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PETERS SHORTHAND REPORTING CORPORATION (916) 362-2345
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PETERS SHORTHAND REPORTING CORPORATION (916) 362-2345
CHAIRPERSON FROINES: We will open the meeting of the Scientific Review Panel for June 18, 2008. And the first items on the agenda are the continuation of the panel's review of the draft report, Air Toxic Hot Spots Risk Assessment Guidelines, and we're talking about the technical support document. So Melanie, I think you're up.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Hi, good morning. Melanie Marty.

CHAIRPERSON FROINES: Melanie Marty.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. There is a -- what we want to do today is go over the revisions that were made to the main body of the report, the technical support document, pursuant to the last meeting and the comments that the Panel made as well some comments from the Lead and a few of the other Panel members. So we'll go over that. Then we'll move on to the last three remaining chemicals that we haven't given a presentation to you yet but you have seen -- you've read the report. That would be acrolein, formaldehyde, and manganese.

But before we begin, I did want to mention one legal technical issue that happened when we noticed the
meeting. The meeting had the correct title of the
document, but it had April 2008 as the date rather than
June 2008.

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

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

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

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

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

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

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

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

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

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

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

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

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

It is interesting that you brought up the fiber issue because there is a recent paper that looked
at carbon nanotube fibers in a rodent study and was
able to produce some of the early lesions that asbestos
produces in a rodent model.

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

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

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

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

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

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

PANEL MEMBER GLANTZ: This is a symptom of
PTSD.

(Laughter)

CHAIRPERSON FROINES: What, the lights?

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

(Laughter)
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

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

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

We added a brief discussion of elderly --

CHAIRPERSON FROINES: Is this that -- is this?

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

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

We clarified the summary of proposed changes.

So I had staff go back and look and make sure that everything that was embedded in the document that was a proposed change was actually in the summary.

We revised the weight of evidence discussion per Panel comments from the last meeting and suggested edits from Drs. Glantz and Blanc. These included
expanding the selected methodological issues that one considers in looking at epidemiology data as well as toxicology data.

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

Those changes were all in revisions mode in the document.

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

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

(Laughter)

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

And we added a sentence summarizing the implications of the information in Table 4.4.2.
We added examples of when application of the
database deficiency uncertainty factor might be
appropriate. That was in response to a lengthy
discussion at the last meeting.

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

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

PANEL MEMBER GLANTZ: Yes.

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

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

One other thing. We'll get on to the findings
that you'd asked us to draft, and I apologize; I
thought these had been sent out to the Panel, but they hadn’t.

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

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

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

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

CHAIRPERSON FROINES: Yeah. Like MTBE, we never wrote a word, and that was a big one.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

CHAIRPERSON FROINES: It is a strategic question.

PANEL MEMBER GLANTZ: Well, no --

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

And you folks did do findings when we established the first list of five in 2001 related to the TAC prioritization document which you all reviewed. In those findings, you talked about how we'd prioritized and then the evidence for each of those five chemicals with respect to differential impacts on kids.
So that would be useful.

CHAIRPERSON FROINES: Gary looks troubled.

PANEL MEMBER FRIEDMAN: About something else.

CHAIRPERSON FROINES: Okay.

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

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

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

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

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

CHAIRPERSON FROINES: Go ahead.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: No.

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

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

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

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

CHAIRPERSON FROINES: Please.

PANEL MEMBER FRIEDMAN: I really appreciated
all the responses to all my comments, but there's one
little residual nitpick that I have, and that relates
to Roman numeral page XII. This is of the executive
summary.
When you talk about trigeminal nerve mediated irritation of the eyes, nose, and upper airway. It seems to me that this sounds like something is happening to the nerve and that therefore, as a secondary effect, that affects the eyes, nose, and upper airway, and it's really the reverse. These things get irritated, and it's the trigeminal nerve that transmits those to the brain. So when you say trigeminal mediated, it just doesn't make sense to me.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

PANEL MEMBER FRIEDMAN: That's my only --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: The trigeminal nerve is --

PANEL MEMBER HAMMOND: Transmitted.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: -- speaking to the brain.

PANEL MEMBER FRIEDMAN: Right.

PANEL MEMBER HAMMOND: It's being transmitted.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Transmitted. How about trigeminal nerve
transmitted?

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

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

(Recess)

CHAIRPERSON FROINES: We're back on the record.

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

Gary, did you have changes?

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

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

PANEL MEMBER FRIEDMAN: Should I write it on this?

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER FRIEDMAN: That's all I have.
CHAIRPERSON FROINES: Joe?

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

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

PANEL MEMBER LANDOLPH: To?

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

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

CHAIRPERSON FROINES: Stan?

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

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

CHAIRPERSON FROINES: Kathy?

PANEL MEMBER HAMMOND: Fine.

CHAIRPERSON FROINES: Charlie?

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

( Interruption by the reporter)

PANEL MEMBER PLOPPER: Number one, just a
comment about undeveloped metabolic and elimination
capabilities resulting in longer clearance half-times.

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

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

And --

CHAIRPERSON FROINES: Where are you?

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

PANEL MEMBER GLANTZ: What wording change did
you want?

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

So what that -- to my interpretation, that
would mean that if the clearance is the same in
children as it is in adults, then there is no toxic difference, and that's not going to be the case.

CHAIRPERSON FROINES: How would you change it?

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

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

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

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

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

PANEL MEMBER PLOPPER: Okay.

PANEL MEMBER GLANTZ: Maybe the thing to do, because I actually -- that, the specific, you know, underdeveloped metabolic and elimination capabilities is what the report mostly talks about. So maybe we
should add another phrase. Keep that and add --

PANEL MEMBER BLANC: Comma, although other

imbalances could also occur.

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER PLOPPER: Yes. Resulting in

heightened toxicity.

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

PANEL MEMBER PLOPPER: That sounds good.

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

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

CHAIRPERSON FROINES: Wait. I have to find
it.

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

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

CHAIRPERSON FROINES: Okay. Because of
underdeveloped --

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

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

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

PANEL MEMBER GLANTZ: Okay. Well --

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

PANEL MEMBER GLANTZ: That's true.

PANEL MEMBER BLANC: Other metabolic --

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

CHAIRPERSON FROINES: There are other metabolic differences?

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

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

Well -- no, this is a way to -- and here's the wording she suggested which I thought was -- dealt with this. To change it to say: Differentially affected by
some compounds because of developmentally related
differences in meta- -- instead of underdeveloped, and
elimination -- metabolic and elimination capabilities
resulting in longer clearance half-times.
I think that does what you want.

PANEL MEMBER PLOPPER: That -- that's great.
PANEL MEMBER GLANTZ: Okay. So the specific
change is to change the word "underdeveloped," delete
that word, and change it to developmentally related
differences in.
Okay. Are you happy with that?
PANEL MEMBER PLOPPER: All right.
PANEL MEMBER GLANTZ: Actually, that was my
idea, right? No.

CHAIRPERSON FROINES: These all come from the
Panel.
PANEL MEMBER GLANTZ: Yeah. But we are
allowed to accept good suggestions. That's a
clarification. So I think that gets at what you're
talking about.
PANEL MEMBER PLOPPER: That's fine.
PANEL MEMBER GLANTZ: So just again, to be
really clear: We're deleting the word "underdeveloped"
and changing it to say: Developmentally related
differences in.
CHAIRPERSON FROINES: Okay.

PANEL MEMBER PLOPPER: That's good.

PANEL MEMBER GLANTZ: That's better.

PANEL MEMBER PLOPPER: Good.

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

CHAIRPERSON FROINES: Wait. Is Charlie finished?

PANEL MEMBER PLOPPER: That was my main.

PANEL MEMBER BYUS: On the sentence above this about the pharmacodynamic differences.

I might say in parentheses you have to account for differences in interactions at the receptor by age. I might say to account for the quantitative and qualitative differences in interaction at the receptors.

And I would make it parentheses S, because there is more than one necessarily. I mean you don't know what -- it isn't a classic receptor. Sometimes it is for these things, and sometimes it isn't. It's just a macromolecule that binds to it.

So I don't know what -- you might even put the term receptor in parentheses -- I don't -- if you wanted to. But I would certainly put a parentheses S because there is oftentimes more than one.
CHAIRPERSON FROINES: Walk us through it.

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

CHAIRPERSON FROINES: For differences at the receptor --

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

PANEL MEMBER BYUS: That's it.

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

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

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

PANEL MEMBER BLANC: Well, I think that's inappropriate.
PANEL MEMBER GLANTZ: Okay. We can delete it if you want.

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

PANEL MEMBER GLANTZ: Okay.

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

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

CHAIRPERSON FROINES: And what's point 6?

That --

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

PANEL MEMBER HAMMOND: Stand alone.

CHAIRPERSON FROINES: Is that correct?

PANEL MEMBER BLANC: Yeah, that was my
suggestion. If you believe it's important enough.

PANEL MEMBER GLANTZ: It doesn't matter to me.

I'm happy to do it.

PANEL MEMBER BLANC: And also --

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

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

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

PANEL MEMBER GLANTZ: Right. Okay.

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

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

CHAIRPERSON FROINES: Andy?

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

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The clearest specific example where we would
I want to do this is in cases we are using what we describe as the US EPA's effective concentration of the HEC calculation which is a deposition model which has data about the test species, but it isn't chemical specific, if you have some particle size or something like that.

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

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

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

PANEL MEMBER BLANC: Well, then I would suggest simply deleting the words "when using a partial dissymmetry model" and say the Panel also agrees that a pharmacokinetic uncertainty factor could still be applied to account for residual uncertainty for either interspecies or intraspecies extrapolation.
PANEL MEMBER GLANTZ: All right. That's good, yeah.

CHAIRPERSON FROINES: Help me here, Paul.

For --

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

CHAIRPERSON FROINES: I understand all that.

You're taking out when using a partial dissymmetry model from either --

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

CHAIRPERSON FROINES: Okay. Good.

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

(Laughter)

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

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

Because again, it presumes a certain . . .

And also, similarly, a bit later in that point on the
very last page as we currently have it, OEHHA recommends increasing the default exponent in the modified Haber's law from 2 to 3. I think it should be the default exponent for concentration, just to make that clear, because that's what you're talking about, right? And John, I have a few other just grammatical things, and I'll just pass that on. I think --

CHAIRPERSON FROINES: Pass it on to Jim.
PANEL MEMBER BLANC: -- Stan and I clearly differ on our views on commas and where they should be used, for example.

CHAIRPERSON FROINES: So --
PANEL MEMBER BLANC: I'll be happy to get you a copy of Strunk & White at some point if you'd like to revisit it.
PANEL MEMBER GLANTZ: I have one.
PANEL MEMBER BLANC: Do you.
(Laughter)

CHAIRPERSON FROINES: So everybody will give their changes to Jim, and Jim will give all the changes to me, and I'll make the changes. And I think what we should do is to vote pending --
PANEL MEMBER BLANC: I only have one other question for Stan, basically. And that is: Do you
feel that there's any need for a numeric point related
to the summary of causality, et cetera, in the document
or not?

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

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

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

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

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

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

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

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

PANEL MEMBER GLANTZ: Okay. All right. Well,
28

I will go do that.

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

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

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

Wait one second. I'm sorry to delay you.

Yeah, it's in the very first paragraph. There's a
parenthetic comment: The actual approved RELs for
these chemicals are addressed in a separate set of
findings.

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

PANEL MEMBER GLANTZ: Mm-hmm.

CHAIRPERSON FROINES: Are you going to go?

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

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

PANEL MEMBER GLANTZ: Yeah, I'll do that.

I'll just sit here and do it.
PANEL MEMBER BLANC: I think I have a question for Melanie.

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

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

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

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

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

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

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

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

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

And right now, this document is not a document
one could be successful with because it would be
confusing when you get into the square root of 3 and
what have you.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

PANEL MEMBER HAMMOND: How many lectures are you doing?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: OEHHA is doing the whole course.

CHAIRPERSON FROINES: So you'll make those -- PANEL MEMBER GLANTZ: Can we take it?

(Laughter)

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Sure.

CHAIRPERSON FROINES: -- teach a risk assessment class?

I think it's important. I think that the trouble is we live in this very enclosed world. And
obviously industry groups are interested in what is happening because it affects them directly, but the -- it's very internalized. So the more explicit we can make it, I think it's to everybody's advantage. So shall we move on to the specific chemicals, Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes.

CHAIRPERSON FROINES: Gary?

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

CHAIRPERSON FROINES: Can we do arsenic first?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Absolutely.

CHAIRPERSON FROINES: I have a question that relates to arsenic. I'm assuming that this is an apples and oranges issue, and that is that you have a PHG which shows a very high degree of potency for arsenic in drinking water, and yet today we're talking about noncancer risk assessment, so that PHG is not germane to this discussion; is that correct?
MARTY: Right, right. We also have a potency factor for inhalation exposure to arsenic as well.

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

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

OEHHA STAFF TOXICOLOGIST BROWN: Joe Brown, OEHHA.

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

Next slide, please.

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

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

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

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

Next slide, please.

PANEL MEMBER FRIEDMAN: Could I interrupt there?

OEHHA STAFF TOXICOLOGIST BROWN: Sure.

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

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

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

OEHHA STAFF TOXICOLOGIST BROWN: It didn't fit, but if you look at the graph, it doesn't look that bad. It's one of these, if you want to -- it's one of
these statistical versus biological significance questions.

PANEL MEMBER FRIEDMAN: So compared to other models --

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

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

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

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

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

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

OEHHA STAFF TOXICOLOGIST BROWN: This is --
Dr. Blanc suggested that we ought to take a look at the loss of lung function as a function of intake of arsenic.

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

Next slide, please.

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

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

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

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

We did not change the REL. So these are basically additional values trying to put things in
perspective, but did not change the bottom line values that we had.

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

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

PANEL MEMBER BLANC: -- of the value --

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It also showed that the choice of the study for the reference exposure level was the most sensitive human study.

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We skipped to arsenic first, so they're --

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- towards the back.

OEHHA STAFF TOXICOLOGIST BROWN: Toward the back.
CHAIRPERSON FROINES: I got it. We're okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

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

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

PANEL MEMBER BLANC: I commend you for doing that.

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

PANEL MEMBER BLANC: I also think it's an extremely thoroughly referenced REL, and I'm going to come back to that topic later in our meeting today.
OEHHA STAFF TOXICOLOGIST BROWN: We could add more references because they keep growing.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: There is a huge amount of data on our side.

