availability of experimental data or
5 mechanistic theories consistent with
6 epidemiological observations strengthens
7 conclusions of causation.

8 The Panel concurs with this approach.

9 PANEL MEMBER LANDOLPH: You had 2, 3, and 4.
10 Did you say 1?

11 PANEL MEMBER GLANTZ: I was -- I'll fix that.
12 There's a 1. I forgot to write it down.

13 So people are happy with that?

14 PANEL MEMBER LANDOLPH: Great.

15 PANEL MEMBER GLANTZ: If that's the case,
16 could I move we accept the findings and the report?

17 CHAIRPERSON FROINES: Have people had a chance
18 to read the findings sufficiently to make --

19 PANEL MEMBER BLANC: Yes.

20 PANEL MEMBER BYUS: Yes, I think we did.

21 CHAIRPERSON FROINES: You read them when you
22 got here.

23 PANEL MEMBER FRIEDMAN: You gave us five
24 minutes, remember?

25 CHAIRPERSON FROINES: I understand.

1 PANEL MEMBER BLANC: Just to take a friendly
2 modification of that? I would move that we accept the
3 findings as modified per the discussions today.

4 PANEL MEMBER GLANTZ: Yes, I'll accept that.

5 PANEL MEMBER LANDOLPH: Second.

6 CHAIRPERSON FROINES: Any comments? All in
7 favor?

8 (Ayes)

9 CHAIRPERSON FROINES: Unanimous. The vote was
10 unanimous, 8 to 0. Okay.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Thank you for that.

13 I just wanted to -- one more change that was
14 made in one of the REL summaries. That was mercury,
15 which we reviewed last time.

16 We were requested to add a description which
17 is on page 4 of studies done in the Amazon basin
18 looking at sort of lots of exposure to mercury, both
19 from the air and from the contaminated environment
20 which included then methylmercury in the waterways and
21 therefore the fish.

22 So we added that.

23 And then we also reworded the description of
24 Lowendowski's analysis of in vivo data to remove the
25 reference to the parallelogram approach, or remove the

1 focus on it, because all it is is a comparative
2 approach and it's kind of a funny word, so we did that.

3 And those were the only changes in that
4 document.

5 CHAIRPERSON FROINES: So let's move on unless
6 there are comments.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: Okay.

9 CHAIRPERSON FROINES: Melanie, we have now
10 formaldehyde, acrolein and --

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Manganese.

13 CHAIRPERSON FROINES: Manganese. We have
14 three.

15 What time is it, somebody?

16 PANEL MEMBER FRIEDMAN: 11:40.

17 CHAIRPERSON FROINES: Let's try -- are people
18 willing to try and see how we -- as far as we can go as
19 opposed to taking a lunch break? If we need a lunch
20 break, we will. But if we don't, we won't.

21 PANEL MEMBER BLANC: I don't think it's
22 realistic that we can do manganese before lunch. It's
23 not realistic.

24 CHAIRPERSON FROINES: Not, okay.

25 PANEL MEMBER BLANC: It's a major -- going to

1 be a major discussion.

2 CHAIRPERSON FROINES: Okay. So why don't we
3 plan then to try and get through the next two, take a
4 lunch break, and then go to manganese. Is that all
5 right with everybody?

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Okay. Bruce Winder is going to make the
8 presentation on the acrolein REL.

9 CHAIRPERSON FROINES: Did I leave out
10 formaldehyde?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Do you want to do formaldehyde first?

13 CHAIRPERSON FROINES: No, no. I was just
14 thinking about what I said. I just would -- did I
15 forget to say formaldehyde?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

17 MARTY: No, you said it.

18 OEHHA STAFF TOXICOLOGIST WINDER: What we see
19 here is, presenting the REL document, the acute REL for
20 acrolein here is 2.5 micrograms per meter cubed based
21 on ocular irritation in humans.

22 The eight-hour and the chronic RELs, as you
23 see, are .70 and .35 micrograms per meter cubed. Both
24 these are based on lesions in respiratory epithelium of
25 rats.

1 Now for the acute REL, this is based on
2 actually two studies. The principal one here is the
3 Darley study of 1964 in which 36 adults were exposed to
4 acrolein by a face mask for five minutes.

5 And the endpoint here is subjective ocular
6 irritation.

7 Now in that study, they estimate a LOAEL of
8 .06 parts per million. We consider this at this point
9 to be a relatively mild effect, so we're using a LOAEL
10 to NOAEL conversion uncertainty factor of 6.

11 Now since the study was done in humans, there
12 is no interspecies toxicodynamic or toxicokinetic
13 uncertainty factors involved.

14 However, in terms of intraspecies
15 toxicokinetic factors, we figure that with respect to
16 deposition and the kinetics associated with this
17 exposure, we don't anticipate a difference between
18 children and adults, and so there's no uncertainty
19 factor associated with that.

20 However, with respect to the toxicodynamic --

21 CHAIRPERSON FROINES: Can I ask you a
22 question?

23 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

24 CHAIRPERSON FROINES: In SB 25, we listed five
25 compounds, one of which had greater effects in children

1 than in adults. And acrolein was one of them, and here
2 you're saying that there is no difference.

3 OEHHA STAFF TOXICOLOGIST WINDER: No, we're
4 saying in terms of toxicokinetics we don't think
5 there's a difference.

6 CHAIRPERSON FROINES: Okay.

7 OEHHA STAFF TOXICOLOGIST WINDER: Which brings
8 me to the next one which is with respect to
9 toxicodynamics we do think there's a difference; and
10 for that reason, we give it an full uncertainty factor
11 of 10.

12 And the major concern here is with respect to
13 the potential to exacerbate asthma in children.

14 So this gives us a cumulative uncertainty
15 factor of 60. So from this study, we calculate an
16 acute REL of 2.3 micrograms per meter cubed.

17 Next.

18 Now as a support or an additional study, we
19 used the Weber-Tschopp study which also looks at
20 adults. Here they're exposed in an exposure chamber
21 exposed by face masks.

22 Again, we're looking at the same endpoint of
23 ocular irritation. And the LOAEL here is very similar.
24 It's .07 versus .06 in the previous study.

25 For the same reason as before, we have an

1 uncertainty factor of 6. And again, there are no
2 interspecies uncertainty factors, but we do have the
3 intraspecies toxicodynamic factor of 10 for the same
4 reason, asthma exacerbation.

5 Once again, the cumulative uncertainty factor
6 is 60. This gives us an acute REL of 2.7.

7 So what I did here is took the mean of these
8 two studies for the REL that we're presenting, which
9 is --

10 CHAIRPERSON FROINES: Can I ask you a
11 question?

12 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

13 CHAIRPERSON FROINES: When these two studies
14 are done, the air that they're breathing: Is it clean
15 air that's been filtered?

16 OEHHA STAFF TOXICOLOGIST WINDER: I believe
17 that's -- in the Weber-Tschopp, it is. The other is
18 direct application to eyes.

19 CHAIRPERSON FROINES: So we don't know if
20 you're breathing lousy Los Angeles air, and you throw
21 in some acrolein, whether you're going to see the same
22 type of effect at these kinds of levels.

23 I would predict that you'll see a stronger
24 effect.

25 And the problem of our studying things with

1 clean air as the air of choice, as it were --

2 OEHHA STAFF TOXICOLOGIST WINDER: Correct.

3 CHAIRPERSON FROINES: -- is that it really
4 underestimates what people are actually breathing.

5 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, and
6 that's a problem we -- since we're continually exposed
7 to a combination of things, for example, formaldehyde
8 and acrolein and acetaldehyde together, they tend to
9 exacerbate each other.

10 CHAIRPERSON FROINES: Right.

11 OEHHA STAFF TOXICOLOGIST WINDER: So that
12 is -- we recognize that as an issue. That will come up
13 a little while later. But, yeah, that's a problem and
14 we're starting to deal with that with respect to --

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: We do consider it when we're doing a risk
17 assessment of a stationary source facility, those
18 hazard indices would be added.

19 So in other words, we don't look -- when we're
20 applying these Reference Exposure Levels in a risk
21 assessment for a stationary source, we would include an
22 additive effect of all those chemicals.

23 When you're looking at the Los Angeles basin,
24 you know, we haven't done risk assessments for the Los
25 Angeles basin as a whole. That's where, you know, we

1 could use a little more consideration of additive
2 effects or synergistic effects, when those occur.

3 PANEL MEMBER FRIEDMAN: Are you suggesting
4 that there should be a Los Angeles factor in addition
5 to the uncertainty factor? Is that what you're
6 thinking, John?

7 (Laughter)

8 CHAIRPERSON FROINES: No, I'm thinking about
9 chemical interactions. Like formaldehyde and acrolein
10 are two classics that you would expect that there would
11 be some interaction.

12 OEHHA STAFF TOXICOLOGIST WINDER: Well, there
13 is.

14 CHAIRPERSON FROINES: Yeah.

15 OEHHA STAFF TOXICOLOGIST WINDER: And there's
16 competition between the two at some of the receptors,
17 so.

18 CHAIRPERSON FROINES: Correct, exactly.

19 So it's an issue -- it's a research issue at
20 some level, if not wholly a risk assessment issue.

21 PANEL MEMBER BLANC: I just want to clarify
22 something for the record.

23 You had -- I think it was just a slip that you
24 had said face masks, but they're in an exposure
25 chamber.

1 OEHHA STAFF TOXICOLOGIST WINDER: Oh, no, no.
2 The masks is with respect to the first study in which
3 they were actually breathing acrolein directly -- not
4 breathing, but exposed to the eyes. The Darley study.

5 Whereas these guys -- you are correct. I must
6 have misspoken. This one was whole body.

7 PANEL MEMBER BLANC: So how were they doing
8 the exposure in the Darley?

9 OEHHA STAFF TOXICOLOGIST WINDER: Eye --
10 face -- exposing just the eyes.

11 PANEL MEMBER BLANC: It's an eye mask.

12 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

13 PANEL MEMBER BLANC: Okay. And when you write
14 here that the exposure chamber levels were 0 to .6
15 parts per million, what do you mean, exactly?

16 OEHHA STAFF TOXICOLOGIST WINDER: This is what
17 they measured in the chamber during exposure time.

18 Oh -- and yeah, it was increasing levels.

19 PANEL MEMBER BLANC: So what were the dose
20 levels of the study, roughly?

21 OEHHA STAFF TOXICOLOGIST WINDER: I think it
22 was continually increasing. Yeah, I don't believe that
23 was --

24 PANEL MEMBER BLANC: I mean usually these
25 exposure chamber studies are fixed levels. And so I'm

1 just trying to understand.

2 So it wouldn't be that they'd be gradually
3 increasing it over time and then noting when people
4 first had eye irritation. So how exactly --

5 OEHHA STAFF TOXICOLOGIST WINDER: Apparently
6 that is what they were doing, gradually increasing it.

7 PANEL MEMBER BLANC: Then the level of .07 was
8 the first level at which anyone said they had eye
9 irritation?

10 OEHHA STAFF TOXICOLOGIST WINDER: I believe
11 that's correct.

12 PANEL MEMBER BLANC: That's an odd protocol.
13 I just want -- you should just go back and double-check
14 that's what they did. It's a very odd --

15 OEHHA STAFF TOXICOLOGIST WINDER: Odd
16 approach.

17 But either way, the -- it appears that the
18 results of these two studies are pretty much
19 corroborative.

20 PANEL MEMBER BLANC: No, I get that point.
21 I'm just trying to understand if --

22 OEHHA STAFF TOXICOLOGIST WINDER: I can go
23 back and check that.

24 CHAIRPERSON FROINES: Does this mean that a
25 subject was exposed to a level below .07?

1 OEHHA STAFF TOXICOLOGIST WINDER: I'm sorry?

2 CHAIRPERSON FROINES: Does this mean that
3 somebody was exposed to a level below .07?

4 OEHHA STAFF TOXICOLOGIST WINDER: Well
5 presumably, they started at 0. And then -- and yes,
6 it's how it was measured.

7 CHAIRPERSON FROINES: The question I'm asking
8 is: What happened in between 0 and .07?

9 OEHHA STAFF TOXICOLOGIST WINDER: I think .07
10 is when they first reported on the questionnaire that
11 they were experiencing eye irritation. So presumably
12 below that level there was no report of eye irritation.

13 PANEL MEMBER BLANC: Well, then wouldn't .06
14 be a no-effect level? I mean I -- that's why I think
15 that they didn't do what you said that they did.

16 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I'll
17 have to check that.

18 PANEL MEMBER BLANC: I think they might have
19 had some different exposure levels.

20 OEHHA STAFF TOXICOLOGIST WINDER: Levels,
21 yeah.

22 CHAIRPERSON FROINES: And the problem is, this
23 is a very important issue, I think.

24 And we don't know to what degree there's
25 accommodation at very low levels. And so that you --

1 actually, the first time you see something, you're not
2 necessarily -- it's not a pure exposure that would bang
3 you hard.

4 So this design is troublesome, to say the
5 least.

6 PANEL MEMBER HAMMOND: Well, in some -- you
7 know, there's an odor accommodation that people have.
8 But usually irritation is cumulative. And so another
9 reason that, if this were the study design as
10 described, that it would be peculiar is that you'd
11 almost have to look at the area under the curve because
12 of how irritation works as distinct from what the
13 actual level is.

14 And then I guess the other issue in terms of
15 how we translate that to be important for air pollution
16 is that we're talking about much longer periods of time
17 than the 40 minutes so that the irritation, if it's
18 cumulative, you could start having irritation two
19 hours, and that wouldn't be appearing at a particular
20 level.

21 OEHHA STAFF TOXICOLOGIST WINDER: Okay. Now
22 with respect to the eight-hour study, this is by
23 Dorman, et al. It's a 2008 study. They're doing whole
24 body exposure of rats, various levels between .02 and
25 1.8 ppm, for six hours per day, five days per week for

1 65 days. This is a fairly standard protocol for
2 acrolein in rats.

3 They're looking at lesions in respiratory
4 epithelium. And from this study, they report a LOAEL
5 of .6 ppm and a NOAEL of .2. This is the reason we
6 used this study, was that this was one of the first
7 studies that actually reported a NOAEL. As you see,
8 it's about three-fold below the LOAEL.

9 So from this, we extrapolate an eight-hour
10 equivalent 71 ppb. That's where we take the .2 NOAEL.
11 We convert it to continuous exposure, six hours in 24,
12 and the 5/7 makes it the entire week.

13 20 over 10 is the factor that converts it back
14 to the eight-hour exposure. That's the breathing rate,
15 the idea being that individuals working breathe at
16 faster rates. They're consuming about, in their
17 eight-hour exposure, ten of the cubic meters that a
18 resting person would consume -- of the 20 that a
19 resting person would consume in 24 hours.

20 CHAIRPERSON FROINES: Did they look -- this is
21 a 2008 study, so it's relatively modern by comparison.
22 Did they look at other immunological or biochemical
23 markers as -- in other words, they're using lesions in
24 the respiratory epithelium, but were there other --

25 PANEL MEMBER BLANC: Endpoints.

1 CHAIRPERSON FROINES: -- in vitro endpoints,
2 if you will, that were -- that may have been relevant?
3 Because this is a, you know, it's a club. Lesions in
4 respiratory epithelium.

5 OEHHA STAFF TOXICOLOGIST WINDER: This --

6 CHAIRPERSON FROINES: You might be seeing
7 something else of significance if one had looked.

8 OEHHA STAFF TOXICOLOGIST WINDER: They're
9 looking here -- they looked at some gross effects,
10 things like body weight, this kind of stuff, but the
11 rest of it is a histopathological evaluation of
12 sections through the respiratory system.

13 There's no other biochemical endpoints to
14 which you refer as far as I can --

15 CHAIRPERSON FROINES: Is this an academic
16 study?

17 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

18 PANEL MEMBER BLANC: What --

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: I'm sorry. It's EPA and Hamner Institute.

21 CHAIRPERSON FROINES: So it's not an academic
22 study.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: No.

25 OEHHA STAFF TOXICOLOGIST WINDER: Oh, I see

1 what you're saying. Yeah.

2 So given that, we use this to derive a human
3 concentration since this is a study which is done in
4 animals. We take that 71 ppb and multiply it by our
5 dosimetric adjustment factor of .85.

6 This was -- this factor as we describe in the
7 document is derived from studies in modeling
8 formaldehyde. We feel that, given the behavior of
9 acrolein relative to formaldehyde, this is probably a
10 reasonable thing to use although we will apply an
11 uncertainty factor later.

12 Since there was no -- since there was a NOAEL
13 observed, there was no LOAEL uncertainty factor.

14 The study was subchronic, which is less
15 than -- there was only 8 to 12 percent of the lifetime
16 of the animal.

17 Since this is in rats, we're using
18 intraspecies toxicokinetic factor. Here we're using 2
19 for the dosimetric adjustment factor.

20 In terms of intraspecies toxicodynamics, we're
21 using the square root of ten for just individual
22 variation. And again, we have that intraspecies
23 toxicodynamic factor 10 for the asthma exacerbation of
24 children.

25 So this gives a cumulative uncertainty factor

1 of 200 and an eight-hour REL of 70. Or, excuse me, .7
2 micrograms per meter cubed.

3 Now to support this, we have these two studies
4 by Kutzman and Feron. These are whole body rat
5 studies, very similar with respect to design to the
6 Dorman study. Again they're looking at lesions and
7 respiratory epithelium, and both studies came up with a
8 LOAEL of .4 ppm. There was no NOAEL reported in either
9 of these studies.

10 So we do the extrapolation to eight hours in
11 the same fashion as before. We come up with 143 parts
12 per billion. And again, the -- this is converted to a
13 human concentration of 122.

14 Now, we're applying here an uncertainty factor
15 of 3 for this LOAEL-to-NOAEL conversion, and this is
16 based on the Dorman study in that the NOAEL they
17 observed was about three-fold lower than the LOAEL. So
18 we're going to assume that this is likely to be what's
19 going on in these studies as well.

20 So I gave this an uncertainty factor of 3.
21 Again for intraspecies toxicokinetics, we're using 2
22 for the dosimetric adjustment factor in case there's
23 some residual differences between acrolein and
24 formaldehyde.

25 Intraspecies toxicodynamic factor square root

1 of 10. This is the default for these sorts of things.
2 And then again, 10 for the toxicodynamics with respect
3 to asthma exacerbation in children.

4 So this gives a cumulative uncertainty factor
5 of 600 and an eight-hour REL of .46. So this is a
6 little bit lower than the .7 of the Dorman study but
7 right in the same general area.

8 Now for the chronic study and the REL --

9 PANEL MEMBER BLANC: Can I just ask a
10 question.

11 OEHHA STAFF TOXICOLOGIST WINDER: Sure.

12 PANEL MEMBER BLANC: In terms of benchmark
13 approach, given the recent nature of the animal data
14 doesn't allow you to do that?