PANEL MEMBER BLANC: I understand.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We have that.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Shall we continue with --

CHAIRPERSON FROINES: Please.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- changes made to --

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

CHAIRPERSON FROINES: Oh, sorry. My fault.

PANEL MEMBER FRIEDMAN: Well, I just want to thank you. You made a lot of changes according my
recommendations. They were mostly minor clarifications.

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

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

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

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

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

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

PANEL MEMBER FRIEDMAN: That would solve it.

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

PANEL MEMBER FRIEDMAN: That was my only
CHAIRPERSON FROINES: Do we want to vote on an individual chemical basis? Yes?

PANEL MEMBER BLANC: I think if you do that, you're going to lock yourself into findings, separate findings for each chemical. And as little things come up today with the presentations, rather than putting ourselves into the position of having to say we would approve it contingent on the minor changes that we've discussed, we'll be able -- since we know we can't approve all five of them today, it will allow us to avoid any confusion about this issue with the dates and all that. So I wouldn't at this point vote on any of the specific RELs.

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

PANEL MEMBER BLANC: Yep.

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

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

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: Melanie, I had to apologize. I sent in my comments late, and I think
they were too late to get into this document.

But when you have time, could you look at them

and find if they're appropriate?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes.

PANEL MEMBER LANDOLPH: My apologies for being

late.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: We actually did take most of your comments and

get them in. I think there were a few that we didn't.

CHAIRPERSON FROINES: So we should come to

that when we get to acrolein.

So does everybody agree with Paul that we

should defer overall approval until we have a complete

package?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay.

CHAIRPERSON FROINES: I'm getting nods, so I

think I'll go with the nods.

Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes. Okay. Back to the center of that

handout, acetaldehyde.

Karen Riveles is going to go over the changes

made in response to the last Panel meeting to the
acetaldehyde REL summary.

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Hello.

I'm Karen Riveles, OEHHA.

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

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

So what's the connection between the two agencies?

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

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

And the ARB did model the concentrations of acetaldehyde in the air, and they did find that they
were elevated. But if you take all of the carcinogens
together that were modeled, some went up, some went
down so that there wasn't a change in the cancer risk
from the gasoline-related carcinogens that were
modeled. So that's one thing.

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

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

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

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

PANEL MEMBER FRIEDMAN: John, could you
elaborate a little? It sounded like you said we're
using a lot of ethanol now here, and I don't know where
I can get it for a car. Where is it being used?

CHAIRPERSON FROINES: As an additive to
gasoline.

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

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

PANEL MEMBER FRIEDMAN: What percentage of
the --

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

PANEL MEMBER HAMMOND: I've seen ten percent.

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

CHAIRPERSON FROINES: And from the developing
countries.

PANEL MEMBER BLANC: Perhaps we can proceed.

CHAIRPERSON FROINES: We can proceed. But I
want to raise it as an issue, even with Paul's
hesitation, because I think this is a quite significant
issue which is going to grow over time.
So you're on your own.

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

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

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

These changes and additions are seen in the
revisions mode in the document that was sent to the
Panel.

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

So in the studies, there were four studies
that used Japanese subjects and two studies that used
Caucasian subjects. In the studies that used Japanese subjects, these subjects were either asthmatic or nonasthmatic.

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

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

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

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

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

This is indeed in the similar concentration...
range as our key study for our REL determination which we used a concentration of 25 ppm in human volunteers according to the Silverman study.

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

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

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

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

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

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

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

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

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

And those are the revisions that were made.

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

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

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

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: I have a question.

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

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That was not addressed in the study.
PANEL MEMBER LANDOLPH: Thank you.

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

CHAIRPERSON FROINES: Other comments? Paul.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sorry.

PANEL MEMBER BLANC: Yeah. I want to go back to your acute REL which still uses the 1946 study. There doesn't seem to have been any change in your uncertainty factors based on the observation that at a half-an-order-of-magnitude-lower dose there was an effect which was not the mild eye irritation effect of your reference study but rather a not-mild effect which would be bronchoconstriction.

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

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

I think what we felt was in doing so we were
actually in -- it supported use of the toxicodynamic factor of 10 for potential asthma exacerbation in children. So --

PANEL MEMBER BLANC: I agree with that part.

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

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

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's how we get to 60.

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

PANEL MEMBER BLANC: For that.
MARTY: Right.

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

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

PANEL MEMBER BLANC: Yeah.

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

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

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

CHAIRPERSON FROINES: What's your particle
size in your aerosol?

Air Toxicology and Epidemiology Branch Chief

Marty: I don't think that they have that information.

Panel Member Blanc: Well, they said what kind of nebulizer it was. Wasn't it DeVilbiss or something?

OEHHA Associate Toxicologist Riveles: It's a, yeah, DeBliss.

Panel Member Blanc: DeVilbiss?

OEHHA Associate Toxicologist Riveles: Yes.

Panel Member Blanc: And DeVilbiss does have a standard, characterized particle size. And in fact, there is a wealth of information on delivered dose with an aerosol which is not the same thing as instillation.

Panel Member Plopper: So did they install it -- or was it instillation or was it by inhalation? I don't understand.

Air Toxicology and Epidemiology Branch Chief

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

Panel Member Plopper: I know, but what he's saying is you could -- you can get a fairly accurate measure of the concentration because those nebulizers

Peters Shorthand Reporting Corporation (916) 362-2345
are very well characterized.

PANEL MEMBER HAMMOND: The other part --

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

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

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

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

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

PANEL MEMBER BLANC: Right.

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: -- that
determined the hyper-responsiveness to provocation by
methacholine, yes, it was one dose.

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

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

PANEL MEMBER BLANC: Right.

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

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

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Just as
a geometric mean.

PANEL MEMBER BLANC: Without the data.

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

PANEL MEMBER BLANC: Well, one thing that -- I
actually think this is a rather critical issue. And as
I stated the last time, it partly draws from my discomfort at having to use a 1946 study, certainly. But also we're talking about a much more critical acute endpoint which has public health relevance and where public health-protective standards are quite important coupled, of course, with John's relevant comments about the likely growing importance of this as an air pollutant.

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

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

Because what -- as I understood it from your previous presentation, basically what they've shown with this chemical is that it can be used like a
methacholine test. If that is -- which is unusual.

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

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

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

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

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

And I think it's worth doing extra legwork, if possible, to try to get those data since this is a fairly critical issue and goes to the heart of the
whole intent of children as a high-risk subpopulation
from the point of view of asthma.

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

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

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

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

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

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

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

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: It's
the eye irritation study. We're using the asthma study for the acute REL. And we were using the asthma study to support the tenfold uncertainty factor in toxicodynamics, to support the increased sensitivity of the asthmatics.

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

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

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

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

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

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

PANEL MEMBER HAMMOND: This is not an instillation. Nebulizer --
MARTY: Well, to my mind, it's a lot closer to an instillation than it is to inhalation.

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

MARTY: It's a nebulizer.

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

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

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

PANEL MEMBER BLANC: Yeah, yeah.

PANEL MEMBER HAMMOND: So it's not instillation.

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

I think at our last meeting I suggested that you might want to consult with Dr. Homer Bouschet, in particular. Was that done?
MARTY: We tried, but we didn't get a response.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah.

PANEL MEMBER BLANC: Melanie, why don't you copy me on the e-mail to Homer, and then I can respond. I think the other person who might have some rather interesting comments for you would be Dr. Jay Nadel, if you don't get a response.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

PANEL MEMBER BLANC: That's in this study. But in the study I suggested you get the raw data from it was actually using, if I recall correctly from your previous summary of it, it was actually using acetaldehyde as a bronchoprovocateur, bronchoconstriction provocation chemical. Isn't that
THE WITNESS: Yes, but it was also found that the acetaldehyde was 265 times less sensitive than methacholine.

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

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

PANEL MEMBER BLANC: But I want to see the other data. I mean if you can find the other data. Because again, we're not talking about the mean response. After all, if you look at the mean methacholine response for the general population, for PC20, it would be very, very high. But if you look, you know, order of magnitude higher than for asthmatic -- the mean for asthmatics, I guess.

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

PANEL MEMBER BLANC: That makes me suspicious.

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

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

Can we go back a slide?

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

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

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Is there a suggestion that we should be adding
an additional uncertainty factor or?

PANEL MEMBER BLANC: I think the first
suggestion is to go back and try to figure out these
other things, and that may help you determine whether
you need either to add an additional uncertainty factor
or whether you in fact would be in a position to use
the acute inhalation -- the acute nebulized inhalation
data to generate your acute REL and then support that
with the 1946 data as a corollary, perhaps.

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

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

CHAIRPERSON FROINES: Kathy?

PANEL MEMBER HAMMOND: I'm sorry, I haven't
read the underlying papers here, but it's also
important to recall that acetaldehyde is highly
reactive.
So the actual concentration, especially if there's a mask which would be a high surface-to-volume ratio, if this was with a mask and tubing, you actually might have a much lower concentration.

This may be a high overestimate of the concentration that the subjects actually experienced.

Is that clear?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: I understand your comment.

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

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

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

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

On the other hand, it's particularly important as with such an important issue in California. And since we are talking about a chemical that is being
released in general, especially with some of the new
fuel additives, we need to be pretty careful about
this.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay.

PANEL MEMBER PLOPPER: There's a whole
literature that pretty much defines that.
So don't -- I mean my interpretation when I
read through this was it was -- like Paul said, this
current one that you have for the cubic exposure is too
high.

I thought that's what this document was
leading up to, and then you say that it's not. So I
think you need to get a way to calculate exactly what
those -- closer to what those concentrations are.
Because nebulization, part of the idea, it's
going to be small enough, even if they did something
wrong with their nebulizer, it's going to be small
enough that it's going to be very well inhaled and very
widely distributed. So it will have lots of contact.
May even react less than the gas particle till it gets
to the tissue.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay.

CHAIRPERSON FROINES: I wanted to make two sort of side comments sort of on a general point. One of the things we do here is we do acetaldehyde. But clearly, one of the major toxic issues of acetaldehyde is its chemistry that creates peroxynitrite. And we don't talk about that, even though that's probably a hundred times more toxic than acetaldehyde.

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

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

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

Because they're -- you know, we wrote about
the peroxynitrites in the MTBE document in the '90s and
the condensations of enol forms of acetaldehyde, you
know, every good chemist knows that chemistry.
And so we're missing things that really may
have significant toxicity, and we're focusing on
acetaldehyde, which we should. But it's just not as
simple as the way the picture is drawn.

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

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

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

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

CHAIRPERSON FROINES: Right.
MARTY: And the --

CHAIRPERSON FROINES: For which there is very little.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

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

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah.

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

(Recess)

CHAIRPERSON FROINES: Can we get started?

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

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do people have comments?

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

PANEL MEMBER HAMMOND: We'll just read it.

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

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

CHAIRPERSON FROINES: Gary?

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

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

PANEL MEMBER GLANTZ: Yeah.

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

PANEL MEMBER GLANTZ: Yeah.

PANEL MEMBER FRIEDMAN: Then near the end where you say: If the outcome is serious and the study
small, i.e., low power --

PANEL MEMBER GLANTZ: Wait, wait. Yeah.

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

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

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

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

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

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

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

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

PANEL MEMBER BYUS: Correct.

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

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

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

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

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

PANEL MEMBER BLANC: I understand what you're saying, but what's basically the function of what you're saying is I'm going to have a different threshold for the point at which I'm unwilling to
accept a false positive.

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

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

PANEL MEMBER GLANTZ: Why don't we say --

fitting with John's trying to write this in English --

PANEL MEMBER BLANC: Right.

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

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

PANEL MEMBER GLANTZ: That's true.

CHAIRPERSON FROINES: I think that you are --

I think there needs to be something about what we are measuring. In other words, the measurement itself is an end in itself.

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

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

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

PANEL MEMBER FRIEDMAN: Okay. That's --
PANEL MEMBER BYUS: That's better.
PANEL MEMBER FRIEDMAN: Yeah.
PANEL MEMBER GLANTZ: So put it up there on
the screen. That helps. Are there any other changes
people want?
PANEL MEMBER LANDOLPH: I'll let you do it
however you want, but the sentences -- lines 8 to 14,
it's just one long sentence. It runs on awful long.
If you could just figure out a way to chop it into two
short sentences.
PANEL MEMBER BYUS: Put some commas in.
PANEL MEMBER GLANTZ: The other thing is to
delete all the parenthetical statements inside the
parenthetical statements.
But the reason I kept those is because that
was something that was the subject of a lot of
discussion.
CHAIRPERSON FROINES: But we'd like to read
this into the record so it's in the record.
PANEL MEMBER GLANTZ: No, we will. You want
to let me -- so people just want me to --
CHAIRPERSON FROINES: Take a second.

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

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

PANEL MEMBER BYUS: That's better.

PANEL MEMBER FRIEDMAN: Would that do it?

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

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

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

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

PANEL MEMBER GLANTZ: Right.

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

PANEL MEMBER LANDOLPH: That's right.
CHAIRPERSON FROINES: Stan, will you make those changes, and when we break --

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

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

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

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

Melanie, let's go.

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

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

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

PANEL MEMBER BLANC: Sure.

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

OEHHA uses a weight of evidence approach
to determine whether or not exposure to
a chemical causes a particular effect
including the number and quantity --
Or, pardon me.
-- the number and quality of toxicology
and epidemiological studies and data on
biological plausibility.
In analyzing animal studies, the nature
and extent of the exposure and the
characteristics of the exposed animals
are generally well-controlled.
Issues such as observation of the
dose-response relationship,
reproducibility of findings, and
mechanism of action, including
consideration of its relevance to
humans, are key elements of the weight
of evidence.
For epidemiological studies, it is
important to consider the strength of
the study design. These strengths
include controlling for confounding
variables, including overadjustments for
potential confounders which could lead
to underestimating the effects of the
toxin; 2) obtaining an unbiased sample;
3) the potential for bias in
ascertaining exposure, in particular
nondifferential exposure
misclassification which biases the
sample --
Pardon me.

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

The power of the study to detect
biologically meaningful effects, i.e.,
the risk of excluding a false --
PANEL MEMBER FRIEDMAN: No, the ability to
exclude, I thought we agreed.