15 OEHHA STAFF TOXICOLOGIST WINDER: And the
16 reason is that in the Dorman study they went from 0
17 response, 0 animals in 12, to full 12 out of 12. So we
18 don't really have a dose response curve.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: It doesn't fit any of the models well because
21 of the --

22 PANEL MEMBER BLANC: And suppose you combined
23 the animal data from Dorman with the animal data from
24 the supporting studies, and the endpoint of epithelial
25 lesions is all the same: Would that allow you to do

1 benchmark estimation?

2 OEHHA STAFF TOXICOLOGIST WINDER: I'm not sure
3 how we could do that.

4 PANEL MEMBER BLANC: Well, you'd take them as
5 if they were all one study.

6 OEHHA STAFF TOXICOLOGIST WINDER: Right.

7 PANEL MEMBER BLANC: They're all whole body,
8 rat/rodent exposures with the same endpoint, aren't
9 they?

10 Or alternatively, is there the same problem
11 with the other study where it goes from 0 to 100
12 percent effect, there was no no-effect level, but at
13 the .4 low-effect level were all the animals -- did all
14 the animals have lesions?

15 OEHHA STAFF TOXICOLOGIST WINDER: I believe
16 that's not the case. I don't think they all did. But
17 again, I'd have to check the study to see what sorts of
18 individual data are presented there to be able to --

19 PANEL MEMBER BLANC: And did all the animals
20 have lesions in that study at the equivalent .6
21 low-effect level of the Dorman study?

22 OEHHA STAFF TOXICOLOGIST WINDER: I don't
23 think that level was actually part of their collection,
24 but again, I'm not sure at what point all animals did.

25 PANEL MEMBER BLANC: Again, because we're

1 dealing with the issue of being public
2 health-protective and because, although they're within
3 the same order of magnitude, the other studies would
4 give you a level that was more than half as low, again,
5 .7 versus .2 parts per million, something like that.

6 Perhaps going -- if the data, the combined
7 data, would allow you to do the benchmark, at least as
8 a sensitivity analysis, it might reassure you.

9 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, we
10 could take a look at that. Like I said, I'm not sure I
11 could do that kind of benchmark with the combined
12 studies. Might be worth looking at.

13 PANEL MEMBER BLANC: Maybe Stan has a comment
14 on why that would or would not be acceptable.

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
16 SALMON: It does depend on the extent to which the data
17 from the different studies are actually comparable.
18 We'd have to look at it and see whether we could tease
19 out, you know, something that could be used as a
20 response parameter which would be reasonably comparable
21 across all studies, so we could look at that.

22 PANEL MEMBER BLANC: Well, the response
23 parameter clearly is comparable, which is epithelial
24 lesions.

25 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

1 SALMON: It's also a question how the data were
2 reported numerically.

3 PANEL MEMBER BLANC: Yeah, okay.

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: So there are a lot of issues and problems
6 about combining data across studies which is why it's
7 not usually done. I'm not saying it's impossible. I'm
8 just saying it's something which is not usually done
9 for that reason, but we could certainly look at it and
10 see what happens if we did it.

11 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, the
12 Dorman study, we get into much more detail in terms of
13 where in the respiratory track the lesions occur. This
14 is a much more meticulous assay.

15 I don't know that the other two studies really
16 did that sort of thing, and so there's some question
17 about, well, what areas do you compare and which areas
18 are appropriate for this.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: We'll look.

21 PANEL MEMBER BLANC: Thanks.

22 PANEL MEMBER GLANTZ: That's what I think.

23 That's -- they said what I would have said.

24 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So
25 again, the chronic REL is based on the Dorman study as

1 well. Excuse us while we scan.

2 Once again, the same LOAELs and NOAELs. The
3 time adjustment here is to 36 ppb, because it's now a
4 chronic study as opposed to eight-hour, which gives us
5 a human concentration of 30 parts per billion.

6 CHAIRPERSON FROINES: I'm still concerned
7 about what the dose pattern looked like, so if you
8 could send me an e-mail that says this is what they
9 did, that would be --

10 OEHHA STAFF TOXICOLOGIST WINDER: In the
11 Dorman study or --

12 CHAIRPERSON FROINES: Yeah. Because this
13 notion of going from .02 to 1.8 --

14 OEHHA STAFF TOXICOLOGIST WINDER: That -- his
15 dose there included the .2 -- .02, .06, .2, .6 and 1.8.
16 So he has those five discrete levels in the Dorman
17 study.

18 PANEL MEMBER FRIEDMAN: Could you again define
19 DAF?

20 OEHHA STAFF TOXICOLOGIST WINDER: That's
21 dosimetric adjustment factor. It takes the place of
22 the regional gas dose factor in trying to make
23 comparisons between rodents and humans.

24 So this was based on studies and modeling in
25 rats of formaldehyde and how that compares to humans.

1 Okay. So we have no NOAEL here. I mean no
2 NOAEL-to-LOAEL conversion factor.

3 Again, the subchronic studies scored a 10 to
4 the dosimetric factor, and same uncertainty factors for
5 the interspecies and intraspecies toxicodynamics.

6 So this gives us a chronic REL of .35
7 micrograms per meter cubed which is half of the
8 eight-hour.

9 We used the same studies as previously as
10 supporting studies. Again, it's the same uncertainty
11 factors. The only difference here is the time
12 adjustment, brings us to 71 parts per billion. Human
13 concentration of 60. We're using the LOAEL uncertainty
14 factor, again for the reasons mentioned before.

15 And as you see here, 2 for DAF, squared 10 for
16 interspecies toxicodynamic, 10 for intraspecies
17 toxicodynamic. And UF 600 which gives us a chronic REL
18 of .10. The Dorman study gives us .35. So we consider
19 this to be sufficiently close to be supportive.

20 CHAIRPERSON FROINES: And the reason for
21 choosing that as the supporting study rather than as
22 your primary value?

23 OEHHA STAFF TOXICOLOGIST WINDER: It was the
24 fact that the Dorman study, the critical study is the
25 one that gave us an observed NOAEL. These studies did

1 not. They only came up with LOAELs.

2 PANEL MEMBER BLANC: And I just want to
3 correct something I said earlier. I was a little
4 confused about the closeness of the two estimates. I
5 was confusing them with microgram values so, you know,
6 I acknowledge that the -- either way, you come to
7 LOAELs that are close.

8 But I still would urge, if you can, if you
9 feel comfortable that the data will allow benchmark
10 dosing. And I think that would also be consistent with
11 your generic guidelines approach.

12 And one other thing I might suggest in terms
13 of the acute eye irritation effect is a double-check of
14 the occupational literature just to be sure that there
15 aren't some supporting data there in terms of eye
16 irritation.

17 And I've obviously done a review of the
18 peer-reviewed literature, but one thing I'm thinking of
19 is a quick check of the NIOSH health hazard evaluation
20 database because they did have a tendency to once in a
21 while measure acrolein with industrial hygiene
22 sampling. It's probably a more relevant comment to
23 formaldehyde, but --

24 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

25 CHAIRPERSON FROINES: I would, frankly, worry

1 about those studies, Paul.

2 PANEL MEMBER BLANC: Well, I mean if they --
3 what they -- what you'll find in a health hazard
4 evaluation is that they'll say, you know, 30 percent of
5 the people reported eye irritation, but our measured
6 level was only five parts per billion which is too low
7 to cause that finding. But --

8 OEHHA STAFF TOXICOLOGIST WINDER: See what it
9 is, yeah.

10 CHAIRPERSON FROINES: But I bet that they use
11 DMPH, which doesn't work. I bet that they don't have a
12 method that anybody would consider adequate at this
13 point in history.

14 So it's worth looking at, but I must admit a
15 certain degree of skepticism.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: We have some slides on the public comments on
18 acrolein, so we can go through those.

19 CHAIRPERSON FROINES: Please.

20 OEHHA STAFF TOXICOLOGIST WINDER: So most of
21 these were submitted by the American Forest & Paper
22 Association.

23 They brought to our attention the Dorman --
24 excuse me -- the Schroeter studies that are listed up
25 here. Struve was looking at the efficiency of acrolein

1 uptake in nasal epithelium in rats, a function of level
2 of exposure to acrolein and whether or not the rat had
3 been previously exposed.

4 Schroeter is basically a modeling study based
5 on the work out of Dorman 2008. What Schroeter does is
6 he applies this fluid dynamics model to try to predict
7 nasal dosimetry, and he subsequently calculates an RFC
8 based on that research.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: I should point out that when these were
11 submitted, some papers had been accepted, some only
12 submitted. So they were pre-publication studies in
13 November. They have since been published.

14 CHAIRPERSON FROINES: All three?

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Yes.

17 CHAIRPERSON FROINES: Have been published.

18 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So we
19 reviewed these and as you saw we ended up using the
20 Dorman study for our chronic and eight-hour RELs.

21 The Schroeter study, as I mentioned, tried to
22 calculate an RFC. Now, what they did here is looked at
23 neuronal loss and at what levels of acrolein exposure
24 this occurred. They also looked for respiratory
25 lesions. And they found that these two endpoints

1 differed in the level at which it occurred.

2 Now they argued for using a .6 ppm level NOAEL
3 for this as a basis for a REL -- excuse me -- an RFC
4 calculation. The argument was that this occurred at a
5 lower tissue dose than did the respiratory lesions,
6 even though the lesions occurred in a lower -- in
7 respiratory epithelium occurred in lower applied dose.

8 For this reason, we rejected the use of this
9 because in -- for REL determination, it's not the
10 tissue dose that's really important. What's important
11 is at what level the applied dose is we have the
12 effect. So we have not used the Schroeter for that.

13 And the Struve study, she was finding that the
14 uptake efficiency of acrolein in the upper respiratory
15 tract increased with low level exposure -- previous
16 exposure. As the level of acrolein went down, the
17 efficiency of absorption went up. This is perhaps some
18 import with respect to low level chronic exposures.

19 CHAIRPERSON FROINES: Has anybody looked at
20 how the lungs shut down when you have acrolein
21 exposure? Because that clearly is going to change your
22 dosimetrics.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
24 MARTY: Pretty sure there is an RD50 with the Alarie
25 method on acrolein in rodents, so we would be looking

1 at as far as frequency in a rodent.

2 CHAIRPERSON FROINES: And --

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: And I can't remember the number. But we did
5 look at that. In fact, we -- George and I were looking
6 at a paper getting acute RELs out of these RD50s
7 because there is a number of them.

8 So, but I -- I'm not remembering where it was.

9 PANEL MEMBER BLANC: I have a couple generic
10 questions.

11 One is spurred by your addressing the 2008
12 studies, which I think you should be commended for.
13 Obviously, writing these kinds of documents can't be a
14 never-ending, iterative process where you have to keep
15 changing it every time. New studies come out through
16 the entire process.

17 But I do think it would be helpful for you to
18 state explicitly for each of the RELs in question what
19 is the cutoff date for the literature which is
20 reviewed.

21 In other words, we've reviewed literature
22 through April 1st, 2008, you know, published
23 literature. This is going to become particularly
24 relevant to the manganese, but clearly it's relevant
25 here.

1 And just for transparency's sake, I just think
2 it's important to say what that date is.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
4 MARTY: Okay. We probably could that for the public
5 review draft; but the truth is, we keep looking as the
6 process goes and --

7 PANEL MEMBER BLANC: Well, then, say whatever
8 that date is.

9 PANEL MEMBER HAMMOND: When it's finished, you
10 might want to say that.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
12 MARTY: That makes sense, for the final draft, up to --

13 PANEL MEMBER BLANC: Right.

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: Okay.

16 PANEL MEMBER BLANC: And then the other
17 question has to do with the toxicokinetic adjustment
18 for eye irritation. Is there any generic issue with
19 wearers of contact lenses and exposure to ocular
20 irritants since there is a substantive subset of the
21 population that uses contact lenses?

22 OEHHA STAFF TOXICOLOGIST WINDER: That's an
23 interesting point. I don't know.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
25 MARTY: That's an interesting point. I don't know.

1 PANEL MEMBER BLANC: I mean that was only
2 applicable to acute RELs related to ocular irritation
3 endpoint.

4 OEHHA STAFF TOXICOLOGIST WINDER: I have not
5 seen any studies on that.

6 PANEL MEMBER HAMMOND: There actually is some
7 literature on that. I know that in chemistry
8 laboratories they worry about it.

9 So I can't point you to it, but to say that's
10 one of the areas, and I think that sometimes they worry
11 about which things can be concentrated, there's been
12 some concern about the concentration under the lens.
13 That's a very good point.

14 PANEL MEMBER BLANC: And it would be a
15 toxicokinetic rather than toxicodynamic issue, right?

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: Yeah, we would consider that a kinetic issue.
18 That's a really good point.

19 PANEL MEMBER BLANC: How many of these -- this
20 one is ocular. Wasn't there another one that was an
21 ocular one? Is this the only ocular one? Is
22 formaldehyde also ocular?

23 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I
24 guess both acetaldehyde and formaldehyde have ocular
25 concerns.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yeah.

3 PANEL MEMBER BLANC: And I think that it's
4 worth commenting on, even if there are no data
5 available and you didn't do an adjustment. We'd be
6 saying we did not take them into account.

7 PANEL MEMBER HAMMOND: I think if you are
8 going to go there, I would not say there's no
9 literature but rather do check carefully that
10 literature --

11 PANEL MEMBER BLANC: Yeah.

12 PANEL MEMBER HAMMOND: That may not be
13 specific to this chemical, but it at least talks about
14 how to think about it.

15 PANEL MEMBER BLANC: With irritants in
16 particular. That's where it's an irritant-related --
17 we were -- John, we were talking about contact lenses,
18 contact lenses as a toxicokinetic modifier of ocular
19 irritant chemical effects.

20 CHAIRPERSON FROINES: Are we ready to move on?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: Yep.

23 CHAIRPERSON FROINES: Formaldehyde or
24 manganese? Oh, formaldehyde. Formaldehyde is our rock
25 of Sisyphus, isn't it?

1 PANEL MEMBER BLANC: I think it's more our
2 Stygian stables.

3 CHAIRPERSON FROINES: What?

4 PANEL MEMBER BLANC: I think of it more as our
5 Stygian stables.

6 (Laughter)

7 OEHHA STAFF TOXICOLOGIST WINDER: That said --

8 CHAIRPERSON FROINES: And that was a joke, for
9 the Formaldehyde Institute. We are taking this very
10 seriously.

11 OEHHA STAFF TOXICOLOGIST WINDER: Okay, so for
12 formaldehyde, as was pointed out, this is based on
13 ocular irritation for the acute REL in humans. REL is
14 estimated at 55 micrograms per meter cubed.

15 For the eight-hour and the chronic, these two
16 numbers are 9 micrograms per meter cubed, and they are
17 based on both ocular irritation as well as nasal
18 obstruction and lower airway discomfort in humans.

19 So first study the -- for the acute REL is
20 based on Kulle. 19 humans were exposed for three hours
21 in this range of concentrations, and they are reporting
22 subjective ocular irritation at the endpoint.

23 This study was selected because it was
24 possible from the data to calculate a benchmark dose of
25 .44 ppm. Now we have here -- again, since the study is

1 in humans, there are no interspecies uncertainty
2 factors.

3 We have the intraspecies toxicodynamic factor
4 of 10 for potential asthma exacerbation in children.
5 This gives us a cumulative uncertainty factor of 10 and
6 an acute REL of 55.

7 Now with respect to that use of the 10 as the
8 toxicodynamic factor based on asthma, I would mention
9 this issue here. From our occupational studies, the
10 average LOAEL reported for the formaldehyde is 75 parts
11 per billion. However, the child study or study of
12 children by Krzyzanowski saw effects at 30 parts per
13 billion as well. This is about a 2.5-fold difference
14 between the two values we see here.

15 Now, if you look at the hospitalization rate
16 for asthma in children -- this is from CDC for 2004 --
17 infants in the 0-to-4-year range have a hospitalization
18 rate of 60 per 10,000 whereas adults older than 18
19 years old have 14 per 10,000. So this is about a
20 4-fold difference here.

21 And the combination of these two factors gives
22 us roughly 10.

23 Now, what we're saying here is that this is
24 based on the idea that mainly the studies find symptoms
25 of asthma-like -- well, find asthma-like symptoms in

1 children, and that these symptoms are exacerbated by
2 exposure to formaldehyde.

3 As I mentioned a little earlier, one of the
4 other considerations is that exposure to formaldehyde
5 often occurs in the presence of acrolein, acetaldehyde,
6 and other compounds. One of the things that Cassee
7 reported that's also included in this REL document is
8 that lesion severity is increased during co-exposure.

9 Now there's an interesting thing with
10 formaldehyde and acrolein competing for similar
11 receptors. So with formaldehyde and acrolein in the
12 presence of acetaldehyde, they tend to potentiate the
13 effects of acetaldehyde. This is part of the
14 consideration for that 10.

15 Now our eight-hour REL --

16 CHAIRPERSON FROINES: Why would you call it
17 potentiate? Potentiate is five plus zero is ten.

18 OEHHA STAFF TOXICOLOGIST WINDER: Maybe I
19 should say exacerbate.

20 CHAIRPERSON FROINES: I don't think potentiate
21 is the correct toxicologic term.

22 OEHHA STAFF TOXICOLOGIST WINDER: That's a
23 good point. Perhaps I should say exacerbate here
24 because what the Cassee study showed was the
25 acetaldehyde, I believe it was concentrated up about 10

1 micrograms per cubic meter had no reported effect.
2 However, that level of acetaldehyde in the presence of
3 similar levels of acrolein and formaldehyde did have an
4 effect.

5 So that's the reason for using potentiate.
6 But I think you're right; exacerbate might be a more
7 accurate term.

8 PANEL MEMBER GLANTZ: Yeah, that seems right
9 to me.

10 PANEL MEMBER HAMMOND: That is potentiate,
11 isn't it?

12 CHAIRPERSON FROINES: No. Potentiation is
13 when you have no toxicity with one compound and
14 toxicity in another, and the two give you an increased
15 risk.

16 PANEL MEMBER HAMMOND: It can't be too small?
17 I thought it was --

18 PANEL MEMBER GLANTZ: I always thought
19 potentiate meant that there's basically an interaction
20 so you could have two things, both of which have an
21 effect, that when together --

22 CHAIRPERSON FROINES: No. Potentiation is
23 defined as one substance having no effect.

24 PANEL MEMBER GLANTZ: By itself.

25 CHAIRPERSON FROINES: By itself. Methyl ethyl

1 ketone and hexane. Classic example. Hexane is the
2 toxin, MEK is benign. MEK is a potentiator.

3 PANEL MEMBER BYUS: Synergy is when they both
4 have them at low levels, and together they're greater
5 than the additive effect. That's synergy.

6 PANEL MEMBER GLANTZ: In physiology,
7 potentiate is different.

8 PANEL MEMBER BLANC: Probably.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: Okay.

11 PANEL MEMBER BLANC: But that's why we say
12 toxin and he says toxicant.

13 PANEL MEMBER HAMMOND: Oh, that's why.

14 (Laughter)

15 CHAIRPERSON FROINES: Onward.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: Okay.

18 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So
19 for the eight-hour study -- eight-hour REL, excuse
20 me -- the critical study is this occupational study by
21 Wilhelmsson and Holmstrom. This involved 66 adults,
22 six hours per day, five days per week for an average of
23 10 years. The range was over 36 years.

24 Again, they were looking at ocular irritation
25 as well as nasal obstruction and lower airway

1 discomfort.

2 The NOAEL in this study was .09. This is
3 based on the reference group. And the LOAEL reported
4 was .26 mgs per meter cubed. Since this is a human
5 study, again, there's no interspecies uncertainty
6 factors. And we include the 10 here for toxicodynamic
7 intraspecies uncertainty.

8 This gives a cumulative uncertainty factor of
9 10 and eight-hour REL of 9 micrograms per meter cubed.

10 Now in support of this is a study by
11 Swiecichowski of guinea pigs. These animals were
12 exposed for eight hours, whole body exposure, to the
13 concentration shown here of .11 to 1.05 ppm.

14 And the endpoint here was increased pulmonary
15 resistance.

16 A NOAEL was reported of .59 with a LOAEL of 1.

17 Now here we had to use the regional gas dose
18 ratio of .826, to give us the human equivalent
19 concentration of .49 parts per million.

20 Next slide, please.

21 CHAIRPERSON FROINES: Can I ask you a
22 question? And I'm a little bit off all day today. I
23 apologize for that.

24 What are the implications of this eight part
25 per billion REL if you were setting an OSHA standard

1 for workers? Is this a standard you should set?

2 PANEL MEMBER BLANC: No, the standard should
3 be --

4 PANEL MEMBER HAMMOND: Uncertainty for
5 children. This has uncertainty for children.

6 CHAIRPERSON FROINES: Well, would be 10.

7 Okay, so you set a standard of 80 parts per billion.

8 PANEL MEMBER BLANC: No, because there's no --
9 you don't care about at-risk people with an
10 occupational standard. It's usually a hundred times
11 higher than --

12 PANEL MEMBER HAMMOND: More.

13 PANEL MEMBER BLANC: At least. I don't --
14 actually, it's an interesting philosophical discussion,
15 but I don't think we --

16 CHAIRPERSON FROINES: Well, let's let it go,
17 but I don't agree with what you said.

18 PANEL MEMBER BLANC: No, I'm not saying it
19 should be that way. I'm just telling you that in
20 fact --

21 CHAIRPERSON FROINES: I understand that's the
22 way it is.

23 PANEL MEMBER BLANC: Right.

24 CHAIRPERSON FROINES: But I'm saying that when
25 you find effects like this, then you need to consider

1 how protective your existing standard, which is .1 part
2 per million. And this is obviously not protective of a
3 worker at one part per million given this data, so
4 that's the reason I asked the question.

5 Go ahead.

6 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So
7 the -- this is -- gives us a chronic REL -- oh, I'm
8 sorry.

9 The chronic REL is now based on the same
10 study, obviously same endpoints, LOAEL, NOAEL, et
11 cetera, and gives us a chronic REL of 9. Same for the
12 eight-hour.

13 And then looking at this, looking at the
14 Rumchev et al., this is a study in children both
15 asthmatic and nonasthmatic, and these were kids who
16 were exposed at home.

17 And the endpoint here, asthma-related
18 respiratory symptoms.

19 From this study, we estimated a NOAEL of 30
20 and a LOAEL of 60 micrograms per meter cubed.

21 Here we have an interspecies toxicodynamic
22 factor of square root of 10. The reason for instead of
23 10 is that the study was actually done in children.

24 So this is also our cumulative uncertainty
25 factor, and the chronic REL becomes 10 micrograms per

1 meter cubed which is supportive of the 9 from the
2 previous study.

3 Now, I did mention the eight-hour chronic RELs
4 were the same. The reason for this is that a number of
5 studies in rodents giving near-continuous exposure
6 versus those giving this kind of intermittent exposure,
7 six hours a day, five days a week.

8 When they look at similar endpoints, in this
9 case basal cell metaplasia, squamous cell hyperplasia,
10 they're seeing pretty much the same sorts of effects.

11 Now what this, from the authors, are taking
12 this to is the concentration of formaldehyde exposures
13 tend to be more important than the continuity of
14 exposure.

15 And in addition, there are studies that
16 suggest that individuals may become sensitized to
17 formaldehyde even with relatively short intermittent
18 exposures. This is based on a study by Sorg et al.
19 2001.

20 None of this is to say the duration is totally
21 unimportant because long-term exposures may cause
22 lesions at low levels. And these are supported by
23 studies, again mostly in rats, Kerns and Kamata.

24 PANEL MEMBER BLANC: Can you go back to the
25 asthma/nonasthma study, supportive study, for a second?

1 OEHHA STAFF TOXICOLOGIST WINDER: This one?

2 PANEL MEMBER BLANC: Yeah. So Rumchev was
3 looking at children exposed at home and looking at the
4 level at which the asthmatic children had effects, had
5 symptoms --

6 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

7 PANEL MEMBER BLANC: -- compared to the
8 nonasthmatic?

9 OEHHA STAFF TOXICOLOGIST WINDER: They tended
10 to occur at lower levels, yes.

11 PANEL MEMBER BLANC: Right. Now the Rumchev
12 study was not looking at levels of formaldehyde that
13 cause asthma?

14 OEHHA STAFF TOXICOLOGIST WINDER: No. This is
15 just a report of symptoms.

16 And the reason we didn't use this study for
17 our REL determination is that asthma symptoms in
18 children are kind of a squishy sort of diagnosis. It's
19 hard to come up with a clear diagnosis of --

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
21 MARTY: These kids were six months to three years old.

22 PANEL MEMBER BLANC: But wouldn't this study
23 be actually relevant not to the chronic effect but to
24 your acute REL?

25 Because, in fact, you're not arguing that it

1 was the chronic exposure to formaldehyde that caused
2 them to have asthma. You're saying if you have asthma
3 and you're exposed to formaldehyde at this level,
4 you're going to have more respiratory symptoms. That's
5 an acute effect.

6 OEHHA STAFF TOXICOLOGIST WINDER: There are
7 some issues associated with trying to use this in acute
8 context with respect to the exposure assessment.
9 That's part of the problem here in terms of what are
10 the kids actually seeing over what period of time.

11 The thing does not delineate how much time the
12 children were spending in these individual
13 environments.

14 Again, as I mentioned there's a little problem
15 with the diagnosis of and quantification of
16 asthma-related symptoms in children. It's not real
17 clear exactly all cases were asthma-related or not.

18 PANEL MEMBER BLANC: Well, let's just say it's
19 respiratory symptoms in kids with asthma. Do people
20 see where I'm going here? It's a little confusing to
21 me.

22 PANEL MEMBER HAMMOND: Let me ask -- there's
23 an assumption here, but I'd like to clarify: Were
24 there no effects whatsoever on the 104 nonasthmatic
25 children? Is that true? In that study?

1 OEHHA STAFF TOXICOLOGIST WINDER: I think in
2 this study it was pointed out the asthmatic children
3 tend to be more responsive at lower levels. I believe
4 there were children of the 104 that responded. I can't
5 tell you right offhand at what level.

6 PANEL MEMBER HAMMOND: I mean you have
7 multiple things going on. You have two different
8 populations of children, you've got multiple kinds of
9 symptoms, and the exposure is not an exposure chamber.

10 You could look at what level -- I mean they're
11 exposed at home. If these are very young children, you
12 said under age three, they are likely to be in the home
13 most of the time. So that you probably are talking
14 about more or less continuous.

15 But the question might be how long the
16 exposure was evaluated. If it was an eight-hour
17 sample, one-hour sample, one-week sample? So how
18 stable is that exposure estimate as well?

19 But I would think that the asthma-related
20 respiratory symptoms -- I would not discount those. I
21 would think that those are pretty serious outcomes.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Yeah, we're not discounting those at all.

24 Two issues. First of all, when you do look at
25 that study and generate a REL, you're a tiny bit higher

1 than the one we generated, so --

2 PANEL MEMBER BLANC: For chronic. But you're
3 in fact quite a bit lower than your acute REL.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: Right. But these were not chronic exposures.

6 What they did was they went in a couple of
7 times during a single year and measured formaldehyde in
8 the homes. Then they looked at, they stratified by
9 bins of formaldehyde concentration and then looked at
10 the lowest bin versus the highest bin and what was the
11 relative risk of asthma, asthma-like symptoms --

12 PANEL MEMBER HAMMOND: Symptoms.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
14 MARTY: -- in the kids. And it was higher in kids in
15 the higher formaldehyde homes.

16 So it really is not looking at acute exposure.
17 It really is looking at chronic exposure, although
18 they're snapshots in time.

19 PANEL MEMBER HAMMOND: And also they don't
20 really have NOAELs in that case.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: That's right. And it doesn't mean there were
23 no asthmatic kids in the lower formaldehyde homes.
24 That's not what it means.

25 PANEL MEMBER HAMMOND: The way you just

1 described it is the comparison of the rates of having
2 the symptoms in the highest and lowest probably tercile
3 or something, the data. But that's not a NOAEL.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Right. That's not a NOAEL. So it's not very
6 easy to use this kind of study.

7 PANEL MEMBER HAMMOND: What were the bins?

8 What were those bins? And were they terciles?

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: They were -- what we did was looked at the ORs
11 reported for -- the bins were 10 to 29 micrograms per
12 cubic meter, 30 to 49, and those are not elevated yet.
13 50 to 59, then you're getting an elevated OR of 1.2,
14 although it's not -- it includes 1. And then 60-plus
15 which is statistically significant OR of 1.4 in the
16 lower boundary above 1.

17 So we took that bottom range of the bin where
18 there was no elevation yet in risk -- asthma symptoms
19 as the NOAEL. That's where that comes from.

20 PANEL MEMBER HAMMOND: But that's not quite
21 the same thing, is it?

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: It's not nice and neat like an animal study
24 where you have no observed effect. It's not --

25 PANEL MEMBER HAMMOND: Right. Because you

1 could certainly have differences in susceptibility of
2 people who have asthma, children who have asthma, under
3 different ages in the group, and so the lowest bin and
4 the next lowest bin don't have a difference in the
5 response, but they might still -- they might each have
6 had 15 percent or 20 percent of the children
7 responding, having symptoms, which could be due to
8 other things. But it's very hard at that point to say
9 that's a NOAEL.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: They also adjusted for things like family
12 history of asthma, age, gender, SES, and so forth, so
13 it's actually a relatively well-conducted study. But
14 it was in Australia which has very high rates of asthma
15 for some reason.

16 PANEL MEMBER BLANC: Since we're talking about
17 asthma, the issue of formaldehyde as a potential
18 sensitizer, which is a pretty murky literature, and the
19 exposure level at which asthma might -- formaldehyde
20 might induce asthma or be an adjuvant for sensitizing
21 allergens: How do you begin to deal with that in the
22 sort of --

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: Yeah. As you note, it is a murky literature.
25 And still, I think the prevailing opinion is that you

1 need a high episodic exposure to formaldehyde to get
2 sensitized. And that comes primarily from occasional
3 setting.

4 There are studies that show concentrations of
5 formaldehyde are associated with asthma symptoms, and
6 then there are chamber studies that used adult, mild
7 asthmatics that didn't see an exacerbation of asthma
8 even at three parts per million.

9 So I don't know if it's a sort of a difference
10 in the way they're measuring respiratory symptoms in an
11 epi-style study versus a chamber. You know, we don't
12 put severe asthmatics in a chamber. You usually don't
13 even put moderate asthmatics in a chamber.

14 So it's hard to really feather out the
15 contribution of formaldehyde-specific sensitization
16 versus the irritant properties of formaldehyde in terms
17 of whether or not the person has asthma or is
18 experiencing an exacerbation.

19 PANEL MEMBER PLOPPER: I think it was a good
20 idea not to use this study to base things on because
21 some of the measurements varied within rooms and times,
22 and you -- this is not anything you can use as an
23 exposure because it may just be the short period of
24 time at very high concentration that produces the
25 problems. It's not a good study.

1 PANEL MEMBER BLANC: And is there any data
2 that's emerged from the FEMA trailer -- you know, does
3 CDC have any data? I mean I know they've been
4 gathering data recently on --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: I don't think they have --

7 PANEL MEMBER BYUS: -- exposure-related
8 symptoms --

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: -- conclusory -- or I don't think they have a
11 report that concludes that they exacerbated asthma in
12 any children or -- you know, it's my understanding that
13 they're still looking at that.

14 PANEL MEMBER BLANC: I meant more just
15 generically symptom-related dose response with that.

16 CHAIRPERSON FROINES: Do you have any idea
17 what levels we are talking about?

18 PANEL MEMBER HAMMOND: They were much higher.

19 PANEL MEMBER BYUS: Were they?

20 PANEL MEMBER HAMMOND: Yeah, they were much
21 higher than this.

22 PANEL MEMBER BLANC: Parts per million.

23 PANEL MEMBER HAMMOND: I think in the parts
24 per million range.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: They went up to -- it was a very wide range
2 that I'm recalling. It was pretty high.

3 PANEL MEMBER HAMMOND: When you look at this
4 and look at the trailers, you cringe.

5 PANEL MEMBER PLOPPER: Can we go back to this
6 issue of asthma-like respiratory symptoms? My big
7 concern with this whole section was your reliance on
8 asthma-like respiratory symptoms.

9 And I thought you addressed it better by your
10 first slide by just saying ocular irritation, nasal
11 obstruction, lower airway discomfort.

12 I think that's -- one of the concerns with
13 this is all this issue of asthma and formaldehyde is
14 just so unclear. And it doesn't affect the document
15 any. It just sort of destroys some of the credibility.

16 Right on the first page to list asthma-like
17 respiratory symptoms when the documentation is not --
18 why get nitpicky over something that doesn't matter?
19 Because you didn't use any of those studies to
20 establish these RELs, right?

21 OEHHA STAFF TOXICOLOGIST WINDER: Right.

22 PANEL MEMBER PLOPPER: So why not just change
23 that throughout the document and just -- and I would
24 also -- I think you need to list what asthma-like
25 respiratory symptoms you're talking about.

1 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

2 PANEL MEMBER PLOPPER: Because that includes a
3 whole bunch of things that aren't related to asthma but
4 you identify them in specific spots. Why not just say
5 what they are?

6 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

7 PANEL MEMBER PLOPPER: And I think you
8 addressed most of my other concerns. I thought leaving
9 those studies in Australia alone is a good idea.

10 OEHHA STAFF TOXICOLOGIST WINDER: So in this
11 context, for example, you want us to change the
12 asthma-like wording or clarify that?

13 PANEL MEMBER PLOPPER: Well, what you have
14 here is that, say formaldehyde eight-hour REL, critical
15 effects, asthma-like respiratory symptoms; and yet what
16 you've actually used and what the document relies on is
17 ocular irritation, nasal obstruction, lower airway
18 discomfort, which are or are not associated with
19 asthma-like symptoms. Why not put that in place of it?

20 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

21 Because at least in this slide for this study it would
22 just be irritation, but you're right, with respect to
23 the --

24 PANEL MEMBER PLOPPER: No, I'm talking about
25 the whole document.

1 OEHHA STAFF TOXICOLOGIST WINDER: Right.

2 PANEL MEMBER PLOPPER: The data and the
3 studies that you relied on, I thought, are probably the
4 most reliable you could get. And they're better
5 controlled.

6 And these human studies with asthma, they're
7 saying this is a whole issue that actually could be
8 besides the point. It's important, but it's not -- it
9 doesn't inform the document that much. All it does --
10 you have this over -- you go and you look at direct
11 scientific studies in here, and then you overlay it
12 with this business of asthma exacerbation, and there is
13 not really good documentation for that. It's not as
14 solid as the rest.

15 I don't -- and I circled it every time I ran
16 across it, and all it did was just detract from the
17 quality of the thing because then you say okay, where
18 is the evidence? And the evidence is not -- is still
19 highly controversial.

20 OEHHA STAFF TOXICOLOGIST WINDER: And that's
21 partly the reason for the uncertainty factor is that
22 there are studies which support it and studies, as you
23 say, which are finding different results. So that
24 uncertainty is what we're trying to capture here.

25 PANEL MEMBER PLOPPER: I got into the middle

1 of one of these discussions in a meeting once, and
2 there are as many opinions as there are people that
3 work in this area.

4 So it's sort of -- all it does is just say
5 well, it makes it less solid. It's a concern, it's a
6 major problem, but I think as an informative thing to
7 use asthma is fine but not to base the document on.

8 Does that make sense? I mean it won't change
9 much, but the wording here and there.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: So where we have asthma-like symptoms, be more
12 specific, and if it's wheezing say wheezing.

13 PANEL MEMBER PLOPPER: If it's wheezing. I
14 mean really what you base the RELs on is --

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Not that --

17 PANEL MEMBER PLOPPER: -- nasal obstruction
18 and lower airway discomfort.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: Right. Because these are the --

21 PANEL MEMBER PLOPPER: It's still --

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: That's what was measured in the studies we used
24 as a basis for the REL. We still want to argue that
25 there is a need for the tenfold toxicodynamic factor

1 for potential exacerbation of asthma.

2 PANEL MEMBER PLOPPER: We've already accepted
3 that --

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Okay.

6 PANEL MEMBER PLOPPER: -- other things as well
7 for children. I don't think that's going to make --
8 anyone that realizes that this is based on lower airway
9 discomfort is going to know that that's going to have a
10 tremendous impact on asthmatic kids.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: Make sure you --

13 CHAIRPERSON FROINES: You may need to spell it
14 out a bit more.

15 PANEL MEMBER PLOPPER: That was my other
16 thing. It needs that all the way through. Just say
17 what they are.

18 Because asthma-like symptoms, there's -- most
19 of the people that did these studies did not use the
20 guidelines that are accepted by the people who work in
21 asthma as being asthma-like symptoms, so you can't
22 compare these two. It's a different type of issue
23 altogether.

24 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Okay.

2 We have a few slides on the comments that were
3 made on the draft, so we'll go over those quickly
4 before lunch.

5 CHAIRPERSON FROINES: Please.

6 OEHHA STAFF TOXICOLOGIST WINDER: One of the
7 comments here is that the asthma induction and allergic
8 sensitization conclusions that we reached were not
9 representative of the weight of evidence in the IOM
10 2000 report or ATSDR's 1999 report.

11 Many of the studies included in our document
12 were not included in the IOM or this ATSDR review, plus
13 ATSDR does not conclude there's no evidence of
14 association between asthma and formaldehyde. It's
15 still up in the air, as this discussion sort of
16 indicated.