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

-- to exclude a false negative error is
important in considering studies that do
not reach traditional statistical
significance, particularly if the
biological endpoint is serious.
If the outcome is serious and the study
small, i.e. low power, a larger P value, e.g., P less than .10, may be used to identify an effect. The availability of experimental data or mechanistic theories consistent with epidemiological observations strengthens conclusions of causation. The Panel concurs with this approach.

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

PANEL MEMBER GLANTZ: I was -- I'll fix that.

There's a 1. I forgot to write it down.

So people are happy with that?

PANEL MEMBER LANDOLPH: Great.

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

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

PANEL MEMBER BLANC: Yes.

PANEL MEMBER BYUS: Yes, I think we did.

CHAIRPERSON FROINES: You read them when you got here.

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

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

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

PANEL MEMBER LANDOLPH: Second.

CHAIRPERSON FROINES: Any comments? All in favor?

(Ayes)

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Thank you for that.

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

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

So we added that.

And then we also reworded the description of Lowendowski's analysis of in vivo data to remove the reference to the parallelogram approach, or remove the
focus on it, because all it is is a comparative approach and it's kind of a funny word, so we did that. And those were the only changes in that document.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Manganese.

CHAIRPERSON FROINES: Manganese. We have three.

What time is it, somebody?

PANEL MEMBER FRIEDMAN: 11:40.

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

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

CHAIRPERSON FROINES: Not, okay.

PANEL MEMBER BLANC: It's a major -- going to
be a major discussion.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Bruce Winder is going to make the presentation on the acrolein REL.

CHAIRPERSON FROINES: Did I leave out formaldehyde?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Do you want to do formaldehyde first?

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, you said it.

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

The eight-hour and the chronic RELs, as you see, are .70 and .35 micrograms per meter cubed. Both these are based on lesions in respiratory epithelium of rats.
Now for the acute REL, this is based on actually two studies. The principal one here is the Darley study of 1964 in which 36 adults were exposed to acrolein by a face mask for five minutes.

And the endpoint here is subjective ocular irritation.

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

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

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

However, with respect to the toxicodynamic --

CHAIRPERSON FROINES: Can I ask you a question?

OEHHA STAFF TOXICOLOGIST WINDER: Sure.

CHAIRPERSON FROINES: In SB 25, we listed five compounds, one of which had greater effects in children
than in adults. And acrolein was one of them, and here
you're saying that there is no difference.

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

CHAIRPERSON FROINES: Okay.

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

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

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

Next.

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

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

For the same reason as before, we have an
uncertainty factor of 6. And again, there are no
interspecies uncertainty factors, but we do have the
intraspecies toxicodynamic factor of 10 for the same
reason, asthma exacerbation.

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

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

CHAIRPERSON FROINES: Can I ask you a
question?

OEHHA STAFF TOXICOLOGIST WINDER: Sure.

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

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

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

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

And the problem of our studying things with
clean air as the air of choice, as it were --

OEHHA STAFF TOXICOLOGIST WINDER: Correct.

CHAIRPERSON FROINES: -- is that it really

underestimates what people are actually breathing.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, and

that's a problem we -- since we're continually exposed

to a combination of things, for example, formaldehyde

and acrolein and acetaldehyde together, they tend to

exacerbate each other.

CHAIRPERSON FROINES: Right.

OEHHA STAFF TOXICOLOGIST WINDER: So that

is -- we recognize that as an issue. That will come up

a little while later. But, yeah, that's a problem and

we're starting to deal with that with respect to --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: We do consider it when we're doing a risk

assessment of a stationary source facility, those

hazard indices would be added.

So in other words, we don't look -- when we're

applying these Reference Exposure Levels in a risk

assessment for a stationary source, we would include an

additive effect of all those chemicals.

When you're looking at the Los Angeles basin,

you know, we haven't done risk assessments for the Los

Angeles basin as a whole. That's where, you know, we
could use a little more consideration of additive
effects or synergistic effects, when those occur.

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

(Laughter)

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

OEHHA STAFF TOXICOLOGIST WINDER: Well, there
is.

CHAIRPERSON FROINES: Yeah.

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

CHAIRPERSON FROINES: Correct, exactly.

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

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

You had -- I think it was just a slip that you
had said face masks, but they're in an exposure
chamber.
OEHHA STAFF TOXICOLOGIST WINDER: Oh, no, no.
The masks is with respect to the first study in which they were actually breathing acrolein directly -- not breathing, but exposed to the eyes. The Darley study.

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

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

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

PANEL MEMBER BLANC: It's an eye mask.

OEHHA STAFF TOXICOLOGIST WINDER: Yes.

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

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

Oh -- and yeah, it was increasing levels.

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

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

PANEL MEMBER BLANC: I mean usually these exposure chamber studies are fixed levels. And so I'm
just trying to understand.

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

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

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

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Odd approach.

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

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

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

CHAIRPERSON FROINES: Does this mean that a subject was exposed to a level below .07?
OEHHA STAFF TOXICOLOGIST WINDER: I'm sorry?

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

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

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

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

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

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Levels, yeah.

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

And we don't know to what degree there's accommodation at very low levels. And so that you --
actually, the first time you see something, you're not necessarily -- it's not a pure exposure that would bang you hard.

So this design is troublesome, to say the least.

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Okay. Now with respect to the eight-hour study, this is by Dorman, et al. It's a 2008 study. They're doing whole body exposure of rats, various levels between .02 and 1.8 ppm, for six hours per day, five days per week for
65 days. This is a fairly standard protocol for acrolein in rats. They're looking at lesions in respiratory epithelium. And from this study, they report a LOAEL of .6 ppm and a NOAEL of .2. This is the reason we used this study, was that this was one of the first studies that actually reported a NOAEL. As you see, it's about three-fold below the LOAEL.

So from this, we extrapolate an eight-hour equivalent 71 ppb. That's where we take the .2 NOAEL. We convert it to continuous exposure, six hours in 24, and the 5/7 makes it the entire week. 20 over 10 is the factor that converts it back to the eight-hour exposure. That's the breathing rate, the idea being that individuals working breathe at faster rates. They're consuming about, in their eight-hour exposure, ten of the cubic meters that a resting person would consume -- of the 20 that a resting person would consume in 24 hours.

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

PANEL MEMBER BLANC: Endpoints.
CHAIRPERSON FROINES: -- in vitro endpoints, if you will, that were -- that may have been relevant? Because this is a, you know, it's a club. Lesions in respiratory epithelium.

OEHHA STAFF TOXICOLOGIST WINDER: This --

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

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

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

CHAIRPERSON FROINES: Is this an academic study?

OEHHA STAFF TOXICOLOGIST WINDER: Yes.

PANEL MEMBER BLANC: What --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I'm sorry. It's EPA and Hamner Institute.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No.

OEHHA STAFF TOXICOLOGIST WINDER: Oh, I see
what you're saying. Yeah.

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

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

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

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

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

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

So this gives a cumulative uncertainty factor
of 200 and an eight-hour REL of 70. Or, excuse me, .7 micrograms per meter cubed.

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

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

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

So I gave this an uncertainty factor of 3.

Again for intraspecies toxicokinetics, we're using 2 for the dosimetric adjustment factor in case there's some residual differences between acrolein and formaldehyde.

Intraspecies toxicodynamic factor square root
of 10. This is the default for these sorts of things.
And then again, 10 for the toxicodynamics with respect
to asthma exacerbation in children.
So this gives a cumulative uncertainty factor
of 600 and an eight-hour REL of .46. So this is a
little bit lower than the .7 of the Dorman study but
right in the same general area.
Now for the chronic study and the REL --
PANEL MEMBER BLANC: Can I just ask a
question.
OEHHA STAFF TOXICOLOGIST WINDER: Sure.
OEHHA STAFF TOXICOLOGIST WINDER: And the
reason is that in the Dorman study they went from 0
response, 0 animals in 12, to full 12 out of 12. So we
don't really have a dose response curve.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: It doesn't fit any of the models well because
of the --
PANEL MEMBER BLANC: And suppose you combined
the animal data from Dorman with the animal data from
the supporting studies, and the endpoint of epithelial
lesions is all the same: Would that allow you to do
benchmark estimation?

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Right.

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

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

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

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

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

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

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

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

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

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

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

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

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

PANEL MEMBER BLANC: Yeah, okay.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

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

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: We'll look.

PANEL MEMBER BLANC: Thanks.

PANEL MEMBER GLANTZ: That's what I think.

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

OEHHA STAFF TOXICOLOGIST WINDER: Okay. So again, the chronic REL is based on the Dorman study as
well. Excuse us while we scan.

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

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

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

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

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

PANEL MEMBER FRIEDMAN: Could you again define DAF?

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

So this was based on studies and modeling in rats of formaldehyde and how that compares to humans.
Okay. So we have no NOAEL here. I mean no NOAEL-to-LOAEL conversion factor.

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

So this gives us a chronic REL of 0.35 micrograms per meter cubed which is half of the eight-hour.

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

And as you see here, 2 for DAF, squared 10 for interspecies toxicodynamic, 10 for intraspecies toxicodynamic. And UF 600 which gives us a chronic REL of 0.10. The Dorman study gives us 0.35. So we consider this to be sufficiently close to be supportive.

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

OEHHA STAFF TOXICOLOGIST WINDER: It was the fact that the Dorman study, the critical study is the one that gave us an observed NOAEL. These studies did
not. They only came up with LOAELs.

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

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

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

CHAIRPERSON FROINES: I would, frankly, worry
about those studies, Paul.

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

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

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

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

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

CHAIRPERSON FROINES: Please.

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

They brought to our attention the Dormand --
excuse me -- the Schroeter studies that are listed up
here. Struve was looking at the efficiency of acrolein
uptake in nasal epithelium in rats, a function of level
of exposure to acrolein and whether or not the rat had
been previously exposed.

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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

CHAIRPERSON FROINES: All three?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes.

CHAIRPERSON FROINES: Have been published.

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

The Schroeter study, as I mentioned, tried to
calculate an RFC. Now, what they did here is looked at
neuronal loss and at what levels of acrolein exposure
this occurred. They also looked for respiratory
lesions. And they found that these two endpoints
differed in the level at which it occurred.

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

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

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Pretty sure there is an RD50 with the Alarie method on acrolein in rodents, so we would be looking
at as far as frequency in a rodent.

CHAIRPERSON FROINES: And --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: And I can't remember the number. But we did

look at that. In fact, we -- George and I were looking

at a paper getting acute RELs out of these RD50s

because there is a number of them.

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

PANEL MEMBER BLANC: I have a couple generic

questions.

One is spurred by your addressing the 2008

studies, which I think you should be commended for.

Obviously, writing these kinds of documents can't be a

never-ending, iterative process where you have to keep

changing it every time. New studies come out through

the entire process.

But I do think it would be helpful for you to

state explicitly for each of the RELs in question what

is the cutoff date for the literature which is

reviewed.

In other words, we've reviewed literature

through April 1st, 2008, you know, published

literature. This is going to become particularly

relevant to the manganese, but clearly it's relevant

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

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

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

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

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

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

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

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

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's an interesting point. I don't know.
PANEL MEMBER BLANC: I mean that was only applicable to acute RELs related to ocular irritation endpoint.

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

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

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

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

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

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

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I guess both acetaldehyde and formaldehyde have ocular concerns.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah.

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

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

PANEL MEMBER BLANC: Yeah.

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

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

CHAIRPERSON FROINES: Are we ready to move on?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yep.

CHAIRPERSON FROINES: Formaldehyde or manganese? Oh, formaldehyde. Formaldehyde is our rock of Sisyphus, isn't it?
PANEL MEMBER BLANC: I think it's more our Stygian stables.

CHAIRPERSON FROINES: What?

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

(Laughter)

OEHHA STAFF TOXICOLOGIST WINDER: That said --

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

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

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

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

This study was selected because it was possible from the data to calculate a benchmark dose of .44 ppm. Now we have here -- again, since the study is
in humans, there are no interspecies uncertainty factors.

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

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

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

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

Now, what we're saying here is that this is based on the idea that mainly the studies find symptoms of asthma-like -- well, find asthma-like symptoms in
children, and that these symptoms are exacerbated by exposure to formaldehyde.

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

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

Now our eight-hour REL --

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

OEHHA STAFF TOXICOLOGIST WINDER: Maybe I should say exacerbate.

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

OEHHA STAFF TOXICOLOGIST WINDER: That's a good point. Perhaps I should say exacerbate here because what the Cassee study showed was the acetaldehyde, I believe it was concentrated up about 10
micrograms per cubic meter had no reported effect.

However, that level of acetaldehyde in the presence of similar levels of acrolein and formaldehyde did have an effect.

So that's the reason for using potentiate.

But I think you're right; exacerbate might be a more accurate term.

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

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

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

PANEL MEMBER HAMMOND: It can't be too small?

I thought it was --

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

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

PANEL MEMBER GLANTZ: By itself.

CHAIRPERSON FROINES: By itself. Methyl ethyl
ketone and hexane. Classic example. Hexane is the

toxin, MEK is benign. MEK is a potentiator.

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

PANEL MEMBER GLANTZ: In physiology,
potentiate is different.

PANEL MEMBER BLANC: Probably.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Okay.

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

PANEL MEMBER HAMMOND: Oh, that's why.

(Laughter)

CHAIRPERSON FROINES: Onward.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Okay.

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

Again, they were looking at ocular irritation
as well as nasal obstruction and lower airway
discomfort.

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

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

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

And the endpoint here was increased pulmonary resistance.

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

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

Next slide, please.

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

What are the implications of this eight part per billion REL if you were setting an OSHA standard
for workers? Is this a standard you should set?

PANEL MEMBER BLANC: No, the standard should be --

PANEL MEMBER HAMMOND: Uncertainty for children. This has uncertainty for children.

CHAIRPERSON FROINES: Well, would be 10.

Okay, so you set a standard of 80 parts per billion.

PANEL MEMBER BLANC: No, because there's no -- you don't care about at-risk people with an occupational standard. It's usually a hundred times higher than --

PANEL MEMBER HAMMOND: More.

PANEL MEMBER BLANC: At least. I don't -- actually, it's an interesting philosophical discussion, but I don't think we --

CHAIRPERSON FROINES: Well, let's let it go, but I don't agree with what you said.

PANEL MEMBER BLANC: No, I'm not saying it should be that way. I'm just telling you that in fact --

CHAIRPERSON FROINES: I understand that's the way it is.

PANEL MEMBER BLANC: Right.

CHAIRPERSON FROINES: But I'm saying that when you find effects like this, then you need to consider
how protective your existing standard, which is .1 part per million. And this is obviously not protective of a worker at one part per million given this data, so that's the reason I asked the question.

Go ahead.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. So the -- this is -- gives us a chronic REL -- oh, I'm sorry.

The chronic REL is now based on the same study, obviously same endpoints, LOAEL, NOAEL, et cetera, and gives us a chronic REL of 9. Same for the eight-hour.

And then looking at this, looking at the Rumchev et al., this is a study in children both asthmatic and nonasthmatic, and these were kids who were exposed at home.

And the endpoint here, asthma-related respiratory symptoms.

From this study, we estimated a NOAEL of 30 and a LOAEL of 60 micrograms per meter cubed.

Here we have an interspecies toxicodynamic factor of square root of 10. The reason for instead of 10 is that the study was actually done in children.

So this is also our cumulative uncertainty factor, and the chronic REL becomes 10 micrograms per
meter cubed which is supportive of the 9 from the
previous study.

Now, I did mention the eight-hour chronic RELs
were the same. The reason for this is that a number of
studies in rodents giving near-continuous exposure
versus those giving this kind of intermittent exposure,
six hours a day, five days a week.

When they look at similar endpoints, in this
case basal cell metaplasia, squamous cell hyperplasia,
they're seeing pretty much the same sorts of effects.

Now what this, from the authors, are taking
this to is the concentration of formaldehyde exposures
tend to be more important than the continuity of
exposure.

And in addition, there are studies that
suggest that individuals may become sensitized to
formaldehyde even with relatively short intermittent
exposures. This is based on a study by Sorg et al.

None of this is to say the duration is totally
unimportant because long-term exposures may cause
lesions at low levels. And these are supported by
studies, again mostly in rats, Kerns and Kamata.

PANEL MEMBER BLANC: Can you go back to the
asthma/nonasthma study, supportive study, for a second?
OEHHA STAFF TOXICOLOGIST WINDER: This one?

PANEL MEMBER BLANC: Yeah. So Rumchev was looking at children exposed at home and looking at the level at which the asthmatic children had effects, had symptoms --

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER BLANC: -- compared to the nonasthmatic?

OEHHA STAFF TOXICOLOGIST WINDER: They tended to occur at lower levels, yes.

PANEL MEMBER BLANC: Right. Now the Rumchev study was not looking at levels of formaldehyde that cause asthma?

OEHHA STAFF TOXICOLOGIST WINDER: No. This is just a report of symptoms.

And the reason we didn't use this study for our REL determination is that asthma symptoms in children are kind of a squishy sort of diagnosis. It's hard to come up with a clear diagnosis of --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: These kids were six months to three years old.

PANEL MEMBER BLANC: But wouldn't this study be actually relevant not to the chronic effect but to your acute REL?

Because, in fact, you're not arguing that it
was the chronic exposure to formaldehyde that caused
them to have asthma. You're saying if you have asthma
and you're exposed to formaldehyde at this level,
you're going to have more respiratory symptoms. That's
an acute effect.

OEHHA STAFF TOXICOLOGIST WINDER: There are
some issues associated with trying to use this in acute
context with respect to the exposure assessment.
That's part of the problem here in terms of what are
the kids actually seeing over what period of time.
The thing does not delineate how much time the
children were spending in these individual
environments.

Again, as I mentioned there's a little problem
with the diagnosis of and quantification of
asthma-related symptoms in children. It's not real
clear exactly all cases were asthma-related or not.

PANEL MEMBER BLANC: Well, let's just say it's
respiratory symptoms in kids with asthma. Do people
see where I'm going here? It's a little confusing to
me.

PANEL MEMBER HAMMOND: Let me ask -- there's
an assumption here, but I'd like to clarify: Were
there no effects whatsoever on the 104 nonasthmatic
children? Is that true? In that study?
OEHHA STAFF TOXICOLOGIST WINDER: I think in this study it was pointed out the asthmatic children tend to be more responsive at lower levels. I believe there were children of the 104 that responded. I can't tell you right offhand at what level.

PANEL MEMBER HAMMOND: I mean you have multiple things going on. You have two different populations of children, you've got multiple kinds of symptoms, and the exposure is not an exposure chamber. You could look at what level -- I mean they're exposed at home. If these are very young children, you said under age three, they are likely to be in the home most of the time. So that you probably are talking about more or less continuous. But the question might be how long the exposure was evaluated. If it was an eight-hour sample, one-hour sample, one-week sample? So how stable is that exposure estimate as well? But I would think that the asthma-related respiratory symptoms -- I would not discount those. I would think that those are pretty serious outcomes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, we're not discounting those at all. Two issues. First of all, when you do look at that study and generate a REL, you're a tiny bit higher
than the one we generated, so --

PANEL MEMBER BLANC: For chronic. But you're in fact quite a bit lower than your acute REL.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right. But these were not chronic exposures.

What they did was they went in a couple of times during a single year and measured formaldehyde in the homes. Then they looked at, they stratified by bins of formaldehyde concentration and then looked at the lowest bin versus the highest bin and what was the relative risk of asthma, asthma-like symptoms --

PANEL MEMBER HAMMOND: Symptoms.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- in the kids. And it was higher in kids in the higher formaldehyde homes.

So it really is not looking at acute exposure. It really is looking at chronic exposure, although they're snapshots in time.

PANEL MEMBER HAMMOND: And also they don't really have NOAELs in that case.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's right. And it doesn't mean there were no asthmatic kids in the lower formaldehyde homes.

That's not what it means.

PANEL MEMBER HAMMOND: The way you just
described it is the comparison of the rates of having
the symptoms in the highest and lowest probably tercile
or something, the data. But that's not a NOAEL.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Right. That's not a NOAEL. So it's not very
easy to use this kind of study.

PANEL MEMBER HAMMOND: What were the bins?

What were those bins? And were they terciles?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: They were -- what we did was looked at the ORs
reported for -- the bins were 10 to 29 micrograms per
cubic meter, 30 to 49, and those are not elevated yet.
50 to 59, then you're getting an elevated OR of 1.2,
although it's not -- it includes 1. And then 60-plus
which is statistically significant OR of 1.4 in the
lower boundary above 1.

So we took that bottom range of the bin where
there was no elevation yet in risk -- asthma symptoms
as the NOAEL. That's were that comes from.

PANEL MEMBER HAMMOND: But that's not quite
the same thing, is it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: It's not nice and neat like an animal study
where you have no observed effect. It's not --

PANEL MEMBER HAMMOND: Right. Because you
could certainly have differences in susceptibility of people who have asthma, children who have asthma, under different ages in the group, and so the lowest bin and the next lowest bin don't have a difference in the response, but they might still -- they might each have had 15 percent or 20 percent of the children responding, having symptoms, which could be due to other things. But it's very hard at that point to say that's a NOAEL.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: They also adjusted for things like family history of asthma, age, gender, SES, and so forth, so it's actually a relatively well-conducted study. But it was in Australia which has very high rates of asthma for some reason.

PANEL MEMBER BLANC: Since we're talking about asthma, the issue of formaldehyde as a potential sensitizer, which is a pretty murky literature, and the exposure level at which asthma might -- formaldehyde might induce asthma or be an adjuvant for sensitizing allergens: How do you begin to deal with that in the sort of --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. As you note, it is a murky literature. And still, I think the prevailing opinion is that you
need a high episodic exposure to formaldehyde to get sensitized. And that comes primarily from occasional setting.

There are studies that show concentrations of formaldehyde are associated with asthma symptoms, and then there are chamber studies that used adult, mild asthmatics that didn't see an exacerbation of asthma even at three parts per million.

So I don't know if it's a sort of a difference in the way they're measuring respiratory symptoms in an epi-style study versus a chamber. You know, we don't put severe asthmatics in a chamber. You usually don't even put moderate asthmatics in a chamber.

So it's hard to really feather out the contribution of formaldehyde-specific sensitization versus the irritant properties of formaldehyde in terms of whether or not the person has asthma or is experiencing an exacerbation.

PANEL MEMBER PLOPPER: I think it was a good idea not to use this study to base things on because some of the measurements varied within rooms and times, and you -- this is not anything you can use as an exposure because it may just be the short period of time at very high concentration that produces the problems. It's not a good study.
PANEL MEMBER BLANC: And is there any data that's emerged from the FEMA trailer -- you know, does CDC have any data? I mean I know they've been gathering data recently on --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I don't think they have --

PANEL MEMBER BYUS: -- exposure-related symptoms --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: -- conclusory -- or I don't think they have a report that concludes that they exacerbated asthma in any children or -- you know, it's my understanding that they're still looking at that.

PANEL MEMBER BLANC: I meant more just generically symptom-related dose response with that.

CHAIRPERSON FROINES: Do you have any idea what levels we are talking about?

PANEL MEMBER HAMMOND: They were much higher.

PANEL MEMBER BYUS: Were they?

PANEL MEMBER HAMMOND: Yeah, they were much higher than this.

PANEL MEMBER BLANC: Parts per million.

PANEL MEMBER HAMMOND: I think in the parts per million range.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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MARTY: They went up to -- it was a very wide range that I'm recalling. It was pretty high.

PANEL MEMBER HAMMOND: When you look at this and look at the trailers, you cringe.

PANEL MEMBER PLOPPER: Can we go back to this issue of asthma-like respiratory symptoms? My big concern with this whole section was your reliance on asthma-like respiratory symptoms.

And I thought you addressed it better by your first slide by just saying ocular irritation, nasal obstruction, lower airway discomfort.

I think that's -- one of the concerns with this is all this issue of asthma and formaldehyde is just so unclear. And it doesn't affect the document any. It just sort of destroys some of the credibility.

Right on the first page to list asthma-like respiratory symptoms when the documentation is not -- why get nitpicky over something that doesn't matter?

Because you didn't use any of those studies to establish these RELs, right?

OEHHA STAFF TOXICOLOGIST WINDER: Right.

PANEL MEMBER PLOPPER: So why not just change that throughout the document and just -- and I would also -- I think you need to list what asthma-like respiratory symptoms you're talking about.
OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER PLOPPER: Because that includes a whole bunch of things that aren't related to asthma but you identify them in specific spots. Why not just say what they are?

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

PANEL MEMBER PLOPPER: And I think you addressed most of my other concerns. I thought leaving those studies in Australia alone is a good idea.

OEHHA STAFF TOXICOLOGIST WINDER: So in this context, for example, you want us to change the asthma-like wording or clarify that?

PANEL MEMBER PLOPPER: Well, what you have here is that, say formaldehyde eight-hour REL, critical effects, asthma-like respiratory symptoms; and yet what you've actually used and what the document relies on is ocular irritation, nasal obstruction, lower airway discomfort, which are or are not associated with asthma-like symptoms. Why not put that in place of it?

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

Because at least in this slide for this study it would just be irritation, but you're right, with respect to the --

PANEL MEMBER PLOPPER: No, I'm talking about the whole document.
OEHHA STAFF TOXICOLOGIST WINDER: Right.

PANEL MEMBER PLOPPER: The data and the studies that you relied on, I thought, are probably the most reliable you could get. And they're better controlled.

And these human studies with asthma, they're saying this is a whole issue that actually could be besides the point. It's important, but it's not -- it doesn't inform the document that much. All it does -- you have this over -- you go and you look at direct scientific studies in here, and then you overlay it with this business of asthma exacerbation, and there is not really good documentation for that. It's not as solid as the rest.

I don't -- and I circled it every time I ran across it, and all it did was just detract from the quality of the thing because then you say okay, where is the evidence? And the evidence is not -- is still highly controversial.

OEHHA STAFF TOXICOLOGIST WINDER: And that's partly the reason for the uncertainty factor is that there are studies which support it and studies, as you say, which are finding different results. So that uncertainty is what we're trying to capture here.

PANEL MEMBER PLOPPER: I got into the middle
of one of these discussions in a meeting once, and
there are as many opinions as there are people that
work in this area.

So it's sort of -- all it does is just say
well, it makes it less solid. It's a concern, it's a
major problem, but I think as an informative thing to
use asthma is fine but not to base the document on.

Does that make sense? I mean it won't change
much, but the wording here and there.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: So where we have asthma-like symptoms, be more
specific, and if it's wheezing say wheezing.

PANEL MEMBER PLOPPER: If it's wheezing. I
mean really what you base the RELs on is --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Not that --

PANEL MEMBER PLOPPER: -- nasal obstruction
and lower airway discomfort.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Right. Because these are the --

PANEL MEMBER PLOPPER: It's still --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: That's what was measured in the studies we used
as a basis for the REL. We still want to argue that
there is a need for the tenfold toxicodynamic factor
for potential exacerbation of asthma.

PANEL MEMBER PLOPPER: We've already accepted

that --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay.

PANEL MEMBER PLOPPER: -- other things as well

for children. I don't think that's going to make --

anyone that realizes that this is based on lower airway

discomfort is going to know that that's going to have a

tremendous impact on asthmatic kids.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Make sure you --

CHAIRPERSON FROINES: You may need to spell it

out a bit more.

PANEL MEMBER PLOPPER: That was my other

thing. It needs that all the way through. Just say

what they are.

Because asthma-like symptoms, there's -- most

of the people that did these studies did not use the

guidelines that are accepted by the people who work in

asthma as being asthma-like symptoms, so you can't

compare these two. It's a different type of issue

altogether.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Okay.

We have a few slides on the comments that were made on the draft, so we'll go over those quickly before lunch.

CHAIRPERSON FROINES: Please.

OEHHA STAFF TOXICOLOGIST WINDER: One of the comments here is that the asthma induction and allergic sensitization conclusions that we reached were not representative of the weight of evidence in the IOM 2000 report or ATSDR's 1999 report.

Many of the studies included in our document were not included in the IOM or this ATSDR review, plus ATSDR does not conclude there's no evidence of association between asthma and formaldehyde. It's still up in the air, as this discussion sort of indicated.

And we're saying that formaldehyde inhalation, there are a number of data, number of studies which support that formaldehyde inhalation alters immune response to a variety of antigens, and you can get hypersensitivity as a consequence. This would exacerbate asthma.

There's a comment the IOM report concludes only house dust mite antigen had sufficient evidence of a causal association with childhood asthma.
They argue there is evidence of an association between formaldehyde and asthma-like symptoms in children which is what we've been discussing.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: We also didn't say there was a causal association. We didn't say any of that. The commenter over-read, I think. Anyway.