17 And we're saying that formaldehyde inhalation,
18 there are a number of data, number of studies which
19 support that formaldehyde inhalation alters immune
20 response to a variety of antigens, and you can get
21 hypersensitivity as a consequence. This would
22 exacerbate asthma.

23 There's a comment the IOM report concludes
24 only house dust mite antigen had sufficient evidence of
25 a causal association with childhood asthma.

1 They argue there is evidence of an association
2 between formaldehyde and asthma-like symptoms in
3 children which is what we've been discussing.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: We also didn't say there was a causal
6 association. We didn't say any of that. The commenter
7 over-read, I think. Anyway.

8 OEHHA STAFF TOXICOLOGIST WINDER: Right.

9 And the IOM report has elevated its estimation
10 of formaldehyde to a limited or suggestive evidence of
11 association with respect to asthma exacerbation.

12 Again, many of these studies that we've
13 included were not in the IOM 2000.

14 And as before, we indicated on a previous
15 slide, children tend to be more significantly affected
16 by the asthma morbidity than older children or adults.
17 They have smaller airways and as a consequence they're
18 more dramatically affected and end up in the hospital
19 more often.

20 There is a fair attempt to try to pick apart
21 the sundry studies that were included including, for
22 example -- epi studies -- including this Franklin
23 study. The commenter seemed to question: What is the
24 significance of this elevated expired nitric oxide? As
25 though we were trying to say this in fact was an

1 indication of asthma.

2 All we're saying and all the authors were
3 saying with respect to that was that the higher level
4 of expired nitric oxide indicates there's an
5 inflammatory concern with respect to the lungs. And
6 again, we just provided additional evidence that
7 formaldehyde exposure exacerbates the asthma-like
8 symptoms in children.

9 A number of limitations in all the epi studies
10 that involve children, and we tried in the document to
11 indicate those limitations. We say taken together
12 these various studies suggest and support the
13 association of formaldehyde with respiratory symptoms
14 as well as lung function in children.

15 CHAIRPERSON FROINES: I may be a minority in
16 the room and in the community, but I still think this
17 issue of expelled nitric oxide is questionable.

18 And so I would be happier if there were
19 some -- something that said further research in this
20 area is relevant.

21 OEHHA STAFF TOXICOLOGIST WINDER: Indicated --

22 CHAIRPERSON FROINES: I think that --

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: We'll add that.

25 CHAIRPERSON FROINES: -- all these clinicians

1 who look at exhaled nitric oxide and draw lots of
2 conclusions, I've always felt that the toxicokinetics
3 were not well-thought-through.

4 OEHHA STAFF TOXICOLOGIST WINDER: There is
5 still some uncertainty in this.

6 CHAIRPERSON FROINES: I don't think there is
7 any question. Paul might disagree, but I personally
8 think that there is some question.

9 OEHHA STAFF TOXICOLOGIST WINDER: We can add
10 that.

11 CHAIRPERSON FROINES: People overinterpret.

12 OEHHA STAFF TOXICOLOGIST WINDER: One of the
13 other concerns expressed by comments was that the --
14 this issue of sensory irritation testing where odor may
15 in fact influence the response.

16 And we're saying we recognize that the odor is
17 -- foul odor is an effect of exposure, but we're not
18 using odor response perception as a --

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: There's a mistake, and that's my fault, on the
21 slide. It should say we didn't use odor perception or
22 odor threshold to set an acute REL. Sorry.

23 OEHHA STAFF TOXICOLOGIST WINDER: In fact, the
24 REL was based on eye irritation instead. So.

25 The -- it was brought to our attention that

1 Lang, et al. has a new study just published of sensory
2 irritation to formaldehyde.

3 We looked at the study and discovered they
4 were reporting sensory irritation of .5 parts per
5 million. And this is consistent with what Kulle
6 reported. They had a NOAEL of .5 and LOAEL of .1, so
7 we figured this is supportive of the results so far.

8 PANEL MEMBER BLANC: I'm sorry, the line
9 before, sensory irritation at .5 to 1? What do you
10 mean?

11 OEHHA STAFF TOXICOLOGIST WINDER: I believe
12 that was a range.

13 PANEL MEMBER BLANC: But he did see irritation
14 at .5?

15 OEHHA STAFF TOXICOLOGIST WINDER: Within that
16 range.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
18 MARTY: If you look at the studies, they're trying to
19 figure out where the sensory irritation threshold is.

20 PANEL MEMBER BLANC: Yeah.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: And it's somewhere between those, .5 and 1,
23 somewhere in there.

24 PANEL MEMBER HAMMOND: Does he give a period
25 of time? Talking about irritation?

1 PANEL MEMBER BLANC: So the threshold suggests
2 that the NOAEL is no lower than .5 is what you are
3 trying to say.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: It might be lower.

6 PANEL MEMBER BLANC: Why? If he says it's
7 between -- the no-effect level is between .5 and .1?
8 Or is he saying that he saw an effect as low as .5?

9 I mean it's a critical thing because either
10 you're -- there's now data which says that .5 is not a
11 NOAEL but a LOAEL or we're not.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: Four-hour exposure is what he says was that
14 there's minimal objective eye irritation at a level of
15 .5 with peaks of 1. So --

16 PANEL MEMBER BLANC: I see. So it's really
17 hard to say.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
19 MARTY: Not sure the 1 or somewhere in between.

20 PANEL MEMBER BLANC: Couldn't control the
21 exposure.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: They didn't do a continuous exposure at the
24 same concentration. They threw in peaks.

25 PANEL MEMBER HAMMOND: Did they introduce

1 formaldehyde at set intervals? Is that what you're
2 saying?

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: The atmosphere was generated by vaporizing
5 power of formaldehyde on a magnetic hot plate stirrer,
6 and it basically looks like they didn't have what you
7 consider a steady atmosphere-generating system.

8 This was a -- you know, I think they kind of
9 threw some on the hot plate and heated it till it got
10 up to the level they wanted.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: What we'll do is put a description of this
13 study into the document. Right now we've just reviewed
14 it the responses to comments and didn't add it yet.

15 PANEL MEMBER BLANC: That would be a good
16 idea, if you can.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: I think we should do that.

19 PANEL MEMBER BLANC: Yeah.

20 PANEL MEMBER HAMMOND: Did you say that's
21 four-hour exposure, but this is the acute REL?

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: Right.

24 PANEL MEMBER HAMMOND: Is that REL the acute
25 REL or?

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Well, the acute RELs are supposed to be for
3 one-hour exposures.

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: We've done quite a bit of work looking at the
6 time course of exposure of these sensory irritation
7 type of responses.

8 And in fact, Dennis Shusterman and various
9 co-workers, including myself, published a paper on this
10 not so long ago. And the conclusion there was that for
11 most of the -- well, for the sensory irritants for
12 which we actually had data that we could look at, what
13 you see typically is an increase in the irritation
14 response which goes up with the duration of exposure up
15 to a certain point and then plateaus.

16 And the ones that we were looking at, the time
17 course over which this increase was occurring was
18 something between a matter of a few seconds and several
19 minutes. And then in fact the response plateaued for a
20 period of up to a few hours. But there was then, in
21 fact, evidence of some accommodations of the sensory
22 response if you went out for, you know, many hours.

23 But the reason that we were particularly
24 concerned about this was that we felt that the response
25 would have plateaued within the time frame of interest

1 to the acute REL and would have stayed at that level
2 for periods of a little bit longer than that.

3 So -- and that's the reason why we in the
4 guidelines proposed that we not do time adjustments for
5 the sensory irritation response, at least where we had
6 studies which were, you know, somewhere in the relevant
7 period of exposure for the acute REL.

8 So although we don't have details for all
9 these different chemicals, the database where the time
10 course is actually being measured is quite limited;
11 nevertheless, that was the pattern we saw.

12 So anyway, that was the basis of our analysis.

13 OEHHA STAFF TOXICOLOGIST WINDER: Several
14 comments have been made about formaldehyde that it's
15 occurring in nature and our bodies naturally and the
16 environment, which is sort of a non sequitur.

17 Many of the toxic chemicals we encounter are
18 also constituents of living systems and found in cells,
19 and the body's ability to handle formaldehyde may be
20 overwhelmed by the exogenous application by inhalation.
21 So that's sort of a nonissue.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
23 MARTY: Okay. That's actually the end of the
24 formaldehyde presentation.

25 CHAIRPERSON FROINES: Are there further

1 questions? So I think we'll take a break for lunch.

2 Joe?

3 PANEL MEMBER LANDOLPH: I wasn't paying
4 attention when you switched from acrolein to
5 formaldehyde. Should I give just my comments to the
6 authors?

7 CHAIRPERSON FROINES: Unless you think it's
8 something the Panel should hear.

9 PANEL MEMBER LANDOLPH: It's up to you.

10 CHAIRPERSON FROINES: No, it's not. It's up
11 to you. Whether -- because I don't know what you've
12 got.

13 PANEL MEMBER LANDOLPH: Okay.

14 CHAIRPERSON FROINES: You have to decide. If
15 it's something that's relatively trivial, then just
16 give them to them. If you think it's something that
17 would lead to discussion, then we should discuss it --
18 then we should hear them.

19 PANEL MEMBER LANDOLPH: Of course, I can't
20 make that decision for you either. I can -- I just
21 have comments.

22 I want them to draw out a metabolic scheme and
23 a little bit of discussion about whether the
24 glycetaldehyde and the glutathione conjugates of
25 acrolein are mutagenic or not and whether they would

1 contribute to cytotoxicity, mutagenesis, and
2 carcinogenesis. Just a short discussion.

3 And let's see.

4 And some discussion -- it wasn't really stated
5 discretely whether acrolein was mutagenic in vitro with
6 or without S9 metabolic activation. Was it mutagenic
7 or bacterial mammalian cells? Did it cause any
8 chromosomal damage? Just some short statements on that
9 from the literature.

10 CHAIRPERSON FROINES: Melanie, are you going
11 to deal with formaldehyde as a carcinogen or --

12 PANEL MEMBER BLANC: This is acrolein.

13 CHAIRPERSON FROINES: Oh, acrolein.

14 PANEL MEMBER LANDOLPH: Acrolein.

15 CHAIRPERSON FROINES: Are you going to deal
16 with it when you bring the cancer guidelines?

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: When we bring the cancer guidelines, we're only
19 talking about methods to derive potency and how they're
20 used and weighting by age at exposure. We're not
21 bringing forth any chemical-specific new potencies. So
22 that's a long answer, no.

23 CHAIRPERSON FROINES: So this document is
24 about noncarcinogens.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: Noncancer --

2 CHAIRPERSON FROINES: -- and Joe's asking you
3 to put in data on carcinogenicity and mutagenicity. So
4 presumably it should be somewhere.

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Yeah. I think that's actually an okay point.

7 And like, for example, arsenic, we talk about
8 it as a carcinogen. We just mention it.

9 So I think it would be fine to do that. I
10 don't think we have a carcinogenicity bioassay or human
11 data like you have with arsenic.

12 CHAIRPERSON FROINES: What worries me about
13 formaldehyde and carcinogenicity is that that's like
14 reopening Pandora's box again.

15 And I really hesitate to do that, to put like
16 a few paragraphs in, and then we will hear -- we'll get
17 a new petition saying we need to reconsider the
18 formaldehyde question.

19 And so I think at some level we should be
20 cautious about what we open up.

21 PANEL MEMBER BLANC: Perhaps the way to make
22 it consistent with the points of the document is
23 there's a link in your view in terms of reproductive
24 hazards vis-a-vis things which are potentially
25 genotoxic, that there tends to be an overlap to an

1 extent, I suppose. Is that correct?

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: In some cases, yes.

4 PANEL MEMBER BLANC: So I would say, Joe, in
5 response to your question, I wouldn't delve deeply with
6 acrolein or formaldehyde into mutagenicity except
7 insofar as toxic attributes which would be relevant to
8 developmental impacts, perhaps, or something.

9 PANEL MEMBER LANDOLPH: Well, my comments were
10 more provoked by some of their comments that were
11 statements which just died in midair.

12 And so I -- just a suggestion to just write a
13 few more sentences just to say what's known and stop.
14 I didn't want to provoke a big carcinogenicity debate
15 or anything like that.

16 CHAIRPERSON FROINES: Is acrolein -- I don't
17 remember now; I apologize. Is acrolein's
18 carcinogenicity covered in the SB 25 document?

19 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

20 SALMON: No.

21 I think the point is that the data on
22 carcinogenicity and mutagenicity are essentially either
23 missing or equivocal for acrolein. So we don't have a
24 clear answer available.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: You might anticipate that it's a carcinogen.

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: People do.

4 But the trouble is that it's sufficiently
5 reactive that firstly it's very difficult to do a
6 satisfactory mutagenicity assay on something that's as
7 reactive as that because it has a tendency to kill all
8 the bacteria on site.

9 And additionally, it's extremely, as you know,
10 extremely reactive, fugitive, hard to measure and so on
11 which makes it a difficult material to handle and
12 difficult material for which to produce a stable
13 atmosphere which would be a prerequisite for doing a
14 satisfactory subchronic or chronic experiment.

15 So essentially, the problems of handling
16 acrolein mean there are no satisfactory data to address
17 the points, as far as I'm aware.

18 CHAIRPERSON FROINES: I would argue that
19 everything you said is correct. I would also argue
20 that it is a tragedy that greater effort hasn't been
21 made to document the carcinogenicity of acrolein.

22 I would bet my bottom dollar that an
23 alpha,beta-unsaturated aldehyde like that is clearly
24 going to be a carcinogen and that I don't think there's
25 any question. But I think it hasn't been documented,

1 and that's where the weakness lies.

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Yes.

4 CHAIRPERSON FROINES: And that's why the
5 mutagenicity data is important.

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7 SALMON: I think there's an argument -- there's
8 certainly an argument for us addressing this, at least
9 briefly, in this document precisely because we don't
10 have the basis to present the discussion in a more
11 extended document evaluating carcinogenicity; whereas,
12 in the case of formaldehyde, I think we probably
13 wouldn't do that because that's covered in detail
14 elsewhere.

15 PANEL MEMBER LANDOLPH: Yeah. That's kind of
16 what provoked my comments, and I would be --

17 CHAIRPERSON FROINES: Well, if people agree
18 that you should put something in, that's perfectly
19 fine.

20 PANEL MEMBER LANDOLPH: Concise. And then I
21 had another quick couple of comments.

22 CHAIRPERSON FROINES: Kathy wanted to make a
23 comment.

24 PANEL MEMBER HAMMOND: I guess I was going to
25 ask: If we have a policy on this, I was -- I thought

1 you had said that these are the noncancer endpoints.

2 That's what the RELs are about.

3 And if a compound also causes cancer, we would
4 still have a REL document. Is that correct?

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: Right.

7 PANEL MEMBER HAMMOND: So on one level, we
8 could say these are two different worlds. On the other
9 hand, I think the worlds ought to at least talk to each
10 other.

11 And so there should probably be in a document
12 a comment about if there's a carcinogenicity document,
13 just refer to it, that there is a carcinogenicity
14 document.

15 I guess as soon as we go beyond that -- but it
16 does seem like you should be able to say there have
17 been some concerns expressed about carcinogenicity, but
18 this has not yet been evaluated by OEHHA.

19 Maybe it goes as far as that? If you could
20 cite any organization that has stated something.

21 CHAIRPERSON FROINES: Well, there are -- you
22 know, it's listed by IARK and --

23 PANEL MEMBER HAMMOND: Yeah.

24 CHAIRPERSON FROINES: The point that it's
25 listing doesn't bring you where I think you would need

1 to go. I think you also have to acknowledge the
2 chemical structure of acrolein and the potential for
3 its having carcinogenicity.

4 PANEL MEMBER HAMMOND: Well, I think that this
5 document should not be a new review of the
6 literature -- or even of the science, maybe more
7 fundamentally is what your concern is.

8 It should at most just point the reader to
9 whether or not they should also have some concern. And
10 if there is another document that OEHHA has put out or
11 if IARK has put a document out, you can refer to those.

12 CHAIRPERSON FROINES: I think you want to say
13 that is an area that needs further scientific testing
14 and research because it's clearly a bad actor.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
16 MARTY: I think it makes sense to refer the reader to,
17 for example, our other part of this risk assessment
18 guidelines where we have all the cancer potencies.

19 CHAIRPERSON FROINES: Joe?

20 PANEL MEMBER LANDOLPH: Yeah, then I have just
21 two quick comments.

22 One was an independent one from one you had
23 about molecular correlates of toxicity and just some
24 question about whether acrolein could form shift bases
25 with the amino acid groups of proteins or with the

1 exocyclic amine groups of DNA bases such as guanine
2 which might contribute to airway sensitization and
3 immunological effects through haptimization of proteins
4 as well as mutagenicity -- some short, concise
5 discussion, and I'll give you these comments.

6 CHAIRPERSON FROINES: You'd better be careful
7 though. Shift bases are irreversible -- are
8 reversible. They -- you can hydrolyze shift bases, and
9 you get your parent compound back.

10 So the fact that it forms a shift base does
11 not make it something that's an irreversible change.

12 PANEL MEMBER LANDOLPH: Yeah, it just struck
13 me it might lead to haptimization or something like
14 that.

15 The last comment was the developmental and
16 reproductive toxicity. And you cited a WHO document.
17 And I didn't agree with WHO.

18 They said that there were two positives --
19 there were two positive studies for teratogenicity and
20 embryo toxicity when acrolein was administered into
21 amniotic fluid or added to rats -- or added to cultured
22 rat embryos; and then when they injected it into
23 chicken embryos, they got embryo toxic and teratogenic
24 effects. But then when it was IV injected into
25 pregnant rats, they showed no effects, so they conclude

1 overall the thing was negative.

2 To me, I disagree with them. And I think a
3 fair statement would be more studies should be done
4 with relevant modes of administration to resolve the
5 question appropriately.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: I think that's fine.

8 CHAIRPERSON FROINES: I think we'd better take
9 the time to break for lunch because it's exactly
10 1 o'clock. And so what, a half hour, 40 minutes?

11 PANEL MEMBER BLANC: I think 45 is more
12 realistic because we have to get served. I could eat
13 in half an hour if I had the food in front of me right
14 now; but that's not true, is it?

15 CHAIRPERSON FROINES: Okay. 45 minutes.

16 (Lunch recess)

17

18

19

20

21

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23

24

25

1 AFTERNOON SESSION

2 --o0o--

3 CHAIRPERSON FROINES: Are we ready to go?

4 Stan are you ready to go?

5 PANEL MEMBER GLANTZ: I'm totally ready.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Bruce Winder is going to present the
8 information on the manganese Reference Exposure Levels.

9 OEHHA STAFF TOXICOLOGIST WINDER: Okay. As
10 indicated in the document here we have not developed an
11 acute REL for manganese at this time largely due to
12 deficiencies in --

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: I don't think our microphones are on.