OEHHA STAFF TOXICOLOGIST WINDER: Right.

And the IOM report has elevated its estimation of formaldehyde to a limited or suggestive evidence of association with respect to asthma exacerbation.

Again, many of these studies that we've included were not in the IOM 2000.

And as before, we indicated on a previous slide, children tend to be more significantly affected by the asthma morbidity than older children or adults. They have smaller airways and as a consequence they're more dramatically affected and end up in the hospital more often.

There is a fair attempt to try to pick apart the sundry studies that were included including, for example -- epi studies -- including this Franklin study. The commenter seemed to question: What is the significance of this elevated expired nitric oxide? As though we were trying to say this in fact was an
indication of asthma.

All we're saying and all the authors were saying with respect to that was that the higher level of expired nitric oxide indicates there's an inflammatory concern with respect to the lungs. And again, we just provided additional evidence that formaldehyde exposure exacerbates the asthma-like symptoms in children.

A number of limitations in all the epi studies that involve children, and we tried in the document to indicate those limitations. We say taken together these various studies suggest and support the association of formaldehyde with respiratory symptoms as well as lung function in children.

CHAIRPERSON FROINES: I may be a minority in the room and in the community, but I still think this issue of expelled nitric oxide is questionable.

And so I would be happier if there were some -- something that said further research in this area is relevant.

OEHHA STAFF TOXICOLOGIST WINDER: Indicated --

CHAIRPERSON FROINES: I think that --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll add that.

CHAIRPERSON FROINES: -- all these clinicians
who look at exhaled nitric oxide and draw lots of
collusions, I've always felt that the toxicokinetics
were not well-thought-through.

OEHHA STAFF TOXICOLOGIST WINDER: There is
still some uncertainty in this.

CHAIRPERSON FROINES: I don't think there is
any question. Paul might disagree, but I personally
think that there is some question.

OEHHA STAFF TOXICOLOGIST WINDER: We can add
that.

CHAIRPERSON FROINES: People overinterpret.

OEHHA STAFF TOXICOLOGIST WINDER: One of the
other concerns expressed by comments was that the --
this issue of sensory irritation testing where odor may
in fact influence the response.

And we're saying we recognize that the odor is
-- foul odor is an effect of exposure, but we're not
using odor response perception as a --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: There's a mistake, and that's my fault, on the
slide. It should say we didn't use odor perception or
odor threshold to set an acute REL. Sorry.

OEHHA STAFF TOXICOLOGIST WINDER: In fact, the
REL was based on eye irritation instead. So.

The -- it was brought to our attention that
Lang, et al. has a new study just published of sensory irritation to formaldehyde.

We looked at the study and discovered they were reporting sensory irritation of .5 parts per million. And this is consistent with what Kulle reported. They had a NOAEL of .5 and LOAEL of .1, so we figured this is supportive of the results so far.

PANEL MEMBER BLANC: I'm sorry, the line before, sensory irritation at .5 to 1? What do you mean?

OEHHA STAFF TOXICOLOGIST WINDER: I believe that was a range.

PANEL MEMBER BLANC: But he did see irritation at .5?

OEHHA STAFF TOXICOLOGIST WINDER: Within that range.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If you look at the studies, they're trying to figure out where the sensory irritation threshold is.

PANEL MEMBER BLANC: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And it's somewhere between those, .5 and 1, somewhere in there.

PANEL MEMBER HAMMOND: Does he give a period of time? Talking about irritation?
PANEL MEMBER BLANC: So the threshold suggests that the NOAEL is no lower than .5 is what you are trying to say.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It might be lower.

PANEL MEMBER BLANC: Why? If he says it's between -- the no-effect level is between .5 and .1? Or is he saying that he saw an effect as low as .5? I mean it's a critical thing because either you're -- there's now data which says that .5 is not a NOAEL but a LOAEL or we're not.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Four-hour exposure is what he says was that there's minimal objective eye irritation at a level of .5 with peaks of 1. So --

PANEL MEMBER BLANC: I see. So it's really hard to say.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Not sure the 1 or somewhere in between.

PANEL MEMBER BLANC: Couldn't control the exposure.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: They didn't do a continuous exposure at the same concentration. They threw in peaks.

PANEL MEMBER HAMMOND: Did they introduce
formaldehyde at set intervals? Is that what you're saying?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: The atmosphere was generated by vaporizing power of formaldehyde on a magnetic hot plate stirrer, and it basically looks like they didn't have what you consider a steady atmosphere-generating system. This was a -- you know, I think they kind of threw some on the hot plate and heated it till it got up to the level they wanted.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: What we'll do is put a description of this study into the document. Right now we've just reviewed it the responses to comments and didn't add it yet.

PANEL MEMBER BLANC: That would be a good idea, if you can.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I think we should do that.

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER HAMMOND: Did you say that's four-hour exposure, but this is the acute REL?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Right.

PANEL MEMBER HAMMOND: Is that REL the acute REL or?
MARTY: Well, the acute RELs are supposed to be for one-hour exposures.

SALMON: We've done quite a bit of work looking at the time course of exposure of these sensory irritation type of responses.

And in fact, Dennis Shusterman and various co-workers, including myself, published a paper on this not so long ago. And the conclusion there was that for most of the -- well, for the sensory irritants for which we actually had data that we could look at, what you see typically is an increase in the irritation response which goes up with the duration of exposure up to a certain point and then plateaus.

And the ones that we were looking at, the time course over which this increase was occurring was something between a matter of a few seconds and several minutes. And then in fact the response plateaued for a period of up to a few hours. But there was then, in fact, evidence of some accommodations of the sensory response if you went out for, you know, many hours.

But the reason that we were particularly concerned about this was that we felt that the response would have plateaued within the time frame of interest.
to the acute REL and would have stayed at that level
for periods of a little bit longer than that.

So -- and that's the reason why we in the
guidelines proposed that we not do time adjustments for
the sensory irritation response, at least where we had
studies which were, you know, somewhere in the relevant
period of exposure for the acute REL.

So although we don't have details for all
these different chemicals, the database where the time
course is actually being measured is quite limited;
evertheless, that was the pattern we saw.

So anyway, that was the basis of our analysis.

OEHHA STAFF TOXICOLOGIST WINDER: Several
comments have been made about formaldehyde that it's
occurring in nature and our bodies naturally and the
environment, which is sort of a non sequitur.

Many of the toxic chemicals we encounter are
also constituents of living systems and found in cells,
and the body's ability to handle formaldehyde may be
overwhelmed by the exogenous application by inhalation.

So that's sort of a nonissue.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Okay. That's actually the end of the
formaldehyde presentation.

CHAIRPERSON FROINES: Are there further
questions? So I think we'll take a break for lunch.

Joe?

PANEL MEMBER LANDOLPH: I wasn't paying attention when you switched from acrolein to formaldehyde. Should I give just my comments to the authors?

CHAIRPERSON FROINES: Unless you think it's something the Panel should hear.

PANEL MEMBER LANDOLPH: It's up to you.

CHAIRPERSON FROINES: No, it's not. It's up to you. Whether -- because I don't know what you've got.

PANEL MEMBER LANDOLPH: Okay.

CHAIRPERSON FROINES: You have to decide. If it's something that's relatively trivial, then just give them to them. If you think it's something that would lead to discussion, then we should discuss it -- then we should hear them.

PANEL MEMBER LANDOLPH: Of course, I can't make that decision for you either. I can -- I just have comments.

I want them to draw out a metabolic scheme and a little bit of discussion about whether the glycetdehyde and the glutathione conjugates of acrolein are mutagenic or not and whether they would
contribute to cytotoxicity, mutagenesis, and
carcinogenesis. Just a short discussion.

And let's see.

And some discussion -- it wasn't really stated
discretely whether acrolein was mutagenic in vitro with
or without S9 metabolic activation. Was it mutagenic
or bacterial mammalian cells? Did it cause any
chromosomal damage? Just some short statements on that
from the literature.

CHAIRPERSON FROINES: Melanie, are you going
to deal with formaldehyde as a carcinogen or--

PANEL MEMBER BLANC: This is acrolein.

CHAIRPERSON FROINES: Oh, acrolein.

PANEL MEMBER LANDOLPH: Acrolein.

CHAIRPERSON FROINES: Are you going to deal
with it when you bring the cancer guidelines?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: When we bring the cancer guidelines, we're only
talking about methods to derive potency and how they're
used and weighting by age at exposure. We're not
bringing forth any chemical-specific new potencies. So
that's a long answer, no.

CHAIRPERSON FROINES: So this document is
about noncarcinogens.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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MARTY: Noncancer --

CHAIRPERSON FROINES: -- and Joe's asking you to put in data on carcinogenicity and mutagenicity. So presumably it should be somewhere.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah. I think that's actually an okay point. And like, for example, arsenic, we talk about it as a carcinogen. We just mention it.

So I think it would be fine to do that. I don't think we have a carcinogenicity bioassay or human data like you have with arsenic.

CHAIRPERSON FROINES: What worries me about formaldehyde and carcinogenicity is that that's like reopening Pandora's box again.

And I really hesitate to do that, to put like a few paragraphs in, and then we will hear -- we'll get a new petition saying we need to reconsider the formaldehyde question.

And so I think at some level we should be cautious about what we open up.

PANEL MEMBER BLANC: Perhaps the way to make it consistent with the points of the document is there's a link in your view in terms of reproductive hazards vis-a-vis things which are potentially genotoxic, that there tends to be an overlap to an

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extent, I suppose. Is that correct?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: In some cases, yes.

PANEL MEMBER BLANC: So I would say, Joe, in response to your question, I wouldn't delve deeply with acrolein or formaldehyde into mutagenicity except insofar as toxic attributes which would be relevant to developmental impacts, perhaps, or something.

PANEL MEMBER LANDOLPH: Well, my comments were more provoked by some of their comments that were statements which just died in midair. And so I -- just a suggestion to just write a few more sentences just to say what's known and stop. I didn't want to provoke a big carcinogenicity debate or anything like that.

CHAIRPERSON FROINES: Is acrolein -- I don't remember now; I apologize. Is acrolein's carcinogenicity covered in the SB 25 document?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: No.

I think the point is that the data on carcinogenicity and mutagenicity are essentially either missing or equivocal for acrolein. So we don't have a clear answer available.
MARTY: You might anticipate that it's a carcinogen.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: People do.

But the trouble is that it's sufficiently reactive that firstly it's very difficult to do a satisfactory mutagenicity assay on something that's as reactive as that because it has a tendency to kill all the bacteria on site.

And additionally, it's extremely, as you know, extremely reactive, fugitive, hard to measure and so on which makes it a difficult material to handle and difficult material for which to produce a stable atmosphere which would be a prerequisite for doing a satisfactory subchronic or chronic experiment.

So essentially, the problems of handling acrolein mean there are no satisfactory data to address the points, as far as I'm aware.

CHAIRPERSON FROINES: I would argue that everything you said is correct. I would also argue that it is a tragedy that greater effort hasn't been made to document the carcinogenicity of acrolein.

I would bet my bottom dollar that an alpha,beta-unsaturated aldehyde like that is clearly going to be a carcinogen and that I don't think there's any question. But I think it hasn't been documented,
and that's where the weakness lies.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes.

CHAIRPERSON FROINES: And that's why the mutagenicity data is important.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think there's an argument -- there's certainly an argument for us addressing this, at least briefly, in this document precisely because we don't have the basis to present the discussion in a more extended document evaluating carcinogenicity; whereas, in the case of formaldehyde, I think we probably wouldn't do that because that's covered in detail elsewhere.

PANEL MEMBER LANDOLPH: Yeah. That's kind of what provoked my comments, and I would be --

CHAIRPERSON FROINES: Well, if people agree that you should put something in, that's perfectly fine.

PANEL MEMBER LANDOLPH: Concise. And then I had another quick couple of comments.

CHAIRPERSON FROINES: Kathy wanted to make a comment.

PANEL MEMBER HAMMOND: I guess I was going to ask: If we have a policy on this, I was -- I thought
you had said that these are the noncancer endpoints.

That's what the RELs are about.

And if a compound also causes cancer, we would still have a REL document. Is that correct?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Right.

PANEL MEMBER HAMMOND: So on one level, we could say these are two different worlds. On the other hand, I think the worlds aught to at least talk to each other.

And so there should probably be in a document a comment about if there's a carcinogenicity document, just refer to it, that there is a carcinogenicity document.

I guess as soon as we go beyond that -- but it does seem like you should be able to say there have been some concerns expressed about carcinogenicity, but this has not yet been evaluated by OEHHA.

Maybe it goes as far as that? If you could cite any organization that has stated something.

CHAIRPERSON FROINES: Well, there are -- you know, it's listed by IARK and --

PANEL MEMBER HAMMOND: Yeah.

CHAIRPERSON FROINES: The point that it's listing doesn't bring you where I think you would need
to go. I think you also have to acknowledge the chemical structure of acrolein and the potential for its having carcinogenicity.

PANEL MEMBER HAMMOND: Well, I think that this document should not be a new review of the literature -- or even of the science, maybe more fundamentally is what your concern is. It should at most just point the reader to whether or not they should also have some concern. And if there is another document that OEHHA has put out or if IARK has put a document out, you can refer to those.

CHAIRPERSON FROINES: I think you want to say that is an area that needs further scientific testing and research because it's clearly a bad actor.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think it makes sense to refer the reader to, for example, our other part of this risk assessment guidelines where we have all the cancer potencies.

CHAIRPERSON FROINES: Joe?

PANEL MEMBER LANDOLPH: Yeah, then I have just two quick comments.

One was an independent one from one you had about molecular correlates of toxicity and just some question about whether acrolein could form shift bases with the amino acid groups of proteins or with the

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exocyclic amine groups of DNA bases such as guanine which might contribute to airway sensitization and immunological effects through haptenization of proteins as well as mutagenicity -- some short, concise discussion, and I'll give you these comments.

CHAIRPERSON FROINES: You'd better be careful though. Shift bases are irreversible -- are reversible. They -- you can hydrolyze shift bases, and you get your parent compound back.

So the fact that it forms a shift base does not make it something that's an irreversible change.

PANEL MEMBER LANDOLPH: Yeah, it just struck me it might lead to haptenization or something like that.

The last comment was the developmental and reproductive toxicity. And you cited a WHO document. And I didn't agree with WHO.

They said that there were two positives -- there were two positive studies for teratogenicity and embryo toxicity when acrolein was administered into amniotic fluid or added to rats -- or added to cultured rat embryos; and then when they injected it into chicken embryos, they got embryo toxic and teratogenic effects. But then when it was IV injected into pregnant rats, they showed no effects, so they conclude
overall the thing was negative.

To me, I disagree with them. And I think a fair statement would be more studies should be done with relevant modes of administration to resolve the question appropriately.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think that's fine.

CHAIRPERSON FROINES: I think we'd better take the time to break for lunch because it's exactly 1 o'clock. And so what, a half hour, 40 minutes?

PANEL MEMBER BLANC: I think 45 is more realistic because we have to get served. I could eat in half an hour if I had the food in front of me right now; but that's not true, is it?

CHAIRPERSON FROINES: Okay. 45 minutes.

(Lunch recess)
AFTERNOON SESSION

---o0o---

CHAIRPERSON FROINES: Are we ready to go?

Stan are you ready to go?

PANEL MEMBER GLANTZ: I'm totally ready.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Bruce Winder is going to present the
information on the manganese Reference Exposure Levels.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. As indicated in the document here we have not developed an acute REL for manganese at this time largely due to deficiencies in --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I don't think our microphones are on.

OEHHA STAFF TOXICOLOGIST WINDER: Here we go.

At any rate, like I said, the acute REL -- we haven't developed an acute REL at this point due to lack of studies of short-term exposure effects.

However, we have developed an eight-hour REL, .26 micrograms per meter cubed and a chronic REL .13 micrograms per meter cubed. Both of these are based on impaired neurobehavioral function in humans.

CHAIRPERSON FROINES: Is manganese a TAC?

PANEL MEMBER GLANTZ: I don't believe so.

CHAIRPERSON FROINES: Is it a half, that's the
question.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: If it's a half, it's a TAC. And I'm pretty sure it's a half. I will double-check that.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

The critical study here was a study done by Roels in '92, an occupational study in a battery plant looking at the exposure of 92 workers for eight hours a day, five days a week.

These individuals were employed there for a mean of 5.3 years, and you can see the range here of .2 years to 17.1 years.

The endpoints measured in that study include impaired visual reaction time, eye-hand coordination, and hand steadiness.

From that study, a LOAEL was calculated of 150 micrograms per meter cubed. However, we subsequently were able to get hold of individual data from this Roels study with a benchmark analysis and came up with a concentration of 109 micrograms per meter cubed.

We adjusted this to a 24-hour exposure with -- to a full-week exposure with this 109 times 5/7 so this gave us a time-adjusted value of 78 micrograms per meter cubed.
This was a subchronic study, so we used a subchronic uncertainty factor of 10.

Again, there's no interspecies uncertainty factor since this study is in humans.

We have a toxicokinetic uncertainty factor of 10. The reason for this is that infants and children have a much greater absorption of manganese than do adults in the diet, and lung deposition in children is likely to be higher based on some work by Ginsberg.

We included a toxicodynamic uncertainty factor of 10, and this addresses the anticipated higher sensitivity of children to neurotoxicity for a cumulative uncertainty factor of 300 and an eight-hour REL of 2.6 micrograms per meter cubed.

Same study we used here for the chronic REL.

Again, the same sorts of situation applied. This time for our time adjustment, since the original study was an eight-hour worker study, we're adjusting here upwards to the chronic study by 10 over 20.

So our time adjusted factor here is 39 micrograms per meter cubed.

And the reason we have no LOAEL-to-NOAEL conversion factor, we're using a BMD analysis on this.

So we have the same subchronic uncertainty factor, same intraspecies toxicokinetic factor of 10,
toxicodynamic factor of 10 again for neurotoxicity, and
the chronic REL here is .13, so it's about half the
eight-hour REL.

Now just to put this in some kind of
perspective, we're proposing .13 micrograms per meter
cubed.

WHO has their air guidelines of
.15 micrograms.

US EPA is currently -- their RfC currently is
.05 and -- but subsequent papers from people at US EPA,
Dr. Michael Davis in particular, suggest that this
number is highly dependent on what models were used and
the assumptions that go into it, and suggested a range
of .09 to .2 micrograms per meter cubed as being
appropriate.

Health Canada's current value is .11. They're
considering .05.

So the comments we've gotten on this --
CHAIRPERSON FROINES: Wait, wait one second.

You're at .13, and the US EPA RfC is .05. What's the
basis for that value that --

OEHHA STAFF TOXICOLOGIST WINDER: The .05 --
CHAIRPERSON FROINES: -- would make it
different than what you would find?

OEHHA STAFF TOXICOLOGIST WINDER: The biggest
difference there is this .05 is based on the LOAEL. So
they have a threefold NOAEL conversion factor involved
there, pretty much the difference between the two of
these. We don't have the LOAEL-to-NOAEL conversion
because we're using the benchmark dose approach.

But --

PANEL MEMBER BLANC: Can you just clarify on
your benchmark, and I'll have other comments later, but
the outcome measures in the Roels study would, on face
value, seem to be continuous variables.

Did they dichotomize in some way to
normal/abnormal?

OEHHA STAFF TOXICOLOGIST WINDER: We
dichotomized based on his assessment normal/abnormal,
so we have data for the individual data, and those we
categorized -- we dichotomized that into what he called
abnormal versus normal.

PANEL MEMBER BLANC: And how did you do that?

OEHHA STAFF TOXICOLOGIST WINDER: I believe
his data actually refers to these individual responses
as normal versus abnormal. They aren't qualified.

PANEL MEMBER BLANC: Based on what? So his
original data were normal -- go back to the outcome
variables he used, if you might, on your slide. Okay.

Impaired visual reaction time, eye-hand
coordination, hand steadiness. Are you saying there
was a variable that he had that was hand unsteadiness
present/absent?

OEHHA STAFF TOXICOLOGIST WINDER: He called it
abnormal/normal in that context.

PANEL MEMBER BLANC: Most of these are based
on continuous variables. Certainly visual reaction
time is a continuous variable. That I know for sure.

OEHHA STAFF TOXICOLOGIST WINDER: Well, we
based ours actually on eye-hand coordination, a more
sensitive response. He --

PANEL MEMBER BLANC: But these are -- I mean I
think you need to be pretty clear.

OEHHA STAFF TOXICOLOGIST WINDER: And then
here he did represent -- in the paper presented a
percentage of abnormal value, so it's -- I'm not clear
the criterion he's using for normal versus abnormal in
the context of --

PANEL MEMBER BLANC: Well, it must be in his
method, isn't it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I'm looking.

Well, his methods are described more fully in
a previous paper, which I don't have in front of me.

So anyway, what was the issue?
PANEL MEMBER BLANC: Well, in a way, you've answered the question technically, which is I couldn't figure out how you did a benchmark if it's a continuous outcome variable because most of your benchmark calculations require a dichotomous outcome variable of some kind with percentages, right?

OEHHA STAFF TOXICOLOGIST WINDER: Right.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: You can use the benchmark analysis with continuous variables. It's a different -- different models used to fit, but it works much the same way.

PANEL MEMBER BLANC: Well, might it -- and -- well, I'm going to hold some questions until a little bit later on, unless you think -- well, maybe I should just ask them about this very specific thing.

The other uncertainty factor that your methods, your generic methods, allow you to throw in, your sort of existential uncertainty factor that could be up to 3?

OEHHA STAFF TOXICOLOGIST WINDER: You're talking about the database uncertainty factor? I'm not clear.

PANEL MEMBER BLANC: I forget what you called it, but we discussed it at length, maybe --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: The database deficiency factor?

PANEL MEMBER BLANC: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I'm sorry; ask the question again? I didn't understand the question.

PANEL MEMBER BLANC: That's not involved in this calculation, doesn't add that.

What would it -- it seems to me that it might be worth considering. It wasn't just -- do people remember the discussion last time? We didn't rediscuss it this time, but you know what I'm referring to?

Was that only -- it was a kind of a global sense of there's too much missing data here for us to feel completely comfortable with.

PANEL MEMBER GLANTZ: Right.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes, it was where we had reasons to anticipate that there might be adverse effects in the critical concentration range, but we didn't have enough data to make a qualitative assessment what the protected level would be. So it's basically missing data in the -- in terms of types of effects or things like that, for instance, in the developmental area.

As opposed to the other uncertainty factors which we have applied, most of which have to do with we
know what the endpoint is, and we have -- we have some
assessment of what the critical levels of that endpoint
would be, but there is an uncertainty associated with
the data on that endpoint. That was the distinction
between the --

PANEL MEMBER BLANC: And for that you would
apply a square root of three -- square root of 10 to?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
SALMON: Well, we -- in principal, we could choose
either. But square root of 3 or square root of 10.

PANEL MEMBER BLANC: And you haven't applied
that in this case?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
SALMON: No.

PANEL MEMBER GLANTZ: You don't have a square
root of 3.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
SALMON: Sorry. Square root of 10 or 10. I'm sorry.
Excuse me. Getting confused here. Yes. 10 or 3 --

PANEL MEMBER BLANC: Do you think the issue of
having had data which has been reduced to a dichotomous
outcome when in fact that's likely to . . .

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
SALMON: Just firstly, no, we haven't done that in the
past, and we don't consider that it's necessary to do
that. One of the -- I'm just wanting to check something here in the calculation. Yes.

I think -- well, one of the points is that if we are -- if we're using a case like this where the score is either, just be either normal or abnormal, then if you had a continuous variable, and you --

PANEL MEMBER BLANC: Instead of abnormal/normal, you're saying?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, and if you were to fit that, you would have -- you know, conceptually, you would have a cutoff point which you would have to decide where in that continuous range the cutoff would be.

So you have to make this decision at some point in the process by either method.

The dichotomizing the data can impair in some circumstances, if it's not done appropriately or if the data are difficult, it can, if you like, increase the spread. That would probably be -- remember where the benchmark we're calculating is the lower confidence bound.

So if the process of dichotomizing the data actually, you know, built in a little bit of extra variation into the underlying data, then that would actually be reflected in the calculated confidence.
bounds on the EC05 or whatever the benchmark was because we're using a lower bound as the benchmark.

So the dichotomization could, I think in principal, increase the spread around the MLE --

PANEL MEMBER BLANC: If it's random. But suppose his dichotomization of normal eye-to-hand coordination is an eye-to-hand coordination which is beyond the 95th percent confidence interval for the test, and that's what he calls abnormal based on some referent population data?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Hm.

PANEL MEMBER BLANC: And in fact it's a conservative definition, although, you know, very consistent with test definitions when you want to be very sensitive.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah. I don't -- does he actually say what the test definition was for that dichotomization? No. I mean, yeah, I -- I don't know that -- whether it was an especially conservative criterion. I don't think I have an answer to that right away.

In general, we have not felt that the dichotomization made a huge difference. We did actually do a test about it. I'm trying to think back...
to which -- was it the fluoride one?

I know one of them we did actually compare the continuous and dichotomized. The continuous actually produced a better-looking fit, but it didn't produce a substantially different result in that particular case.

Trying to think of which one it was.

But we'll have to get back to you on that.

PANEL MEMBER HAMMOND: Actually, I have a couple questions. First, would you help me? I know it was on a previous slide as well, about the time adjustment. What's the 109?

OEHHA STAFF TOXICOLOGIST WINDER: That's the benchmark concentration.

PANEL MEMBER HAMMOND: Okay. All right.

Then the second thing, I was reading what you have here which is a little different than what you've written up there.

My concern is we're talking about chronic exposure, and so therefore it's a cumulative exposure that I think is the relevant metric, exposure metric, which would be milligram per cubic meter years, which is what you cite in the document. You do mention that.

But the way you -- I'm sure -- I would imagine the paper, they continually use milligram per cubic meter years, but what you did was to take the geometric
mean divided by the average exposure time.

And I think it would be more useful to actually use the actual values and -- because you don't necessarily get the true sense of what the exposures were to the people so I'm not quite sure why you did it that way.

But I would rather see this done in milligram per cubic meter years and working from that as the exposure metric. And then only at the end correcting for the number of years you want to protect people from environmental exposure.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We are not for the chronic REL derivation looking at, you know, saying that five years is half as bad as ten years.

We're looking for an -- essentially for an annual average rate which would be protected.

So we're not assuming that the cumulation is going to occur -- I mean we certainly anticipate cumulation will occur over a significant period. We're not assuming that it's cumulative over a lifetime in the same way that we do for cancer, for instance.

PANEL MEMBER HAMMOND: Well, first of all, I'm speaking at the moment about the data that you're working with, the occupational data.

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So for instance, someone who works .2 years --

at least one of the subjects worked just a couple of

months, apparently -- might well have been exposed to a

very high concentration. That's not unusual in an

occupational setting. Short-term employees have high

exposures. I don't know that.

And often people, the longer they're there,

the more the -- the exposure changes through those

17 years and may have been declining.

Now I guess you'd want to start with the

biology, but if we think there's a cumulative effect

over 17 years, you'd want to do that, or you might want

to work something else out.

But I don't think taking the average exposure

divided -- geometric mean exposure and dividing by the

average number of years to say what the dose was is an

appropriate exposure metric.

CHAIRPERSON FROINES: I don't either. I don't

think the geometric mean is --

PANEL MEMBER HAMMOND: So I guess I'm just

concerned about that. And a more easily remediable,

other, second issue, I'll just say quickly to get it

done with -- the other may be more important -- is that

in the paper, RELs, it's talking about respirable --

these are the respirable concentrations, and that's
what you use, and that's appropriate.

But it would seem to me that in that case the REL should also be referring to respirable.

We know that the biologic availability is very much a function of the particle size. And people have done studies where people with total exposures to manganese higher than another respirable exposure don't have the same effects.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, we can clarify that. But it's -- there are always -- the implicit assumption of risk assessment is it's respirable if it's a particulate.

PANEL MEMBER HAMMOND: Is that for everything?

Whenever you do particles?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER HAMMOND: It is? I think it actually should be stated as such if that's true because that's not true in other standards.

But meanwhile, I am concerned about how the exposure metric was used to do these calculations.

CHAIRPERSON FROINES: Doesn't that -- it has the potential for underestimating the dose.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Pardon me. I'm not exactly sure what it is
you're proposing that we should do instead of what we did. Can I ask you to clarify that?

PANEL MEMBER HAMMOND: If you're trying to say at what level a response was seen, I think that that should be at a microgram per cubic meter years metric, not micrograms per cubic meter.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The calculation that we did was based on the geometric mean of the lifetime integrated respirable dust levels reported in the paper divided by the average exposure time.