15 OEHHA STAFF TOXICOLOGIST WINDER: Here we go.

16 At any rate, like I said, the acute REL -- we
17 haven't developed an acute REL at this point due to
18 lack of studies of short-term exposure effects.

19 However, we have developed an eight-hour REL,
20 .26 micrograms per meter cubed and a chronic REL .13
21 micrograms per meter cubed. Both of these are based on
22 impaired neurobehavioral function in humans.

23 CHAIRPERSON FROINES: Is manganese a TAC?

24 PANEL MEMBER GLANTZ: I don't believe so.

25 CHAIRPERSON FROINES: Is it a half, that's the

1 question.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: If it's a half, it's a TAC. And I'm pretty
4 sure it's a half. I will double-check that.

5 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

6 The critical study here was a study done by
7 Roels in '92, an occupational study in a battery plant
8 looking at the exposure of 92 workers for eight hours a
9 day, five days a week.

10 These individuals were employed there for a
11 mean of 5.3 years, and you can see the range here of .2
12 years to 17.1 years.

13 The endpoints measured in that study include
14 impaired visual reaction time, eye-hand coordination,
15 and hand steadiness.

16 From that study, a LOAEL was calculated of
17 150 micrograms per meter cubed. However, we
18 subsequently were able to get hold of individual data
19 from this Roels study with a benchmark analysis and
20 came up with a concentration of 109 micrograms per
21 meter cubed.

22 We adjusted this to a 24-hour exposure with --
23 to a full-week exposure with this 109 times 5/7 so this
24 gave us a time-adjusted value of 78 micrograms per
25 meter cubed.

1 This was a subchronic study, so we used a
2 subchronic uncertainty factor of 10.

3 Again, there's no interspecies uncertainty
4 factor since this study is in humans.

5 We have a toxicokinetic uncertainty factor of
6 10. The reason for this is that infants and children
7 have a much greater absorption of manganese than do
8 adults in the diet, and lung deposition in children is
9 likely to be higher based on some work by Ginsberg.

10 We included a toxicodynamic uncertainty factor
11 of 10, and this addresses the anticipated higher
12 sensitivity of children to neurotoxicity for a
13 cumulative uncertainty factor of 300 and an eight-hour
14 REL of 2.6 micrograms per meter cubed.

15 Same study we used here for the chronic REL.
16 Again, the same sorts of situation applied. This time
17 for our time adjustment, since the original study was
18 an eight-hour worker study, we're adjusting here
19 upwards to the chronic study by 10 over 20.

20 So our time adjusted factor here is 39
21 micrograms per meter cubed.

22 And the reason we have no LOAEL-to-NOAEL
23 conversion factor, we're using a BMD analysis on this.

24 So we have the same subchronic uncertainty
25 factor, same intraspecies toxicokinetic factor of 10,

1 toxicodynamic factor of 10 again for neurotoxicity, and
2 the chronic REL here is .13, so it's about half the
3 eight-hour REL.

4 Now just to put this in some kind of
5 perspective, we're proposing .13 micrograms per meter
6 cubed.

7 WHO has their air guidelines of
8 .15 micrograms.

9 US EPA is currently -- their RfC currently is
10 .05 and -- but subsequent papers from people at US EPA,
11 Dr. Michael Davis in particular, suggest that this
12 number is highly dependent on what models were used and
13 the assumptions that go into it, and suggested a range
14 of .09 to .2 micrograms per meter cubed as being
15 appropriate.

16 Health Canada's current value is .11. They're
17 considering .05.

18 So the comments we've gotten on this --

19 CHAIRPERSON FROINES: Wait, wait one second.
20 You're at .13, and the US EPA RfC is .05. What's the
21 basis for that value that --

22 OEHHA STAFF TOXICOLOGIST WINDER: The .05 --

23 CHAIRPERSON FROINES: -- would make it
24 different than what you would find?

25 OEHHA STAFF TOXICOLOGIST WINDER: The biggest

1 difference there is this .05 is based on the LOAEL. So
2 they have a threefold NOAEL conversion factor involved
3 there, pretty much the difference between the two of
4 these. We don't have the LOAEL-to-NOAEL conversion
5 because we're using the benchmark dose approach.

6 But --

7 PANEL MEMBER BLANC: Can you just clarify on
8 your benchmark, and I'll have other comments later, but
9 the outcome measures in the Roels study would, on face
10 value, seem to be continuous variables.

11 Did they dichotomize in some way to
12 normal/abnormal?

13 OEHHA STAFF TOXICOLOGIST WINDER: We
14 dichotomized based on his assessment normal/abnormal,
15 so we have data for the individual data, and those we
16 categorized -- we dichotomized that into what he called
17 abnormal versus normal.

18 PANEL MEMBER BLANC: And how did you do that?

19 OEHHA STAFF TOXICOLOGIST WINDER: I believe
20 his data actually refers to these individual responses
21 as normal versus abnormal. They aren't qualified.

22 PANEL MEMBER BLANC: Based on what? So his
23 original data were normal -- go back to the outcome
24 variables he used, if you might, on your slide. Okay.

25 Impaired visual reaction time, eye-hand

1 coordination, hand steadiness. Are you saying there
2 was a variable that he had that was hand unsteadiness
3 present/absent?

4 OEHHA STAFF TOXICOLOGIST WINDER: He called it
5 abnormal/normal in that context.

6 PANEL MEMBER BLANC: Most of these are based
7 on continuous variables. Certainly visual reaction
8 time is a continuous variable. That I know for sure.

9 OEHHA STAFF TOXICOLOGIST WINDER: Well, we
10 based ours actually on eye-hand coordination, a more
11 sensitive response. He --

12 PANEL MEMBER BLANC: But these are -- I mean I
13 think you need to be pretty clear.

14 OEHHA STAFF TOXICOLOGIST WINDER: And then
15 here he did represent -- in the paper presented a
16 percentage of abnormal value, so it's -- I'm not clear
17 the criterion he's using for normal versus abnormal in
18 the context of --

19 PANEL MEMBER BLANC: Well, it must be in his
20 method, isn't it?

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
22 MARTY: I'm looking.

23 Well, his methods are described more fully in
24 a previous paper, which I don't have in front of me.
25 So anyway, what was the issue?

1 PANEL MEMBER BLANC: Well, in a way, you've
2 answered the question technically, which is I couldn't
3 figure out how you did a benchmark if it's a continuous
4 outcome variable because most of your benchmark
5 calculations require a dichotomous outcome variable of
6 some kind with percentages, right?

7 OEHHA STAFF TOXICOLOGIST WINDER: Right.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
9 SALMON: You can use the benchmark analysis with
10 continuous variables. It's a different -- different
11 models used to fit, but it works much the same way.

12 PANEL MEMBER BLANC: Well, might it -- and --
13 well, I'm going to hold some questions until a little
14 bit later on, unless you think -- well, maybe I should
15 just ask them about this very specific thing.

16 The other uncertainty factor that your
17 methods, your generic methods, allow you to throw in,
18 your sort of existential uncertainty factor that could
19 be up to 3?

20 OEHHA STAFF TOXICOLOGIST WINDER: You're
21 talking about the database uncertainty factor? I'm not
22 clear.

23 PANEL MEMBER BLANC: I forget what you called
24 it, but we discussed it at length, maybe --

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: The database deficiency factor?

2 PANEL MEMBER BLANC: Yeah.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: I'm sorry; ask the question again? I didn't
5 understand the question.

6 PANEL MEMBER BLANC: That's not involved in
7 this calculation, doesn't add that.

8 What would it -- it seems to me that it might
9 be worth considering. It wasn't just -- do people
10 remember the discussion last time? We didn't rediscuss
11 it this time, but you know what I'm referring to?

12 Was that only -- it was a kind of a global
13 sense of there's too much missing data here for us to
14 feel completely comfortable with.

15 PANEL MEMBER GLANTZ: Right.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: Yes, it was where we had reasons to anticipate
18 that there might be adverse effects in the critical
19 concentration range, but we didn't have enough data to
20 make a qualitative assessment what the protected level
21 would be. So it's basically missing data in the -- in
22 terms of types of effects or things like that, for
23 instance, in the developmental area.

24 As opposed to the other uncertainty factors
25 which we have applied, most of which have to do with we

1 know what the endpoint is, and we have -- we have some
2 assessment of what the critical levels of that endpoint
3 would be, but there is an uncertainty associated with
4 the data on that endpoint. That was the distinction
5 between the --

6 PANEL MEMBER BLANC: And for that you would
7 apply a square root of three -- square root of 10 to?

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
9 SALMON: Well, we -- in principal, we could choose
10 either. But square root of 3 or square root of 10.

11 PANEL MEMBER BLANC: And you haven't applied
12 that in this case?

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

14 SALMON: No.

15 PANEL MEMBER GLANTZ: You don't have a square
16 root of 3.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: Sorry. Square root of 10 or 10. I'm sorry.

19 Excuse me. Getting confused here. Yes. 10 or 3 --

20 PANEL MEMBER BLANC: Do you think the issue of
21 having had data which has been reduced to a dichotomous
22 outcome when in fact that's likely to . . .

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

24 SALMON: Just firstly, no, we haven't done that in the
25 past, and we don't consider that it's necessary to do

1 that. One of the -- I'm just wanting to check
2 something here in the calculation. Yes.

3 I think -- well, one of the points is that if
4 we are -- if we're using a case like this where the
5 score is either, just be either normal or abnormal,
6 then if you had a continuous variable, and you --

7 PANEL MEMBER BLANC: Instead of
8 abnormal/normal, you're saying?

9 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
10 SALMON: Yeah, and if you were to fit that, you would
11 have -- you know, conceptually, you would have a cutoff
12 point which you would have to decide where in that
13 continuous range the cutoff would be.

14 So you have to make this decision at some
15 point in the process by either method.

16 The dichotomizing the data can impair in some
17 circumstances, if it's not done appropriately or if the
18 data are difficult, it can, if you like, increase the
19 spread. That would probably be -- remember where the
20 benchmark we're calculating is the lower confidence
21 bound.

22 So if the process of dichotomizing the data
23 actually, you know, built in a little bit of extra
24 variation into the underlying data, then that would
25 actually be reflected in the calculated confidence

1 bounds on the EC05 or whatever the benchmark was
2 because we're using a lower bound as the benchmark.

3 So the dichotomization could, I think in
4 principal, increase the spread around the MLE --

5 PANEL MEMBER BLANC: If it's random. But
6 suppose his dichotomization of normal eye-to-hand
7 coordination is an eye-to-hand coordination which is
8 beyond the 95th percent confidence interval for the
9 test, and that's what he calls abnormal based on some
10 referent population data?

11 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

12 SALMON: Hm.

13 PANEL MEMBER BLANC: And in fact it's a
14 conservative definition, although, you know, very
15 consistent with test definitions when you want to be
16 very sensitive.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: Yeah. I don't -- does he actually say what
19 the test definition was for that dichotomization? No.

20 I mean, yeah, I -- I don't know that --
21 whether it was an especially conservative criterion. I
22 don't think I have an answer to that right away.

23 In general, we have not felt that the
24 dichotomization made a huge difference. We did
25 actually do a test about it. I'm trying to think back

1 to which -- was it the fluoride one?

2 I know one of them we did actually compare the
3 continuous and dichotomized. The continuous actually
4 produced a better-looking fit, but it didn't produce a
5 substantially different result in that particular case.
6 Trying to think of which one it was.

7 But we'll have to get back to you on that.

8 PANEL MEMBER HAMMOND: Actually, I have a
9 couple questions. First, would you help me? I know it
10 was on a previous slide as well, about the time
11 adjustment. What's the 109?

12 OEHHA STAFF TOXICOLOGIST WINDER: That's the
13 benchmark concentration.

14 PANEL MEMBER HAMMOND: Okay. All right.

15 Then the second thing, I was reading what you
16 have here which is a little different than what you've
17 written up there.

18 My concern is we're talking about chronic
19 exposure, and so therefore it's a cumulative exposure
20 that I think is the relevant metric, exposure metric,
21 which would be milligram per cubic meter years, which
22 is what you cite in the document. You do mention that.

23 But the way you -- I'm sure -- I would imagine
24 the paper, they continually use milligram per cubic
25 meter years, but what you did was to take the geometric

1 mean divided by the average exposure time.

2 And I think it would be more useful to
3 actually use the actual values and -- because you don't
4 necessarily get the true sense of what the exposures
5 were to the people so I'm not quite sure why you did it
6 that way.

7 But I would rather see this done in milligram
8 per cubic meter years and working from that as the
9 exposure metric. And then only at the end correcting
10 for the number of years you want to protect people from
11 environmental exposure.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
13 SALMON: We are not for the chronic REL derivation
14 looking at, you know, saying that five years is half as
15 bad as ten years.

16 We're looking for an -- essentially for an
17 annual average rate which would be protected.

18 So we're not assuming that the cumulation is
19 going to occur -- I mean we certainly anticipate
20 cumulation will occur over a significant period. We're
21 not assuming that it's cumulative over a lifetime in
22 the same way that we do for cancer, for instance.

23 PANEL MEMBER HAMMOND: Well, first of all, I'm
24 speaking at the moment about the data that you're
25 working with, the occupational data.

1 So for instance, someone who works .2 years --
2 at least one of the subjects worked just a couple of
3 months, apparently -- might well have been exposed to a
4 very high concentration. That's not unusual in an
5 occupational setting. Short-term employees have high
6 exposures. I don't know that.

7 And often people, the longer they're there,
8 the more the -- the exposure changes through those
9 17 years and may have been declining.

10 Now I guess you'd want to start with the
11 biology, but if we think there's a cumulative effect
12 over 17 years, you'd want to do that, or you might want
13 to work something else out.

14 But I don't think taking the average exposure
15 divided -- geometric mean exposure and dividing by the
16 average number of years to say what the dose was is an
17 appropriate exposure metric.

18 CHAIRPERSON FROINES: I don't either. I don't
19 think the geometric mean is --

20 PANEL MEMBER HAMMOND: So I guess I'm just
21 concerned about that. And a more easily remediable,
22 other, second issue, I'll just say quickly to get it
23 done with -- the other may be more important -- is that
24 in the paper, RELs, it's talking about respirable --
25 these are the respirable concentrations, and that's

1 what you use, and that's appropriate.

2 But it would seem to me that in that case the
3 REL should also be referring to respirable.

4 We know that the biologic availability is very
5 much a function of the particle size. And people have
6 done studies where people with total exposures to
7 manganese higher than another respirable exposure don't
8 have the same effects.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Yeah, we can clarify that. But it's -- there
11 are always -- the implicit assumption of risk
12 assessment is it's respirable if it's a particulate.

13 PANEL MEMBER HAMMOND: Is that for everything?
14 Whenever you do particles?

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Yeah.

17 PANEL MEMBER HAMMOND: It is? I think it
18 actually should be stated as such if that's true
19 because that's not true in other standards.

20 But meanwhile, I am concerned about how the
21 exposure metric was used to do these calculations.

22 CHAIRPERSON FROINES: Doesn't that -- it has
23 the potential for underestimating the dose.

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

25 SALMON: Pardon me. I'm not exactly sure what it is

1 you're proposing that we should do instead of what we
2 did. Can I ask you to clarify that?

3 PANEL MEMBER HAMMOND: If you're trying to say
4 at what level a response was seen, I think that that
5 should be at a microgram per cubic meter years metric,
6 not micrograms per cubic meter.

7 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
8 SALMON: The calculation that we did was based on the
9 geometric mean of the lifetime integrated respirable
10 dust levels reported in the paper divided by the
11 average exposure time.

12 PANEL MEMBER HAMMOND: I see that. I think
13 that that's incorrect on two bases.

14 First of all, it shouldn't be -- the proper
15 metric for an exposure that's a cumulative exposure
16 should be arithmetic mean, not the geometric mean.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
18 SALMON: Yes.

19 PANEL MEMBER HAMMOND: If you want to know
20 what the predicted daily exposures, the geometric mean
21 is appropriate. But if you're looking at cumulative
22 effect, then you need the arithmetic mean for that.

23 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
24 SALMON: Okay.

25 PANEL MEMBER HAMMOND: Secondly, I don't think

1 you -- I think you would take each individual. The
2 normal way that research is done -- I haven't read this
3 paper -- but the normal way that research is done is
4 for each individual they calculate the individual's
5 microgram per cubic meter years exposures --

6 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

7 SALMON: That's what they did.

8 PANEL MEMBER HAMMOND: Right, but you've taken
9 the average of those things and divided them --

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: We've taken the average of the individual
12 LIRDS.

13 PANEL MEMBER HAMMOND: Tell me again what LIRD
14 is?

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

16 SALMON: Lifetime integrated risk --

17 PANEL MEMBER HAMMOND: Right, and I don't
18 think that's appropriate, all right?

19 I think what you want to do is you would look
20 at these as the different doses. You have a hundred --
21 you have 92 different doses that these individual had.

22 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

23 SALMON: Yes.

24 PANEL MEMBER HAMMOND: And you try to see for
25 each a microgram per cubic meter year, and you try to

1 see which of those doses is where you start seeing the
2 effects or some plot of degree of severity.

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: In other words, you want us to look at the
5 individual exposure data on the -- in order to derive
6 the benchmark rather than --

7 PANEL MEMBER HAMMOND: Well, this is just
8 looking at -- I mean I think you're losing too much
9 data.

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: Well --

12 PANEL MEMBER HAMMOND: It looks to me like
13 you're losing much too much data.

14 But just saying this is a study that -- the
15 way I'm reading it, this is a study that saw an effect,
16 and the average exposure these people had was 150
17 micrograms per cubic meter -- or maybe it's point --
18 793. But that isn't the way one wants to do -- when
19 you have much richer data, you don't want to --

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: I think we're talking at cross-purposes here.

22 The BMD analysis was done on the data on the
23 individuals in the study. This business of the
24 geometric mean of the LIRD divided by the exposure time
25 was used to calculate the LOAEL for the study, but the

1 LOAEL is not what we're using in the benchmark dose
2 calculation.

3 PANEL MEMBER HAMMOND: Well, I think it's an
4 appropriate LOAEL. Okay?

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
6 SALMON: Well, we're not using it anyway, but we can
7 correct it.

8 PANEL MEMBER HAMMOND: But I don't think
9 having an inappropriate way to do it should be in the
10 document.

11 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
12 SALMON: We can throw it out if you want us to do that.

13 PANEL MEMBER HAMMOND: When you did the
14 benchmark does, did you use each individual --

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

16 SALMON: Individual data, yes.

17 PANEL MEMBER HAMMOND: You used the individual
18 data?

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: For all three tests.

21 PANEL MEMBER BLANC: But did you use the
22 geometric or arithmetic mean for that individual?

23 Because for each individual you have multiple --

24 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

25 SALMON: I think we used the lifetime integrated

1 respirable dust level as reported by Roels now.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: For each individual.