PANEL MEMBER HAMMOND: I see that. I think that that's incorrect on two bases.

First of all, it shouldn't be -- the proper metric for an exposure that's a cumulative exposure should be arithmetic mean, not the geometric mean.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER HAMMOND: If you want to know what the predicted daily exposures, the geometric mean is appropriate. But if you're looking at cumulative effect, then you need the arithmetic mean for that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay.

PANEL MEMBER HAMMOND: Secondly, I don't think
you -- I think you would take each individual. The
normal way that research is done -- I haven't read this
paper -- but the normal way that research is done is
for each individual they calculate the individual's
microgram per cubic meter years exposures --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: That's what they did.

PANEL MEMBER HAMMOND: Right, but you've taken
the average of those things and divided them --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: We've taken the average of the individual
LIRDs.

PANEL MEMBER HAMMOND: Tell me again what LIRD
is?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Lifetime integrated risk --

PANEL MEMBER HAMMOND: Right, and I don't
think that's appropriate, all right?

I think what you want to do is you would look
at these as the different doses. You have a hundred --
you have 92 different doses that these individual had.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes.

PANEL MEMBER HAMMOND: And you try to see for
each a microgram per cubic meter year, and you try to
see which of those doses is where you start seeing the effects or some plot of degree of severity.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: In other words, you want us to look at the individual exposure data on the -- in order to derive the benchmark rather than --

PANEL MEMBER HAMMOND: Well, this is just looking at -- I mean I think you're losing too much data.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Well --

PANEL MEMBER HAMMOND: It looks to me like you're losing much too much data.

But just saying this is a study that -- the way I'm reading it, this is a study that saw an effect, and the average exposure these people had was 150 micrograms per cubic meter -- or maybe it's point -- 793. But that isn't the way one wants to do -- when you have much richer data, you don't want to --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think we're talking at cross-purposes here. The BMD analysis was done on the data on the individuals in the study. This business of the geometric mean of the LIRD divided by the exposure time was used to calculate the LOAEL for the study, but the
LOAEL is not what we're using in the benchmark dose calculation.

PANEL MEMBER HAMMOND: Well, I think it's an appropriate LOAEL. Okay?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, we're not using it anyway, but we can correct it.

PANEL MEMBER HAMMOND: But I don't think having an inappropriate way to do it should be in the document.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We can throw it out if you want us to do that.

PANEL MEMBER HAMMOND: When you did the benchmark does, did you use each individual --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Individual data, yes.

PANEL MEMBER HAMMOND: You used the individual data?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: For all three tests.

PANEL MEMBER BLANC: But did you use the geometric or arithmetic mean for that individual?

Because for each individual you have multiple --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think we used the lifetime integrated
respirable dust level as reported by Roels now.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: For each individual.

PANEL MEMBER BLANC: But that would have been

based on a geometric mean?

PANEL MEMBER HAMMOND: Roels may have used the

arithmetic.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think he probably used the arithmetic.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Not in the paper. It's data we got.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yeah, we'd have to plow through the source

data.

CHAIRPERSON FROMES: The arithmetic mean is
the appropriate measure.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think that --

PANEL MEMBER BLANC: I think another point

to -- another monkey wrench to throw in is that in fact
manganese is the rare example of an inhalant for which
an argument can be made that nonrespirable dust could
be more critical than respirable dust, or as critical,
because of the phenomenon of direct nasal uptake in
transport to the central nervous system.
So I think -- and this is something that throughout this document was problem-ridden, I think. There was -- it was alluded to at one point, but then it got maybe turned on its head or ignored at certain points.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well then, we would have underestimated the dose that produced the effect by using just respirable.

PANEL MEMBER BLANC: Possibly. But in certain other points in the document, all I'm saying is that with this particular substance, there is -- the issue of olfactory uptake is something that you're going to have to deal with more clearly than was dealt with, even though it was alluded to in one paragraph.

CHAIRPERSON FROINES: Can I ask a question that's a follow-up to that? Do you have some estimate of the size distribution of that data?

Because, for example, we've done a lot of work on chromium and lead, and the respirable dust that gets to the alveolar region ends up passing through the lung into the systemic circulation and mucociliary cleared dust ends up going to the gut. So you -- so there's a dependence on the relative uptake from the two regions. Not to mention the olfactory issue.

PANEL MEMBER BLANC: I mean I think for
manganese, because unlike lead its GI uptake is tightly
regulated, the issue is somewhat a special case.

And if we didn't have this olfactory
mechanism, then you'd sort of discount stuff that
would --

CHAIRPERSON FROINES: You would assume.

PANEL MEMBER BLANC: -- get into the gut.

PANEL MEMBER HAMMOND: Isn't olfactory for
small particles, not large particles?

PANEL MEMBER BLANC: I thought the olfactory
clearance is effective for larger particles.

PANEL MEMBER HAMMOND: I guess that's direct
olfactory to the brain, very small particles.

PANEL MEMBER BLANC: Well, some of the
experimental data is done with small particles, but I'm
not sure all of the data was done with small particle.

CHAIRPERSON FROINES: Kathy's right, you know,
the Oberdörster data from ultrafine particles is small
stuff going to the olfactory. But that -- but there
may be other literature that we're not familiar with.

PANEL MEMBER BLANC: That's specific to
manganese.

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER BLANC: Yeah. There is other
literature about ultrafine particles bypassing certain
1 mechanisms.
2
3 But what I'm talking about with at least some
4 of the manganese data, you know, is it's not a micro --
5 it's not an ultrafine particle issue. It's a sort of
6 unique.
7
8 CHAIRPERSON FROINES: It's a transport
9 process.
10
11 PANEL MEMBER BLANC: It's a transport process
12 for which there is no reason to invoke the necessity of
13 ultrafine particles.
14
15 CHAIRPERSON FROINES: So on these -- I mean
16 you can get -- the ultrafines can pass into the CNS by
17 diffusion, presumably, and -- but with the large
18 manganese, then you're going to need a transport
19 mechanism of some kind, presumably.
20
21 And presumably that may exist given the nature
22 of manganese.
23
24 OEHHA STAFF TOXICOLOGIST WINDER: Further
25 questions?
26
27 PANEL MEMBER BLANC: Well, I mean there are a
28 lot of questions, but I think you want to finish your
29 presentation.
30
31 AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
32 MARTY: We should go through the comments from the
33 public comment period on the draft.
OEHHA STAFF TOXICOLOGIST WINDER: Okay. One of the fairly common, or more common, comments is that manganese is an essential nutrient and for that reason we need to consider how much the body needs for overall health and in the context of dietary intake, our inhalation levels seem to be unsuitably small.

The only thing we point out in response to that is that the route of exposure here is very critical. That, as has already been alluded to, the dietary intake is fairly well regulated by the body whereas inhalation intake allows manganese to completely bypass the first-pass control by the liver as well as there's a possibility of direct access to the brain by the olfactory nerves.

PANEL MEMBER HAMMOND: Excuse me, just a question. Is there metabolism of manganese in the liver?

OEHHA STAFF TOXICOLOGIST WINDER: Manganese -- there's a cycle that takes manganese from the liver to the bile, bile ducts and back, into the intestinal tract, and the level of the manganese in the diet or in the blood regulates how effective that is. As the blood level of manganese rises, there's more of the stuff back in by bile.

PANEL MEMBER HAMMOND: And it doesn't go
into -- and the bile is excreted.

OEHHA STAFF TOXICOLOGIST WINDER: Yes.

PANEL MEMBER BYUS: That's called enterohepatic circulation, not metabolism.

OEHHA STAFF TOXICOLOGIST WINDER: That's right.

PANEL MEMBER BYUS: So it's called enterohepatic circulation, not metabolism.

OEHHA STAFF TOXICOLOGIST WINDER: Do we call it metabolism?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I don't think so.

PANEL MEMBER BYUS: First-pass metabolism is different than enterohepatic circulation.

PANEL MEMBER BLANC: First-pass clearance.

OEHHA STAFF TOXICOLOGIST WINDER: First-pass clearance would be accurate.

PANEL MEMBER BYUS: Clearance is okay.

OEHHA STAFF TOXICOLOGIST WINDER: You're right.

PANEL MEMBER BLANC: What does this sentence mean to you: Inhalation provides more rapid uptake of manganese into the blood and the lungs, avoids first-pass clearance in the liver, allows direct access to the brain via olfactory nerves.
You say inhalation, the last phrase there, for example. This comes to some of my confusion in the way you wrote things.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. The last phrase makes reference to what happens in the nose whereas the first part is making reference to what happens in the lungs. Yeah, I can see your -- your source of confusion there.

The idea is that, demonstrated in the rats, the manganese that enters the nose can have access to the brain via the olfactory nerves. So it's directly from the nose to the brain, bypassing the blood-brain barrier, clearance from the liver.

With respect to the lungs, manganese is absorbed fairly efficiently in the lungs, and once it gets into the circulation it can go to the brain before it has the chance to --

PANEL MEMBER BLANC: So in fact, both uptake in the lungs and uptake in the nose could avoid first-pass --

OEHHA STAFF TOXICOLOGIST WINDER: That's correct.

PANEL MEMBER BLANC: -- clearance by the liver.

OEHHA STAFF TOXICOLOGIST WINDER: Yes.
PANEL MEMBER BLANC: Okay, so --

CHAIRPERSON FROINES: Except that we don't know the size distribution, so we don't know how much ends up in the airways.

PANEL MEMBER BLANC: Leaving that aside. I'm just pointing out this is a repeated problem with the document where somehow it's not clear -- if I just read this and didn't know anything better, I'd say okay so you mean it gets through the lung into the blood and from the blood goes to the nose and from the nose goes to the brain -- that's not what you're trying to say at all.

OEHHA STAFF TOXICOLOGIST WINDER: No.

PANEL MEMBER BLANC: And just be careful about that.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah.

PANEL MEMBER BLANC: Okay?

OEHHA STAFF TOXICOLOGIST WINDER: Now within the context of manganese, we point out here that children absorb much more manganese than do adults in the diet.

PANEL MEMBER BLANC: And why is that relevant to any of your arguments in any of this REL?

OEHHA STAFF TOXICOLOGIST WINDER: Because that means that a child's blood levels of manganese may be
substantially higher for a given exposure than an adult's would be.

A child that subsequently is breathing manganese on top of the dietary absorption may be at a higher risk level for exceeding the safe levels of manganese.

PANEL MEMBER HAMMOND: I thought it went the other way. I thought you were saying that if you have high blood then you'd divert more to the bile.

OEHHA STAFF TOXICOLOGIST WINDER: That's true. But in the meantime, you have blood levels that are reaching the brain.

PANEL MEMBER HAMMOND: That's already from the diet. Not from the --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Part of the issue is that infants absorb more manganese, and a lot of infants are being fed on soy formula which has actually quite a bit more manganese in it than breast milk.

PANEL MEMBER HAMMOND: So maybe more the point, the point might be more correctly -- if I understand you correctly -- the point might be better stated as that children and infants already have a very high level of manganese, and the environmental level can tip them over to a more dangerous level.
AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: The key point is that --

PANEL MEMBER HAMMOND: Is that true?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: -- the feedback regulation which maintains manganese homeostasis in the older child and the adults is not fully developed in the infant. So the infant doesn't have this same degree of regulation as the adult.

PANEL MEMBER HAMMOND: Well, that's not what's said at all there. Not that bullet point.

PANEL MEMBER PLOPPER: It doesn't say anything.

PANEL MEMBER BYUS: And in fact, but you're not arguing therefore the inhalation of manganese is going to be worse for them because the inhaled dose is not going to be regulated as it would be in an adult.

Your only argument has to be what Kathy said, which is that somehow it would tip them over.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Some infants will have a high level, fairly high level of manganese because they don't regulate their dietary intake.

PANEL MEMBER BLANC: And is there any data that support that?
AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes.

PANEL MEMBER BLANC: And you make that clear?

Like from NHANES or something?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: It relates to the children, the infants being fed on soy-based formulas.

PANEL MEMBER BLANC: But is there data from NHANES showing that childhood --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: No, I don't believe.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: There's no data from NHANES on infants.

PANEL MEMBER BLANC: Is there some --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: It's six years old and up.

PANEL MEMBER BLANC: Is there some other population-based data on infants showing that overall their blood manganese levels are higher than older age infants per nanogram per mL?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: We're not making an argument on a population basis. We're making the argument on the demonstrated existence of a susceptible subpopulation, which is infants, with a high manganese diet.
PANEL MEMBER HAMMOND: This is not --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: There are data that infants lack manganese homeostasis, and that's one of the issues.

PANEL MEMBER HAMMOND: That should be a bullet there.

OEHHA STAFF TOXICOLOGIST WINDER: That's a good point. We go on to point out that a number of compounds that are toxic for inhalation are relatively intoxic or not --

CHAIRPERSON FROINES: Can I stop you? Because I don't want to spend any time on this; we should talk about manganese. But I object strongly to the hexavalent chromium.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes, I do too. Thank you.

PANEL MEMBER HAMMOND: That is a disastrous statement.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: That should not be in there.

OEHHA STAFF TOXICOLOGIST WINDER: Point taken.

PANEL MEMBER BLANC: Moving right along.

PANEL MEMBER HAMMOND: And the others, actually -- just as long as we're there -- the others, crystalline silica and beryllium, at least, are dealing
with the lung as the target.

MARTY: Right.

PANEL MEMBER HAMMOND: So it's not a relevant comparison.

MARTY: Right, exactly.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.

MARTY: Hexavalent chromium, by the way, was struck from the document.

PANEL MEMBER BLANC: Okay.

CHAIRPERSON FROINES: Let's move on. We're all in agreement on that one.

OEHHA STAFF TOXICOLOGIST WINDER: This might have addressed some of the questions with respect to diet and inhalation. These data are presented in the document but in a slightly different way from this.

What I present here is the -- we take a look at the exposure of the average respirable manganese in the Roels study which is .215 mgs per cube meter. If an infant or individuals of the age you see across the X axis here were exposed to this, what I plotted here is how much they would be exposed to by inhalation compared to what they're getting in the diet.
So the portion here -- the colors didn't turn out too well. Let's start with brown. From the Food and Nutrition Board this is an indication of their estimate what an upper limit is for a dietary intake of manganese in different age groups.

The middle bar, sort of a yellow-green, is what they suggest is -- represents adequate intake.