4 PANEL MEMBER BLANC: But that would have been
5 based on a geometric mean?

6 PANEL MEMBER HAMMOND: Roels may have used the
7 arithmetic.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: I think he probably used the arithmetic.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Not in the paper. It's data we got.

12 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

13 SALMON: Yeah, we'd have to plow through the source
14 data.

15 CHAIRPERSON FROINES: The arithmetic mean is
16 the appropriate measure.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: I think that --

19 PANEL MEMBER BLANC: I think another point
20 to -- another monkey wrench to throw in is that in fact
21 manganese is the rare example of an inhalant for which
22 an argument can be made that nonrespirable dust could
23 be more critical than respirable dust, or as critical,
24 because of the phenomenon of direct nasal uptake in
25 transport to the central nervous system.

1 So I think -- and this is something that
2 throughout this document was problem-ridden, I think.
3 There was -- it was alluded to at one point, but then
4 it got maybe turned on its head or ignored at certain
5 points.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: Well then, we would have underestimated the
8 dose that produced the effect by using just respirable.

9 PANEL MEMBER BLANC: Possibly. But in certain
10 other points in the document, all I'm saying is that
11 with this particular substance, there is -- the issue
12 of olfactory uptake is something that you're going to
13 have to deal with more clearly than was dealt with,
14 even though it was alluded to in one paragraph.

15 CHAIRPERSON FROINES: Can I ask a question
16 that's a follow-up to that? Do you have some estimate
17 of the size distribution of that data?

18 Because, for example, we've done a lot of work
19 on chromium and lead, and the respirable dust that gets
20 to the alveolar region ends up passing through the lung
21 into the systemic circulation and mucociliary cleared
22 dust ends up going to the gut. So you -- so there's a
23 dependence on the relative uptake from the two regions.
24 Not to mention the olfactory issue.

25 PANEL MEMBER BLANC: I mean I think for

1 manganese, because unlike lead its GI uptake is tightly
2 regulated, the issue is somewhat a special case.

3 And if we didn't have this olfactory
4 mechanism, then you'd sort of discount stuff that
5 would --

6 CHAIRPERSON FROINES: You would assume.

7 PANEL MEMBER BLANC: -- get into the gut.

8 PANEL MEMBER HAMMOND: Isn't olfactory for
9 small particles, not large particles?

10 PANEL MEMBER BLANC: I thought the olfactory
11 clearance is effective for larger particles.

12 PANEL MEMBER HAMMOND: I guess that's direct
13 olfactory to the brain, very small particles.

14 PANEL MEMBER BLANC: Well, some of the
15 experimental data is done with small particles, but I'm
16 not sure all of the data was done with small particle.

17 CHAIRPERSON FROINES: Kathy's right, you know,
18 the Oberdörster data from ultrafine particles is small
19 stuff going to the olfactory. But that -- but there
20 may be other literature that we're not familiar with.

21 PANEL MEMBER BLANC: That's specific to
22 manganese.

23 CHAIRPERSON FROINES: Yeah.

24 PANEL MEMBER BLANC: Yeah. There is other
25 literature about ultrafine particles bypassing certain

1 mechanisms.

2 But what I'm talking about with at least some
3 of the manganese data, you know, is it's not a micro --
4 it's not an ultrafine particle issue. It's a sort of
5 unique.

6 CHAIRPERSON FROINES: It's a transport
7 process.

8 PANEL MEMBER BLANC: It's a transport process
9 for which there is no reason to invoke the necessity of
10 ultrafine particles.

11 CHAIRPERSON FROINES: So on these -- I mean
12 you can get -- the ultrafines can pass into the CNS by
13 diffusion, presumably, and -- but with the large
14 manganese, then you're going to need a transport
15 mechanism of some kind, presumably.

16 And presumably that may exist given the nature
17 of manganese.

18 OEHHA STAFF TOXICOLOGIST WINDER: Further
19 questions?

20 PANEL MEMBER BLANC: Well, I mean there are a
21 lot of questions, but I think you want to finish your
22 presentation.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
24 MARTY: We should go through the comments from the
25 public comment period on the draft.

1 OEHHA STAFF TOXICOLOGIST WINDER: Okay. One
2 of the fairly common, or more common, comments is that
3 manganese is an essential nutrient and for that reason
4 we need to consider how much the body needs for overall
5 health and in the context of dietary intake, our
6 inhalation levels seem to be unsuitably small.

7 The only thing we point out in response to
8 that is that the route of exposure here is very
9 critical. That, as has already been alluded to, the
10 dietary intake is fairly well regulated by the body
11 whereas inhalation intake allows manganese to
12 completely bypass the first-pass control by the liver
13 as well as there's a possibility of direct access to
14 the brain by the olfactory nerves.

15 PANEL MEMBER HAMMOND: Excuse me, just a
16 question. Is there metabolism of manganese in the
17 liver?

18 OEHHA STAFF TOXICOLOGIST WINDER: Manganese --
19 there's a cycle that takes manganese from the liver to
20 the bile, bile ducts and back, into the intestinal
21 tract, and the level of the manganese in the diet or in
22 the blood regulates how effective that is. As the
23 blood level of manganese rises, there's more of the
24 stuff back in by bile.

25 PANEL MEMBER HAMMOND: And it doesn't go

1 into -- and the bile is excreted.

2 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

3 PANEL MEMBER BYUS: That's called
4 enterohepatic circulation, not metabolism.

5 OEHHA STAFF TOXICOLOGIST WINDER: That's
6 right.

7 PANEL MEMBER BYUS: So it's called
8 enterohepatic circulation, not metabolism.

9 OEHHA STAFF TOXICOLOGIST WINDER: Do we call
10 it metabolism?

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
12 MARTY: I don't think so.

13 PANEL MEMBER BYUS: First-pass metabolism is
14 different than enterohepatic circulation.

15 PANEL MEMBER BLANC: First-pass clearance.

16 OEHHA STAFF TOXICOLOGIST WINDER: First-pass
17 clearance would be accurate.

18 PANEL MEMBER BYUS: Clearance is okay.

19 OEHHA STAFF TOXICOLOGIST WINDER: You're
20 right.

21 PANEL MEMBER BLANC: What does this sentence
22 mean to you: Inhalation provides more rapid uptake of
23 manganese into the blood and the lungs, avoids
24 first-pass clearance in the liver, allows direct access
25 to the brain via olfactory nerves.

1 You say inhalation, the last phrase there, for
2 example. This comes to some of my confusion in the way
3 you wrote things.

4 OEHHA STAFF TOXICOLOGIST WINDER: Okay. The
5 last phrase makes reference to what happens in the nose
6 whereas the first part is making reference to what
7 happens in the lungs. Yeah, I can see your -- your
8 source of confusion there.

9 The idea is that, demonstrated in the rats,
10 the manganese that enters the nose can have access to
11 the brain via the olfactory nerves. So it's directly
12 from the nose to the brain, bypassing the blood-brain
13 barrier, clearance from the liver.

14 With respect to the lungs, manganese is
15 absorbed fairly efficiently in the lungs, and once it
16 gets into the circulation it can go to the brain before
17 it has the chance to --

18 PANEL MEMBER BLANC: So in fact, both uptake
19 in the lungs and uptake in the nose could avoid
20 first-pass --

21 OEHHA STAFF TOXICOLOGIST WINDER: That's
22 correct.

23 PANEL MEMBER BLANC: -- clearance by the
24 liver.

25 OEHHA STAFF TOXICOLOGIST WINDER: Yes.

1 PANEL MEMBER BLANC: Okay, so --

2 CHAIRPERSON FROINES: Except that we don't
3 know the size distribution, so we don't know how much
4 ends up in the airways.

5 PANEL MEMBER BLANC: Leaving that aside. I'm
6 just pointing out this is a repeated problem with the
7 document where somehow it's not clear -- if I just read
8 this and didn't know anything better, I'd say okay so
9 you mean it gets through the lung into the blood and
10 from the blood goes to the nose and from the nose goes
11 to the brain -- that's not what you're trying to say at
12 all.

13 OEHHA STAFF TOXICOLOGIST WINDER: No.

14 PANEL MEMBER BLANC: And just be careful about
15 that.

16 OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

17 PANEL MEMBER BLANC: Okay?

18 OEHHA STAFF TOXICOLOGIST WINDER: Now within
19 the context of manganese, we point out here that
20 children absorb much more manganese than do adults in
21 the diet.

22 PANEL MEMBER BLANC: And why is that relevant
23 to any of your arguments in any of this REL?

24 OEHHA STAFF TOXICOLOGIST WINDER: Because that
25 means that a child's blood levels of manganese may be

1 substantially higher for a given exposure than an
2 adult's would be.

3 A child that subsequently is breathing
4 manganese on top of the dietary absorption may be at a
5 higher risk level for exceeding the safe levels of
6 manganese.

7 PANEL MEMBER HAMMOND: I thought it went the
8 other way. I thought you were saying that if you have
9 high blood then you'd divert more to the bile.

10 OEHHA STAFF TOXICOLOGIST WINDER: That's true.
11 But in the meantime, you have blood levels that are
12 reaching the brain.

13 PANEL MEMBER HAMMOND: That's already from the
14 diet. Not from the --

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
16 MARTY: Part of the issue is that infants absorb more
17 manganese, and a lot of infants are being fed on soy
18 formula which has actually quite a bit more manganese
19 in it than breast milk.

20 PANEL MEMBER HAMMOND: So maybe more the
21 point, the point might be more correctly -- if I
22 understand you correctly -- the point might be better
23 stated as that children and infants already have a very
24 high level of manganese, and the environmental level
25 can tip them over to a more dangerous level.

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: The key point is that --

3 PANEL MEMBER HAMMOND: Is that true?

4 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

5 SALMON: -- the feedback regulation which maintains
6 manganese homeostasis in the older child and the adults
7 is not fully developed in the infant. So the infant
8 doesn't have this same degree of regulation as the
9 adult.

10 PANEL MEMBER HAMMOND: Well, that's not what's
11 said at all there. Not that bullet point.

12 PANEL MEMBER PLOPPER: It doesn't say
13 anything.

14 PANEL MEMBER BYUS: And in fact, but you're
15 not arguing therefore the inhalation of manganese is
16 going to be worse for them because the inhaled dose is
17 not going to be regulated as it would be in an adult.

18 Your only argument has to be what Kathy said,
19 which is that somehow it would tip them over.

20 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

21 SALMON: Some infants will have a high level, fairly
22 high level of manganese because they don't regulate
23 their dietary intake.

24 PANEL MEMBER BLANC: And is there any data
25 that support that?

1 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

2 SALMON: Yes.

3 PANEL MEMBER BLANC: And you make that clear?

4 Like from NHANES or something?

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: It relates to the children, the infants being
7 fed on soy-based formulas.

8 PANEL MEMBER BLANC: But is there data from

9 NHANES showing that childhood --

10 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

11 SALMON: No, I don't believe.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

13 MARTY: There's no data from NHANES on infants.

14 PANEL MEMBER BLANC: Is there some --

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: It's six years old and up.

17 PANEL MEMBER BLANC: Is there some other

18 population-based data on infants showing that overall

19 their blood manganese levels are higher than older age

20 infants per nanogram per mL?

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: We're not making an argument on a population

23 basis. We're making the argument on the demonstrated

24 existence of a susceptible subpopulation, which is

25 infants, with a high manganese diet.

1 PANEL MEMBER HAMMOND: This is not --

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: There are data that infants lack manganese
4 homeostasis, and that's one of the issues.

5 PANEL MEMBER HAMMOND: That should be a bullet
6 there.

7 OEHHA STAFF TOXICOLOGIST WINDER: That's a
8 good point. We go on to point out that a number of
9 compounds that are toxic for inhalation are relatively
10 intoxic or not --

11 CHAIRPERSON FROINES: Can I stop you? Because
12 I don't want to spend any time on this; we should talk
13 about manganese. But I object strongly to the
14 hexavalent chromium.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

16 MARTY: Yes, I do too. Thank you.

17 PANEL MEMBER HAMMOND: That is a disastrous
18 statement.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

20 MARTY: That should not be in there.

21 OEHHA STAFF TOXICOLOGIST WINDER: Point taken.

22 PANEL MEMBER BLANC: Moving right along.

23 PANEL MEMBER HAMMOND: And the others,
24 actually -- just as long as we're there -- the others,
25 crystalline silica and beryllium, at least, are dealing

1 with the lung as the target.

2 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

3 MARTY: Right.

4 PANEL MEMBER HAMMOND: So it's not a relevant
5 comparison.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: Right, exactly.

8 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

10 MARTY: Hexavalent chromium, by the way, was struck
11 from the document.

12 PANEL MEMBER BLANC: Okay.

13 CHAIRPERSON FROINES: Let's move on. We're
14 all in agreement on that one.

15 OEHHA STAFF TOXICOLOGIST WINDER: This might
16 have addressed some of the questions with respect to
17 diet and inhalation. These data are presented in the
18 document but in a slightly different way from this.

19 What I present here is the -- we take a look
20 at the exposure of the average respirable manganese in
21 the Roels study which is .215 mgs per cube meter. If
22 an infant or individuals of the age you see across the
23 X axis here were exposed to this, what I plotted here
24 is how much they would be exposed to by inhalation
25 compared to what they're getting in the diet.

1 So the portion here -- the colors didn't turn
2 out too well. Let's start with brown. From the Food
3 and Nutrition Board this is an indication of their
4 estimate what an upper limit is for a dietary intake of
5 manganese in different age groups.

6 The middle bar, sort of a yellow-green, is
7 what they suggest is -- represents adequate intake.

8 Then the bar on the left, the green one,
9 represents what these individuals would be exposed to
10 were they breathing this amount that's in the Roels
11 study corrected for their weight and respiration rate.

12 So what I'm trying to show by this is that the
13 inhalation exposure for the very young in many cases
14 approaches or may exceed the amount they represent as
15 an upper limit for dietary intake.

16 Another way to look at it is that the safe
17 level is more easily exceeded by a child that's being
18 exposed to these levels whereas an adult would not
19 exceed the upper limit.

20 PANEL MEMBER HAMMOND: Could you put -- what's
21 the upper limit?

22 OEHHA STAFF TOXICOLOGIST WINDER: That's the
23 brown.

24 PANEL MEMBER HAMMOND: Upper limit they should
25 be allowed in the diet or the upper limit they should

1 get in the diet?

2 OEHHA STAFF TOXICOLOGIST WINDER: At which
3 they expect toxicity.

4 PANEL MEMBER HAMMOND: So if this were in the
5 diet -- the brown is if this were in the diet, this is
6 the level at which you have toxicity?

7 OEHHA STAFF TOXICOLOGIST WINDER: Beyond which
8 you'd have --

9 PANEL MEMBER HAMMOND: Okay. I misunderstood.
10 I thought that was the upper limit of what one got in
11 the diet.

12 OEHHA STAFF TOXICOLOGIST WINDER: No.

13 PANEL MEMBER HAMMOND: A soy based diet or
14 something.

15 OEHHA STAFF TOXICOLOGIST WINDER: So what this
16 represents, the gap between adequate and the upper
17 limit represents what a normal individual should be
18 taking in on a daily basis.

19 PANEL MEMBER HAMMOND: And there's no
20 estimation made for infants?

21 OEHHA STAFF TOXICOLOGIST WINDER: These data
22 were derived based on dietary intake and observation of
23 either neurotoxicity or deficiency, and there was no
24 evidence in their collection of toxicity based on
25 breast milk, manganese content.

1 PANEL MEMBER HAMMOND: Wait. Now I'm confused
2 again. I thought the brown is not an estimate of the
3 upper limit of what's in the diet but upper limit of
4 what would be dangerous in the diet.

5 OEHHA STAFF TOXICOLOGIST WINDER: Right. What
6 they're saying is they have no data to say what a toxic
7 upper limit is for the diet of a neonate.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
9 MARTY: Neonate.

10 OEHHA STAFF TOXICOLOGIST WINDER: Probably
11 it's in the same neck of the woods as what we see there
12 for two- to three-year-olds.

13 PANEL MEMBER HAMMOND: Except that there might
14 really be differences in the way --

15 OEHHA STAFF TOXICOLOGIST WINDER: There might.
16 We just don't have the data.

17 PANEL MEMBER BLANC: And the inhalation here
18 is the hypothetical inhalation at the proposed REL?

19 OEHHA STAFF TOXICOLOGIST WINDER: No. This is
20 what the individual would get if they were exposed to
21 what the Roels indicated was the average respirable
22 manganese level.

23 PANEL MEMBER HAMMOND: Could you give us a
24 number that's --

25 OEHHA STAFF TOXICOLOGIST WINDER: .215 mgs per

1 cubic year.

2 PANEL MEMBER HAMMOND: At .215 micrograms per
3 cubic --

4 OEHHA STAFF TOXICOLOGIST WINDER: No,
5 milligrams.

6 PANEL MEMBER HAMMOND: Milligrams.

7 OEHHA STAFF TOXICOLOGIST WINDER: Yes. That's
8 what Roels reported it as average exposure. Just
9 trying to show in the adult this level -- bringing this
10 level would not cause the adult to exceed the upper
11 limit in the diet whereas for an infant it could.
12 Okay.

13 So then we have the assertion that neonates do
14 not accumulate high levels of manganese in the brain
15 more quickly than adults do with similar exposures.

16 Well, the data we have for these kinds of
17 assertions are based on studies in rats. And in
18 particular, this is a study by Dorman et al. in 2000
19 exposing both neonatal and adult male rats orally to
20 manganese chloride, and both cases for a period of
21 21 days.

22 During that period of time, the neonates
23 developed higher levels of manganese than adults in
24 five of six brain areas, and I've listed them here:
25 Cerebellum, hindbrain, hippocampus, hypothalamus, and

1 then there's a category of residual.

2 The neonates compared to the controls had
3 statistically significantly higher levels in six areas
4 at the high dose whereas only three brain areas were
5 elevated in the adult.

6 At the low dose, 25 mgs per kg, four areas in
7 the neonates were significantly higher than the
8 controls whereas only one in adults. This is
9 suggesting that neonates do in fact accumulate higher
10 levels of manganese more quickly than adults do.

11 Then in that same study they observed that
12 neonatal rats had an increase in acoustic startle
13 reflex; adults did not. It's not clear what
14 significance that has in the context of human biology,
15 but the point is that the neonatal exposed individuals
16 were showing some sort of toxicity that the adults were
17 not.

18 CHAIRPERSON FROINES: Just a question. Was
19 this comment based on this study?

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: No. This is our response to that comment.

22 The comment was just made that there are no
23 data to show that neonates accumulate higher levels of
24 manganese in the brain relative to adults.

25 PANEL MEMBER BLANC: In fact -- I mean your

1 argument for carcinogenesis and childhood risk has been
2 twofold. One is that for certain things there might be
3 more carcinogenic potency. But also, they end up
4 having more years of lifetime exposure.

5 So in fact, even if neonates didn't accumulate
6 manganese more quickly than adults, exposure to a
7 neonate provides the opportunity for a bigger
8 cumulative lifetime dose and more target organ damage,
9 doesn't it?

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: It could. It could. It's a little bit of a
12 different -- well, it's a little bit of a different
13 argument.

14 Yes, it could provide more time for exposure,
15 although manganese is not a bioaccumulative toxicant,
16 so.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

18 SALMON: I don't think we're making the argument that
19 the lifetime cumulative dose of manganese is the
20 dosimetric for the toxicity, bearing in mind in
21 particular that manganese is at the lower levels in
22 essential elements and that there is a level of
23 clearance for it for most tissues. We don't know the
24 finer details.

25 CHAIRPERSON FROINES: I don't think this is a

1 toxicokinetic issue that Paul's raising.

2 Paul's raising a question that says neurologic
3 effects that occur over a cumulative basis are going to
4 be irreversible and increasing in severity, and so that
5 would make the cumulative dose an important parameter.

6 PANEL MEMBER HAMMOND: It's the effect that is
7 cumulative.

8 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

9 SALMON: Cumulative effect --

10 PANEL MEMBER BLANC: Let's take the example of
11 age of onset of Parkinsonian findings based on other
12 neurotoxins as well.

13 I mean the argument has been made that persons
14 exposed to the toxic factor in Guam atactic neuropathy,
15 even if they don't evidence the disease, shortly after
16 exposure are at risk of having earlier age onset of
17 Parkinson's because there's some threshold number of
18 basal ganglial cells that once you knock them out, when
19 you hit that threshold, that's when you lose your
20 reserve and start clinically to have Parkinson's.

21 So I would assume that if you were exposed
22 longer and as a child had a chance to knock out basal
23 ganglial cells that weren't going to regenerate, that
24 when you throw on top of that the normal loss with age,
25 you're going to get into trouble at an age where you

1 might have died otherwise long before you would ever
2 manifest Parkinsonism.

3 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

4 SALMON: Essentially your effect -- yeah, I would
5 agree. You would expect to see cumulation of the
6 effects during any period when your exposure was above
7 whatever the threshold for cause and effect is.

8 That's --

9 PANEL MEMBER HAMMOND: No, no. That's not
10 quite what he's saying.

11 PANEL MEMBER BLANC: I'm saying if you knock
12 out a certain percentage of critical cells, and then on
13 top of that you're going to be losing some through
14 aging, had you not knocked out those other ones
15 earlier, and the more you knocked out, the more likely
16 you are to have the disease. So --

17 PANEL MEMBER HAMMOND: And the younger you'll
18 get the disease.

19 PANEL MEMBER BLANC: And the younger you get
20 it.

21 So children are sensitive not because they'll
22 manifest the effect in childhood, but they're a
23 sensitive subpopulation because when they grow up
24 they'll have the condition.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: And as you can see, there's, on top of that,
2 other issues with neurotoxicity in children that have
3 been measured for manganese. So yes, that's another
4 point.

5 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

6 SALMON: That's a contributor. It contributes to the
7 reason why we are especially concerned about
8 neurotoxicity.

9 CHAIRPERSON FROINES: In addition to what Paul
10 said, Cory-Slechta at Rochester has shown very nicely
11 that exposure in the postnatal period creates this
12 susceptibility to the onset to development of
13 Parkinson's at a later time in life. So there is a
14 cumulative effect as well as some sort of postnatal
15 damage.

16 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

17 SALMON: Yes.

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: Early life origins of adult disease, that whole
20 concept.

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

22 SALMON: Yeah.

23 PANEL MEMBER BYUS: I have a question about
24 the blood-brain barrier. Tell me what you're saying
25 about manganese and the blood-brain barrier and

1 children versus adults. Are you saying anything?

2 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

3 SALMON: Well. . . .

4 PANEL MEMBER BYUS: I kind of heard two
5 conflicting things.

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

7 MARTY: I think one thing that you heard was that
8 direct access to the brain from the olfactory nerve --

9 PANEL MEMBER BYUS: Bypass --

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: -- bypasses the blood-brain barrier.

12 PANEL MEMBER BYUS: All right. That's A.

13 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

14 SALMON: I don't think we said B about the blood-brain
15 barrier. I think the B that we said --

16 PANEL MEMBER BYUS: Doesn't cross the
17 blood-brain barrier.

18 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

19 SALMON: There's certainly a limitation on its ability
20 to do so.

21 PANEL MEMBER BYUS: Okay. So really what --
22 actually what the data shows, you're getting better
23 distribution, perhaps, into the brain in an infant.

24 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

25 MARTY: Yes.

1 PANEL MEMBER BYUS: Which means -- which goes
2 along with the thought that infants, well-known, have
3 an incomplete blood-brain barrier.

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

6 PANEL MEMBER BYUS: So distribution -- which
7 is not clearance, strictly distribution -- could in
8 fact be greater in an infant, so by whatever route,
9 except for olfactory, inhalation, or oral, so that
10 would increase the likelihood for neurotoxins.

11 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
12 SALMON: That's certainly possible, particularly when
13 coupled with our other point which was that the
14 intrinsic homeostasis of the blood levels appears to
15 be --

16 PANEL MEMBER BYUS: Correct.

17 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
18 SALMON: -- underdeveloped in the infant.

19 PANEL MEMBER BYUS: But even without that, you
20 don't need to invoke that in a sense. It might be --

21 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
22 SALMON: They're all additional factors.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
24 MARTY: This is not unique to manganese.

25 PANEL MEMBER BYUS: I would think distribution

1 to the brain for the infant would be the most worrisome
2 thing, if it is in fact impeded by the blood-brain
3 barrier. Which, assuming that somebody knows it must
4 be. It's charged, so I would imagine it is.

5 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, there
6 are a number of studies which kind of address what sort
7 of mechanisms --

8 PANEL MEMBER BYUS: So I would really make
9 that -- put a few sentences or a paragraph about
10 infants' incomplete blood-brain barrier. It's classic
11 for early exposure to drugs and whatever.

12 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
13 MARTY: We actually have that on page 12 as a point.

14 PANEL MEMBER BYUS: Okay. Just getting
15 distinct from the olfactory which bypasses. Okay.

16 OEHHA STAFF TOXICOLOGIST WINDER: Okay. And
17 as we point out, even whether the infants accumulate
18 faster than adults, it's not so important here as
19 whether or not the infants experience more severe
20 effects than the adults with comparable exposures or
21 comparable effects with shorter exposures. And there
22 are data that suggest this does in fact happen. These
23 are studies in rats.

24 That after -- adult rats, 120 days of
25 manganese exposure show neural degeneration, but

1 they're seeing the same sorts of levels in neural
2 degeneration in young rats after only 30 days of
3 exposure. There are a couple studies, like Chandra's
4 lab.

5 Now they say here that they have not
6 adequately substantiated the need for a 100-fold UF,
7 uncertainty factor, for the intraspecies sensitivity
8 for children. Well, this is just what we've been
9 discussing here, the idea of children being more
10 sensitive down the road than they are now, manifesting
11 the effects later on in life is one issue.

12 Here I point out that based on studies by
13 Ginsberg, there's a three- to fourfold higher
14 deposition of inhaled particles in this 1-10 micrometer
15 range in neonates versus adults.

16 In addition, from the stuff mentioned earlier,
17 there is a fourfold or higher retention of manganese
18 absorbed from the gut by neonates, and again as we
19 mentioned, lack of efficient homeostasis.

20 PANEL MEMBER BLANC: So one other thing that I
21 think will complete your thinking on this is if there
22 is data on what is the geometry of nasal clearance in a
23 neonate as opposed to an adult for those particles
24 which would normally be cleared by nasal clearance.

25 PANEL MEMBER HAMMOND: What do we know -- I

1 don't know. What do we know about the size
2 distribution of atmosphere -- you know, of
3 environmental -- I mean manganese, of manganese in the
4 environment? What do we know about that? I know more
5 by occupation but --

6 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
7 MARTY: Only what is -- the measurements are either
8 PM10 or PM2.5. I don't think there are very much data
9 on actual distribution.

10 PANEL MEMBER HAMMOND: Is it -- well,
11 between -- for some metals, PM2.5 and PM10 are the same
12 in which case we know it's all PM2.5. Do we know for
13 manganese?

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: I would have to look at ARB's data to know
16 that. It's a little bit -- it's dependent a little bit
17 on its source. If you have a facility that's actually
18 emitting manganese, it would depend on what they're
19 doing to emit it.

20 PANEL MEMBER HAMMOND: I'm just wondering --

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: But we can look at that.

23 PANEL MEMBER BLANC: My point about the nasal
24 deposition in an infant, was that clear?

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: There are some -- there are some data we can
2 put in about nasal deposition.

3 PANEL MEMBER BLANC: Of particles.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

5 MARTY: Of particles.

6 PANEL MEMBER BLANC: In infants. In neonates.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

8 MARTY: There's models.

9 PANEL MEMBER BLANC: All right, models.

10 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

11 MARTY: Well, Ginsberg is a model too.

12 PANEL MEMBER BLANC: Right.

13 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

14 MARTY: And it's, of course, dependent on size.

15 Interestingly, the model shows that there's larger
16 nasal deposition of ultrafine particles than you would
17 think. You would think they would --

18 CHAIRPERSON FROINES: No, of course they --

19 PANEL MEMBER HAMMOND: They diffuse.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

21 MARTY: Because it's diffusion, right.

22 PANEL MEMBER HAMMOND: It's diffusion.

23 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

24 MARTY: So not being a physicist, it was a surprise to
25 me. So yeah, there are some data we can --

1 PANEL MEMBER BLANC: But they're highly
2 relevant to this substance. That's all I'm saying.

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

4 MARTY: -- pull in.

5 CHAIRPERSON FROINES: We've done lots and lots
6 of studies of this, and we will look into the manganese
7 in this three particle sizes and tell you.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Good.

10 OEHHA STAFF TOXICOLOGIST WINDER: In this
11 particular -- in our response here, we're starting to
12 touch on some of the same topics we've just been
13 talking about here, the developing brain, newborns and
14 infants more sensitive to the effects of manganese and
15 that these injuries are likely to be long-lasting or to
16 have long-lasting effects.

17 Also that the neurotoxicity is only partially
18 reversible in adults, and it's likely more severe in
19 the case of infants.

20 And then we've indicated that there are
21 studies which suggest that developmental neurotoxicity
22 has been measured in infants with elevated manganese
23 from drinking water as well as elevated manganese in
24 cord blood, hair, and teeth.

25 So there are data which support that infants

1 receiving high manganese exposures are in fact showing
2 neurotoxicity.

3 Okay. They suggest that we have not
4 considered all relevant studies. Well, we've looked at
5 a large number of studies here, and we feel that the
6 Roels study is probably the best in terms of those that
7 are currently available in terms of being able to
8 quantitate -- quantitatively determine what the risks
9 are.

10 We've included a number of other studies.
11 This includes studies by Luchini and Mergler, this
12 crowd, just mainly for completeness.

13 The -- at the time these comments were
14 submitted, they were suggesting that PBPK modeling --

15 CHAIRPERSON FROINES: Can you go back to the
16 question of the adequacy of your studies? Because you
17 never want to be criticized for cherry-picking,
18 obviously. And so have you looked at those studies in
19 terms -- and I don't remember what's in here, but have
20 you made critical comments about both the adequacy and
21 what they imply?

22 PANEL MEMBER BLANC: The Luchini study is
23 certainly described at great length, and the -- and I
24 think Mergler is described.

25 But I want to -- when we finish with these

1 comments, actually, one of the main issues I want to
2 explore with you is the adequacy of the literature
3 review, the time frame of it. But I'd like to hold on
4 that just for a moment.

5 OEHHA STAFF TOXICOLOGIST WINDER: Anyway, they
6 are saying that PBPK models that were in development
7 would improve our risk assessment process. Well, these
8 models are apparently not published yet, so we're still
9 in the process of developing the REL information we
10 currently have.

11 CHAIRPERSON FROINES: Doing what?

12 OEHHA STAFF TOXICOLOGIST WINDER: We're in the
13 process of continuing with the manganese development.
14 These models are not available, not published yet.

15 PANEL MEMBER BLANC: So does that mean the
16 four-part series of articles on pharmacokinetic model
17 in manganese in the rat based upon IV exposure, not
18 inhalation data, those weren't relevant because that
19 was IV?

20 OEHHA STAFF TOXICOLOGIST WINDER: Pretty much.

21 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

22 MARTY: No, we didn't use -- they -- the folks who
23 commented submitted drafts of their PBPK modeling, but
24 they're not published yet, so they haven't been
25 peer-reviewed.

1 PANEL MEMBER BLANC: That's appropriate. But
2 the other, since there is this raft of pharmacokinetic
3 modeling articles, I mean those aren't really referred
4 to, even to say that because they're IV they're not
5 appropriate to our needs.

6 OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I
7 haven't addressed that at all. I was only looking for
8 inhalation-related exposures in modeling.

9 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
10 MARTY: We didn't comment on those.

11 OEHHA STAFF TOXICOLOGIST WINDER: But you're
12 right.

13 PANEL MEMBER BLANC: Because, for example, I
14 would suggest to you that an article entitled
15 Pharmacokinetic Modeling of Manganese in the Rat IV:
16 Assessing Factors That Contribute to Brain Accumulation
17 During Inhalation Exposure is somehow relevant to your
18 work.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: Is that one that hasn't been -- I'm not sure
21 what you're --

22 OEHHA STAFF TOXICOLOGIST WINDER: Who is the
23 author of that?

24 PANEL MEMBER BLANC: Holding it in my hand.
25 It's Nong, Andy Nong, but it's from that whole --

1 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, it's
2 from the --

3 PANEL MEMBER BLANC: -- Dorman industry.

4 OEHHA STAFF TOXICOLOGIST WINDER: -- Dorman.

5 PANEL MEMBER BLANC: I'm going to return to
6 this issue in a more generic form.

7 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
8 MARTY: Okay. That's the extent of the slides we had.

9 PANEL MEMBER BLANC: Okay. Then with the
10 Chair's permission, then, maybe I should just continue.

11 CHAIRPERSON FROINES: Yes.

12 PANEL MEMBER BLANC: This is a particularly
13 challenging subject area because there's such active
14 research going on, and you could find yourself in a
15 blind loop where no matter what you do it's going to be
16 new stuff coming out.

17 And it was really the driving factor in me
18 asking the question about how you're going to handle
19 what the cutoff time is going to be for your work.

20 But just so I'm clear, what is the cutoff time
21 for what we have before us now? When did you stop
22 looking at the literature?

23 OEHHA STAFF TOXICOLOGIST WINDER: We have been
24 reviewing the literature up to, I believe, prior to the
25 last meeting.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: April.

3 PANEL MEMBER BLANC: April. Okay.

4 Something that struck me as I started to read
5 this and then started to try to look at what was out
6 there was that, given the sensitivity and hotness of
7 this topic, I thought the literature review was
8 really -- really did yourselves a disservice for this
9 REL.

10 And if you look at some of your other RELs,
11 you have three or four times as many citations for some
12 of the other ones. Now some of the other ones are
13 about on this level, but may not be as germane. But
14 certainly the arsenic, as an example, has far more
15 literature that's invoked.

16 And I think that you're obliged in an area
17 where there is so much active research to have more
18 citations.

19 And in particular, I think that there is
20 animal -- there is primate data that is relevant as a
21 backup data to your chronic REL discussion.

22 I was really flummoxed by the nature of the
23 animal data that you cited which was ingestion data as
24 the corollary to your chronic REL. It wasn't
25 inhalation -- it wasn't animal inhalation data,

1 particularly. It was an awful lot of animal dietary
2 exposure data.

3 OEHHA STAFF TOXICOLOGIST WINDER: A number of
4 the studies, especially the Dorman comparing dietary
5 with inhalation and the effects of dietary on
6 inhalation and vice versa.

7 PANEL MEMBER BLANC: There is some of that.
8 But I think that there is a very important 2007 paper
9 from the Dorman group which is called Manganese
10 Inhalation by Rhesus Monkeys is Associated with Brain
11 Regional Changes in Biomarkers of Neurotoxicity.

12 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I
13 haven't included that.

14 PANEL MEMBER BLANC: That paper suggests a
15 fairly low LOAEL, even though they, you know, sort of
16 discount their own findings. But it's -- I think it's
17 60 micrograms per meter. And they definitely see
18 effects which I would interpret as being biomarkers of
19 localized important effects.

20 And of course -- I mean I'm going to give you
21 all this stuff -- but just in my own, you know, my own
22 view of this, I mean I think you've systematically
23 undercited that research group. Or you could be
24 misinterpreted as systematically underciting them.

25 Now I think it's important to state that

1 they -- much of their work is funded by the corporate
2 interests with the main interest in -- with a major
3 interest in manganesic air pollution effects, and
4 I'm -- I think it would be appropriate to state that if
5 you wish without any implications per se, but just to
6 acknowledge it.

7 But I think to not review that literature
8 makes it seem like you don't know what the current
9 literature is, and therefore it undermines your
10 argument.

11 Plus I think there's going to be information
12 here, aside from that, which is going to be quite
13 useful to you.

14 So I think without doing that this document is
15 not adequate.

16 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
17 MARTY: I don't think we systematically undercited the
18 work by Dorman's group.

19 PANEL MEMBER BLANC: Well, there's nothing
20 after 2002 that you cited, seems like. And they've
21 had -- or virtually nothing after 2002. And there is
22 2007, 2008, 2006.

23 Another paper that I think you're going to --
24 another epidemiological study that I think you're going
25 to be forced to summarize, even though I don't think

1 it's going to affect your judgments, it has to be the
2 Bowler study on the bridge welders.

3 I mean we're sitting here looking at where
4 that study happened. And, you know, it has a myriad
5 limitations, but I think you're going to have to
6 summarize it and deal with it in some way.

7 OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I have
8 a hard time trying to decide what to do with the welder
9 data. There are a number of studies that deal with
10 effects on welders. Unfortunately, there's a lot of
11 mixed exposures there, and it's kind of hard to sort
12 that one out.

13 PANEL MEMBER BLANC: Yeah, but since this was
14 not published as an exposure to welding fume but
15 exposure to manganese fume, I think you're obliged.

16 You can critique it by saying there were other
17 concomitant exposures and, you know, but it is a paper
18 with manganese levels and neuropsych effects and, you
19 know --

20 PANEL MEMBER HAMMOND: And any of those welder
21 exposures are not -- how many of those are neuropsych
22 effects?

23 CHAIRPERSON FROINES: Are what?

24 PANEL MEMBER HAMMOND: The other exposures
25 associated with welding are not all having

1 neurobehavioral effects, neuropsych.

2 PANEL MEMBER BLANC: Yeah, this one I think
3 you're just, just -- you just have to deal with it.

4 OEHHA STAFF TOXICOLOGIST WINDER: Sure. Okay.

5 PANEL MEMBER BLANC: Now, that's a sort of a
6 general comment. But there are some other things as
7 well.

8 And let me just ask you when you -- again,
9 this is a somewhat different situation than many of the
10 materials you're dealing with RELs with, you know, of
11 the five because you're forced to have to deal with not
12 only elemental manganese but some of the important
13 species.

14 How did you determine what you wanted to
15 include and not include in the list on table 2.1? You
16 have manganese, manganese oxide, manganese tetroxide,
17 you have manganese chloride. So it's not just element
18 and oxide. You decided to include manganese chloride.

19 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
20 MARTY: Well, that's primarily based on what gets
21 emitted from facilities in the hot spots program.

22 So it could be other manganese compounds too
23 that this would apply to, just apply to the manganese
24 fraction of those salts; but there's other salts too,
25 and they were --

1 PANEL MEMBER BLANC: The reason I ask is
2 because --

3 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
4 MARTY: We would apply this REL to all inorganic
5 manganese compounds.

6 PANEL MEMBER BLANC: Okay. Well, so there are
7 some inorganic manganese compounds which are going to
8 become issues as you go through since a lot of the
9 animal studies are with manganese sulfate.

10 OEHHA STAFF TOXICOLOGIST WINDER: Sulfate.

11 PANEL MEMBER BLANC: I think if you don't
12 include manganese sulfate in your table you should at
13 least say something about manganese sulfate because so
14 much of the data are going to be there.

15 And I think that you're obliged somewhere to
16 talk about permanganate. And I'm going to come back to
17 that a little bit in roots of exposure. But I think
18 that's a kind of a critical player in certain outbreaks
19 and case reports, so it shouldn't be ignored.

20 But when you talk about occurrence and major
21 uses in Section 3, really at the very beginning, the
22 notion that nowhere is alluded to the fact that the
23 breakdown of organic manganese compounds could become a
24 major source of inorganic manganese in the air is a
25 critical oversight in this document.

1 I mean we have a major national and
2 international debate on MMT. There's no way you could
3 know that from anywhere in this document.

4 OEHHA STAFF TOXICOLOGIST WINDER: Okay. So
5 we'll include and expand.

6 PANEL MEMBER BLANC: And as another minor
7 point, in welding, the exposure to manganese oxide,
8 yes, can occur from base metal that's being welded.

9 But I think if you look at the literature,
10 you'll find that the welding rods are the major
11 contributor to manganese exposure. Would you agree
12 with me on that?

13 PANEL MEMBER HAMMOND: Absolutely.

14 PANEL MEMBER BLANC: And the welding rods are
15 not mentioned at all. That sort of suggests a lack of
16 familiarity or a superficial view of the exposure
17 literature that could give the wrong impression.

18 And the same thing is true in the next
19 sections when you talk about how manganese can enter
20 the body. From a health point of view -- I mean you've
21 got one hat on, which is a sort of public health, air
22 pollution, and environmental thing; but since you
23 end up -- one ends up deriving information from other
24 sources, I think it should be acknowledged that
25 parental exposure to manganese has been quite important

1 in human health in terms of the recent outbreak of
2 manganism in IV drug abusers who have used potassium
3 permanganate to generate modified sympathomimetics.

4 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
5 MARTY: Ephedrine.

6 PANEL MEMBER BLANC: Yeah. I think it has to
7 be, I mean, an internal article, you know, that kind of
8 outbreak needs to be alluded to, at least in passing.

9 And certainly historically, parental feeding
10 of manganese and it's an important model because it
11 demonstrates how critical the normal homeostasis is.

12 OEHHA STAFF TOXICOLOGIST WINDER: We refer to
13 parental exposure primarily to show that some of these
14 studies indicate that the effects of high levels of
15 manganese are derived --

16 PANEL MEMBER BLANC: But in fact, a sentence
17 says manganese can enter the body both by oral and
18 inhalation routes. Well, and obviously by parental
19 means, and that's been important.

20 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
21 MARTY: Environmental manganese.

22 PANEL MEMBER BLANC: Well, if that's what you
23 mean. Although we would acknowledge that parental
24 exposure has been important in human disease, or
25 something like that.

1 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

2 MARTY: Yeah.

3 PANEL MEMBER BLANC: As well as subcutaneous,
4 by the way, I think when you say it's -- external
5 absorption of manganese is insignificant through intact
6 skin but, you know, for example use of potassium
7 permanganate on wounded skin, you know, may be not such
8 a trivial thing.

9 And there is stuff here on -- again, this is
10 where you start to get into -- it started to be
11 confusing to me about the olfactory absorption. And
12 when you use the term inhalation, sometimes you mean
13 inhalation to the lung, and sometimes you mean airborne
14 exposure that could lead to upper as well as lower
15 airway tract exposure.

16 And so I think you need to go back and be
17 meticulous when you say what it is you mean when you
18 say certain things because I think it's really, really
19 important for this compound.

20 OEHHA STAFF TOXICOLOGIST WINDER: So
21 distinction between nasal intake versus pulmonary.

22 PANEL MEMBER BLANC: Yeah, just be careful of
23 your wording.

24 And do you feel that you're obliged to
25 acknowledge and then discount this whole thing about

1 aerosol generation of manganese in showers from -- you
2 know how there was this whole little brouhaha about
3 what is the theoretical exposure to people if they have
4 high manganese water --

5 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

6 MARTY: In the water.

7 PANEL MEMBER BLANC: -- that they generate
8 aerosol?

9 OEHHA STAFF TOXICOLOGIST WINDER: Seemed like
10 in the literature that was pretty effectively
11 discounted there, and that's the reason it wasn't
12 included here.

13 PANEL MEMBER BLANC: That's the kind of thing
14 again where, depending on your desires or needs, you
15 can say although this has been raised it has been
16 subsequently discounted, rather than just not
17 mentioning it at all. You know, if in fact that's what
18 you think.

19 And again, I would call your attention to the
20 paragraph on page 5 that deals with the nasal issue,
21 and I want you to go back over that and think about
22 what you're trying to say, what the issues of particle
23 size are.

24 One of the papers you cite has to do with, I
25 think, small particles, but it's not at all clear to me

1 that large particulates can't be taken up by the nose
2 as well. So you need to go back to the papers you
3 cited and really see.

4 Now your decision to not make any acute
5 manganese REL, even though it might be a pretty high
6 REL, is because the data on pulmonary acute lung injury
7 from high-level manganese inhalation which is often
8 alluded to in the literature, there's such poor case
9 reports and so limited. Is that right?

10 OEHHA STAFF TOXICOLOGIST WINDER: That's part
11 of it. And the information seems to suggest -- the
12 pulmonary response associated with acute exposure
13 doesn't seem to be unique to manganese.

14 PANEL MEMBER BLANC: Well, I didn't understand
15 that at all. Your line that -- okay: However, a
16 pulmonary inflammatory response is also associated with
17 inhalation of particulates in general and does not
18 appear to be dependent on the manganese content.

19 OEHHA STAFF TOXICOLOGIST WINDER: So --

20 PANEL MEMBER BLANC: I don't believe that's
21 true at all. And I don't support that statement.

22 OEHHA STAFF TOXICOLOGIST WINDER: I haven't
23 seen data to suggest that the manganese content there
24 was shown to be --

25 PANEL MEMBER BLANC: I haven't seen data that

1 support a generic effect from particulates causing
2 pulmonary edema.

3 PANEL MEMBER HAMMOND: Pulmonary edema?

4 PANEL MEMBER BLANC: Yeah. So I don't know
5 what it is you were trying to say there, but I don't
6 agree with it, and -- or I don't think it was clear.
7 Or I'm disagreeing with something that you didn't mean
8 to say.

9 CHAIRPERSON FROINES: Where is that?

10 PANEL MEMBER BLANC: Point 5.

11 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

12 MARTY: That sentence doesn't seem to follow anyway.
13 It doesn't follow the sentence before it. So I'm not
14 sure if it's left over from an earlier version or what.

15 AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

16 SALMON: Sounds like we need to rework that one.

17 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

18 MARTY: We need to take the sentence out.

19 I think a more pertinent issue is the lack of
20 dose response formation to generate an acute REL.

21 PANEL MEMBER BLANC: Well, you have this --
22 one is a two-hour exposure of mice to manganese oxide
23 aerosols that resulted in a NOAEL of 2.91 milligrams
24 per meter based on pulmonary edema.

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: We can relook at that to see if it's worth it.

2 PANEL MEMBER BLANC: Okay. Because it doesn't
3 hold together, just the way -- God knows you've found
4 acute RELs on less. I don't know.

5 I also wasn't that comfortable with you guys
6 citing at certain key places ATSDR as your source
7 for -- because that in itself is a review.

8 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

9 MARTY: Right.

10 PANEL MEMBER BLANC: I think you should avoid
11 doing that if you can.

12 CHAIRPERSON FROINES: I think as a matter of
13 policy, in general, I think we should use primary
14 references and not secondary sources.

15 I don't necessarily have -- put great stock in
16 ATSDR documents, and it would be better to use the
17 primary references. Just as a general point.

18 Can I ask one question, Paul, before you go
19 on.

20 PANEL MEMBER BLANC: Yeah.

21 CHAIRPERSON FROINES: Do you know for a fact,
22 do you have any evidence from electrochemical
23 potentials that manganese would undergo Fenton
24 reactions with hydrogen peroxide?

25 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

1 MARTY: We have not explored that issue.

2 CHAIRPERSON FROINES: We know iron does. We
3 know copper does. We know metals with a valence state
4 of 2 undergo Fenton reactions and create reactive
5 oxygen, hydroxyl radicals. So it would be worth at
6 least knowing that E0 is not right for that reaction.

7 PANEL MEMBER BLANC: If you go to 6.2.1 on
8 page 12 which is your potential for differential
9 effects in children section. And this comes back to
10 the discussion we just had and the response to the
11 critic. And in fact, it may have been this that
12 generated -- unnecessarily generated some of the
13 response that you got.

14 I don't find this a particularly well-argued
15 bullet point section, and it seems as if they were all
16 toxicokinetic arguments without any toxicodynamic
17 arguments.

18 OEHHA STAFF TOXICOLOGIST WINDER: It's true;
19 they largely are.

20 PANEL MEMBER BLANC: But yet I would say the
21 compelling thing to me would be toxicodynamic -- or as
22 compelling, at least, in this kind of neurotoxin.

23 So I think you need to go back through there,
24 and if there are things, first of all, which are really
25 sort of not so important, I'd just get rid of them, if

1 you think they're more controversial than not, and try
2 to have a balanced argument.

3 Then if you -- just to underscore what I said
4 about the animal studies and how I was a little bit
5 surprised and taken aback, when you get to a section on
6 animal studies of chronic toxicity, you start with an
7 oral study -- which I couldn't figure out why you were
8 starting with that -- then you do go to a study with
9 four rhesus monkeys from 1984, and then you go to an
10 injection study.

11 And that's what made me go look at PubMed. I
12 said really? There is no -- this is all this is for
13 inhalation study? I thought there was a lot of primate
14 stuff going on. What's happening? So that was really
15 weak.

16 And I know you showed that figure -- I mean on
17 the diet. I think that's a -- I think what I would do
18 if I were you is get rid of that figure and make your
19 key point in a couple of sentences.

20 But the figure -- first of all, the legend is
21 not interpretable as it is. I didn't know the upper
22 limit to what, you know. But I think it's really kind
23 of an obscure -- it's not straightforward to me at all.

24 And I think some of the other things we've
25 talked about as we've gone through.

1 So I think that this document which is --
2 could emerge as a major public health protective issue
3 in the State of California, were we to see the
4 introduction of organified manganese into our breathing
5 zones, I want to see this particular document be as
6 strong as it can be.

7 And I think, you know, for better or for
8 worse, you have to respond to a series of -- you know,
9 a very long critique which really wasn't to the -- very
10 much to the point, so then that diverted you to respond
11 to things that ultimately didn't make the document
12 stronger one way or the other because they were sort of
13 off the mark anyway.

14 OEHHA STAFF TOXICOLOGIST WINDER: Okay.

15 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
16 MARTY: Sounds like we have some additional work to do
17 on this REL summary.

18 PANEL MEMBER BLANC: And given your expertise
19 in primate exposure stuff, I think that you could maybe
20 be a resource for them looking at some of these
21 studies. The animal stuff is the first example we've
22 had of a rich data set of primate data.

23 PANEL MEMBER PLOPPER: Sure. That's true.

24 PANEL MEMBER BLANC: That's it.

25 CHAIRPERSON FROINES: I'm sure they'll

1 consider that enough.

2 PANEL MEMBER PLOPPER: Good start.

3 CHAIRPERSON FROINES: Is there a motion to --
4 I don't think there's anything else that I know of.

5 PANEL MEMBER GLANTZ: Did anybody else have
6 anything they wanted to say? I don't.

7 PANEL MEMBER BYUS: I think the document is --
8 the parent document is very good. I think it's very
9 nicely crafted and put together, and most of the REL
10 calculations are also very good. And I think it's
11 going to be a really nice addition, and you did a nice
12 job on it.

13 CHAIRPERSON FROINES: Melanie?

14 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
15 MARTY: Okay. We need another meeting, obviously, for
16 this document. So I was talking with Jim earlier.
17 What we could do is have a meeting, September's time
18 frame, to finish the REL summaries, and also at that
19 time introduce the cancer risk assessment changes.

20 That document is going out for public review
21 starting next week for a 60-day review which might end
22 up being longer, so you won't have in September the
23 public comments and our responses.

24 But we could have a meeting to finish this off
25 and introduce the Panel to the changes that are now

1 being proposed for cancer risk assessment.

2 So just putting that out there.

3 CHAIRPERSON FROINES: So I think, Peter, we're
4 talking about September. We're not talking about
5 anything sooner than that. And then school starts, so
6 that everybody gets pretty busy, so September is
7 probably the best time that I can think of.

8 PANEL MEMBER HAMMOND: School starts in August
9 for me.

10 CHAIRPERSON FROINES: Is Davis quarter or
11 semester?

12 PANEL MEMBER PLOPPER: Quarter.

13 CHAIRPERSON FROINES: So Charlie and I are
14 okay.

15 PANEL MEMBER BYUS: Medical school has blocks.

16 CHAIRPERSON FROINES: Okay. Anything else
17 from OEHHA today?

18 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

19 MARTY: I'm sorry?

20 CHAIRPERSON FROINES: Do you have any other
21 issues.

22 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

23 MARTY: No, just that one.

24 CHAIRPERSON FROINES: Good. Anybody else on
25 the Panel have comments? Joe?

1 PANEL MEMBER LANDOLPH: Is Roger going to come
2 back to us someday, or do we know?

3 CHAIRPERSON FROINES: Jim, do you want to give
4 a report?

5 MR. BEHRMANN: Jim Behrmann, liaison to the
6 Panel.

7 In my several conversations with Roger, he
8 expressed his willingness to continue providing
9 assistance to ARB and OEHHA and DPR but feels that he
10 cannot easily travel at the moment given his wife's
11 condition.

12 She was coming back from very serious surgery,
13 and there were some complications, as I understand it.
14 So he felt that he wanted to be -- he did not feel it
15 was easy for him to travel, so he felt the need to step
16 down from the Panel.

17 CHAIRPERSON FROINES: So the next step is to
18 get a list of names from the university.

19 MR. BEHRMANN: What the next step will be is
20 that we request an updated list from the president of
21 UC. They create a pool of nominees, and that
22 particular category is appointed by the secretary of
23 Cal/EPA.

24 So once that pool of nominees is created, then
25 a decision will be made by Secretary Adams, and an

1 appointment will be made. So we're just initiating
2 that process right now.

3 PANEL MEMBER BYUS: Are you going to ask Roger
4 who he would recommend?

5 MR. BEHRMANN: Yes.

6 PANEL MEMBER BYUS: Very good. I mean that's
7 who I'd ask.

8 CHAIRPERSON FROINES: Well, I think it's
9 important for the Panel to give you input about -- I
10 mean I have rather strong feelings about what our needs
11 might be, but I think that why don't we let people
12 communicate with you?

13 MR. BEHRMANN: Please, if you have names,
14 please do submit them to me, and we can pass them on.

15 As you know, the UC president's office runs
16 its own process, and they run a very careful process in
17 terms of vetting candidates and the like. But I'm sure
18 they would be open to receiving names from us as well.

19 CHAIRPERSON FROINES: Well, we have one, two,
20 three, four people who we would classify as
21 toxicologists, I think. And Stan is a statistician and
22 Kathy is exposure assessment, and Paul's a physician
23 toxicologist/exposure assessor --

24 PANEL MEMBER GLANTZ: Curmudgeon.

25 PANEL MEMBER BYUS: Curmudgeon.

1 (Laughter)

2 CHAIRPERSON FROINES: Just the thing that's
3 important is the data that we review tends to fall into
4 three categories: Epidemiologic data, exposure data,
5 and toxicologic data.

6 So my view is that we need somebody who would
7 help in the exposure area, exposure assessment area.

8 PANEL MEMBER HAMMOND: In particular, I think
9 Roger brought an understanding of atmospheric
10 chemistry.

11 MR. BEHRMANN: That actually is the category
12 in the law that he fulfilled.

13 CHAIRPERSON FROINES: I would argue that I
14 would prefer somebody who had a little bit more
15 understanding of some of the exposure issues that
16 relate to epidemiologic studies.

17 PANEL MEMBER HAMMOND: Oh, I'm not saying it's
18 not important, but I think it shouldn't just be
19 exposure assessment that doesn't know atmospheric
20 chemistry.

21 MR. BEHRMANN: By law they would have to also
22 be an atmospheric chemist or be trained in that field.

23 CHAIRPERSON FROINES: We would like to
24 convince ARB to take up some atmospheric chemistry
25 issues, because that hasn't happened in 20 -- how many

1 years?

2 MR. BEHRMANN: The Panel --

3 CHAIRPERSON FROINES: 25 years, has not
4 happened.

5 MR. BEHRMANN: I'll communicate that to the
6 Air Resources Board, or I can pass this message on.

7 PANEL MEMBER BLANC: I think they should have
8 a Scots accent.

9 CHAIRPERSON FROINES: What did he say?

10 PANEL MEMBER BLANC: They should have a Scots
11 accent because I miss that.

12 CHAIRPERSON FROINES: Anybody want to make a
13 motion to adjourn?

14 PANEL MEMBER BYUS: I move we adjourn.

15 PANEL MEMBER BLANC: Second.

16 CHAIRPERSON FROINES: All in favor?

17 (Ayes)

18 * * *

19 (Thereupon the California Air Resources
20 Board, Scientific Review Panel meeting
21 adjourned at 3:29 p.m.)
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23
24
25

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