Then the bar on the left, the green one, represents what these individuals would be exposed to were they breathing this amount that's in the Roels study corrected for their weight and respiration rate.

So what I'm trying to show by this is that the inhalation exposure for the very young in many cases approaches or may exceed the amount they represent as an upper limit for dietary intake.

Another way to look at it is that the safe level is more easily exceeded by a child that's being exposed to these levels whereas an adult would not exceed the upper limit.

PANEL MEMBER HAMMOND: Could you put -- what's the upper limit?

OEHHA STAFF TOXICOLOGIST WINDER: That's the brown.

PANEL MEMBER HAMMOND: Upper limit they should be allowed in the diet or the upper limit they should
get in the diet?

OEHHA STAFF TOXICOLOGIST WINDER: At which they expect toxicity.

PANEL MEMBER HAMMOND: So if this were in the diet -- the brown is if this were in the diet, this is the level at which you have toxicity?

OEHHA STAFF TOXICOLOGIST WINDER: Beyond which you'd have --

PANEL MEMBER HAMMOND: Okay. I misunderstood. I thought that was the upper limit of what one got in the diet.

OEHHA STAFF TOXICOLOGIST WINDER: No.

PANEL MEMBER HAMMOND: A soy based diet or something.

OEHHA STAFF TOXICOLOGIST WINDER: So what this represents, the gap between adequate and the upper limit represents what a normal individual should be taking in on a daily basis.

PANEL MEMBER HAMMOND: And there's no estimation made for infants?

OEHHA STAFF TOXICOLOGIST WINDER: These data were derived based on dietary intake and observation of either neurotoxicity or deficiency, and there was no evidence in their collection of toxicity based on breast milk, manganese content.
PANEL MEMBER HAMMOND: Wait. Now I'm confused again. I thought the brown is not an estimate of the upper limit of what's in the diet but upper limit of what would be dangerous in the diet.

OEHHA STAFF TOXICOLOGIST WINDER: Right. What they're saying is they have no data to say what a toxic upper limit is for the diet of a neonate.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Neonate.

OEHHA STAFF TOXICOLOGIST WINDER: Probably it's in the same neck of the woods as what we see there for two- to three-year-olds.

PANEL MEMBER HAMMOND: Except that there might really be differences in the way --

OEHHA STAFF TOXICOLOGIST WINDER: There might.

We just don't have the data.

PANEL MEMBER BLANC: And the inhalation here is the hypothetical inhalation at the proposed REL?

OEHHA STAFF TOXICOLOGIST WINDER: No. This is what the individual would get if they were exposed to what the Roels indicated was the average respirable manganese level.

PANEL MEMBER HAMMOND: Could you give us a number that's --

OEHHA STAFF TOXICOLOGIST WINDER: .215 mgs per
cubic year.

PANEL MEMBER HAMMOND: At .215 micrograms per cubic --

OEHHA STAFF TOXICOLOGIST WINDER: No, milligrams.

PANEL MEMBER HAMMOND: Milligrams.

OEHHA STAFF TOXICOLOGIST WINDER: Yes. That's what Roels reported it as average exposure. Just trying to show in the adult this level -- bringing this level would not cause the adult to exceed the upper limit in the diet whereas for an infant it could. Okay.

So then we have the assertion that neonates do not accumulate high levels of manganese in the brain more quickly than adults do with similar exposures.

Well, the data we have for these kinds of assertions are based on studies in rats. And in particular, this is a study by Dorman et al. in 2000 exposing both neonatal and adult male rats orally to manganese chloride, and both cases for a period of 21 days.

During that period of time, the neonates developed higher levels of manganese than adults in five of six brain areas, and I've listed them here: Cerebellum, hindbrain, hippocampus, hypothalamus, and
then there's a category of residual. The neonates compared to the controls had statistically significantly higher levels in six areas at the high dose whereas only three brain areas were elevated in the adult.

At the low dose, 25 mgs per kg, four areas in the neonates were significantly higher than the controls whereas only one in adults. This is suggesting that neonates do in fact accumulate higher levels of manganese more quickly than adults do.

Then in that same study they observed that neonatal rats had an increase in acoustic startle reflex; adults did not. It's not clear what significance that has in the context of human biology, but the point is that the neonatal exposed individuals were showing some sort of toxicity that the adults were not.

CHAIRPERSON FROINES: Just a question. Was this comment based on this study?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No. This is our response to that comment.

The comment was just made that there are no data to show that neonates accumulate higher levels of manganese in the brain relative to adults.

PANEL MEMBER BLANC: In fact -- I mean your
argument for carcinogenesis and childhood risk has been twofold. One is that for certain things there might be more carcinogenic potency. But also, they end up having more years of lifetime exposure.

So in fact, even if neonates didn't accumulate manganese more quickly than adults, exposure to a neonate provides the opportunity for a bigger cumulative lifetime dose and more target organ damage, doesn't it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It could. It could. It's a little bit of a different -- well, it's a little bit of a different argument.

Yes, it could provide more time for exposure, although manganese is not a bioaccumulative toxicant, so.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I don't think we're making the argument that the lifetime cumulative dose of manganese is the dosimetric for the toxicity, bearing in mind in particular that manganese is at the lower levels in essential elements and that there is a level of clearance for it for most tissues. We don't know the finer details.

CHAIRPERSON FROINES: I don't think this is a
toxicokinetic issue that Paul's raising.

Paul's raising a question that says neurologic
effects that occur over a cumulative basis are going to
be irreversible and increasing in severity, and so that
would make the cumulative dose an important parameter.

PANEL MEMBER HAMMOND: It's the effect that is
cumulative.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF
SALMON: Cumulative effect --

PANEL MEMBER BLANC: Let's take the example of
age of onset of Parkinsonian findings based on other
neurotoxins as well.

I mean the argument has been made that persons
exposed to the toxic factor in Guam atactic neuropathy,
even if they don't evidence the disease, shortly after
exposure are at risk of having earlier age onset of
Parkinson's because there's some threshold number of
basal ganglial cells that once you knock them out, when
you hit that threshold, that's when you lose your
reserve and start clinically to have Parkinson's.

So I would assume that if you were exposed
longer and as a child had a chance to knock out basal
ganglial cells that weren't going to regenerate, that
when you throw on top of that the normal loss with age,
you're going to get into trouble at an age where you
might have died otherwise long before you would ever manifest Parkinsonism.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Essentially your effect -- yeah, I would agree. You would expect to see cumulation of the effects during any period when your exposure was above whatever the threshold for cause and effect is.

That's --

PANEL MEMBER HAMMOND: No, no. That's not quite what he's saying.

PANEL MEMBER BLANC: I'm saying if you knock out a certain percentage of critical cells, and then on top of that you're going to be losing some through aging, had you not knocked out those other ones earlier, and the more you knocked out, the more likely you are to have the disease. So --

PANEL MEMBER HAMMOND: And the younger you'll get the disease.

PANEL MEMBER BLANC: And the younger you get it.

So children are sensitive not because they'll manifest the effect in childhood, but they're a sensitive subpopulation because when they grow up they'll have the condition.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

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MARTY: And as you can see, there's, on top of that, other issues with neurotoxicity in children that have been measured for manganese. So yes, that's another point.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: That's a contributor. It contributes to the reason why we are especially concerned about neurotoxicity.

CHAIRPERSON FROINES: In addition to what Paul said, Cory-Slechta at Rochester has shown very nicely that exposure in the postnatal period creates this susceptibility to the onset to development of Parkinson's at a later time in life. So there is a cumulative effect as well as some sort of postnatal damage.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Early life origins of adult disease, that whole concept.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah.

PANEL MEMBER BYUS: I have a question about the blood-brain barrier. Tell me what you're saying about manganese and the blood-brain barrier and
children versus adults. Are you saying anything?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Well. . . .

PANEL MEMBER BYUS: I kind of heard two conflicting things.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I think one thing that you heard was that direct access to the brain from the olfactory nerve --

PANEL MEMBER BYUS: Bypass --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: -- bypasses the blood-brain barrier.

PANEL MEMBER BYUS: All right. That's A.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I don't think we said B about the blood-brain barrier. I think the B that we said --

PANEL MEMBER BYUS: Doesn't cross the blood-brain barrier.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: There's certainly a limitation on its ability to do so.

PANEL MEMBER BYUS: Okay. So really what -- actually what the data shows, you're getting better distribution, perhaps, into the brain in an infant.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yes.
PANEL MEMBER BYUS: Which means -- which goes along with the thought that infants, well-known, have an incomplete blood-brain barrier.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER BYUS: So distribution -- which is not clearance, strictly distribution -- could in fact be greater in an infant, so by whatever route, except for olfactory, inhalation, or oral, so that would increase the likelihood for neurotoxins.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: That's certainly possible, particularly when coupled with our other point which was that the intrinsic homeostasis of the blood levels appears to be --

PANEL MEMBER BYUS: Correct.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: -- underdeveloped in the infant.

PANEL MEMBER BYUS: But even without that, you don't need to invoke that in a sense. It might be --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: They're all additional factors.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: This is not unique to manganese.

PANEL MEMBER BYUS: I would think distribution
to the brain for the infant would be the most worrisome thing, if it is in fact impeded by the blood-brain barrier. Which, assuming that somebody knows it must be. It's charged, so I would imagine it is.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, there are a number of studies which kind of address what sort of mechanisms --

PANEL MEMBER BYUS: So I would really make that -- put a few sentences or a paragraph about infants' incomplete blood-brain barrier. It's classic for early exposure to drugs and whatever.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We actually have that on page 12 as a point.

PANEL MEMBER BYUS: Okay. Just getting distinct from the olfactory which bypasses. Okay.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. And as we point out, even whether the infants accumulate faster than adults, it's not so important here as whether or not the infants experience more severe effects than the adults with comparable exposures or comparable effects with shorter exposures. And there are data that suggest this does in fact happen. These are studies in rats.

That after -- adult rats, 120 days of manganese exposure show neural degeneration, but
they're seeing the same sorts of levels in neural
degeneration in young rats after only 30 days of
exposure. There are a couple studies, like Chandra's
lab.

Now they say here that they have not
adequately substantiated the need for a 100-fold UF,
uncertainty factor, for the intraspecies sensitivity
for children. Well, this is just what we've been
discussing here, the idea of children being more
sensitive down the road than they are now, manifesting
the effects later on in life is one issue.

Here I point out that based on studies by
Ginsberg, there's a three- to fourfold higher
deposition of inhaled particles in this 1-10 micrometer
range in neonates versus adults.

In addition, from the stuff mentioned earlier,
there is a fourfold or higher retention of manganese
absorbed from the gut by neonates, and again as we
mentioned, lack of efficient homeostasis.

PANEL MEMBER BLANC: So one other thing that I
think will complete your thinking on this is if there
is data on what is the geometry of nasal clearance in a
neonate as opposed to an adult for those particles
which would normally be cleared by nasal clearance.

PANEL MEMBER HAMMOND: What do we know -- I
don't know. What do we know about the size
distribution of atmosphere -- you know, of
environmental -- I mean manganese, of manganese in the
environment? What do we know about that? I know more
by occupation but --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Only what is -- the measurements are either
PM10 or PM2.5. I don't think there are very much data
on actual distribution.

PANEL MEMBER HAMMOND: Is it -- well,
between -- for some metals, PM2.5 and PM10 are the same
in which case we know it's all PM2.5. Do we know for
manganese?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I would have to look at ARB's data to know
that. It's a little bit -- it's dependent a little bit
on its source. If you have a facility that's actually
emitting manganese, it would depend on what they're
doing to emit it.

PANEL MEMBER HAMMOND: I'm just wondering --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: But we can look at that.

PANEL MEMBER BLANC: My point about the nasal
deposition in an infant, was that clear?
MARTY: There are some -- there are some data we can
put in about nasal deposition.

PANEL MEMBER BLANC: Of particles.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Of particles.

PANEL MEMBER BLANC: In infants. In neonates.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: There's models.

PANEL MEMBER BLANC: All right, models.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Well, Ginsberg is a model too.

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: And it's, of course, dependent on size.
Interestingly, the model shows that there's larger
nasal deposition of ultrafine particles than you would
think. You would think they would --

CHAIRPERSON FROINES: No, of course they --

PANEL MEMBER HAMMOND: They diffuse.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Because it's diffusion, right.

PANEL MEMBER HAMMOND: It's diffusion.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: So not being a physicist, it was a surprise to
me. So yeah, there are some data we can --
PANEL MEMBER BLANC: But they're highly relevant to this substance. That's all I'm saying.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- pull in.

CHAIRPERSON FROINES: We've done lots and lots of studies of this, and we will look into the manganese in this three particle sizes and tell you.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Good.

OEHHA STAFF TOXICOLOGIST WINDER: In this particular -- in our response here, we're starting to touch on some of the same topics we've just been talking about here, the developing brain, newborns and infants more sensitive to the effects of manganese and that these injuries are likely to be long-lasting or to have long-lasting effects.

Also that the neurotoxicity is only partially reversible in adults, and it's likely more severe in the case of infants.

And then we've indicated that there are studies which suggest that developmental neurotoxicity has been measured in infants with elevated manganese from drinking water as well as elevated manganese in cord blood, hair, and teeth.

So there are data which support that infants
receiving high manganese exposures are in fact showing neurotoxicity.

Okay. They suggest that we have not considered all relevant studies. Well, we've looked at a large number of studies here, and we feel that the Roels study is probably the best in terms of those that are currently available in terms of being able to quantitate -- quantitatively determine what the risks are.

We've included a number of other studies. This includes studies by Luchini and Mergler, this crowd, just mainly for completeness.

The -- at the time these comments were submitted, they were suggesting that PBPK modeling --

CHAIRPERSON FROINES: Can you go back to the question of the adequacy of your studies? Because you never want to be criticized for cherry-picking, obviously. And so have you looked at those studies in terms -- and I don't remember what's in here, but have you made critical comments about both the adequacy and what they imply?

PANEL MEMBER BLANC: The Luchini study is certainly described at great length, and the -- and I think Mergler is described.

But I want to -- when we finish with these
comments, actually, one of the main issues I want to
explore with you is the adequacy of the literature
review, the time frame of it. But I'd like to hold on
that just for a moment.

OEHHA STAFF TOXICOLOGIST WINDER: Anyway, they
are saying that PBPK models that were in development
would improve our risk assessment process. Well, these
models are apparently not published yet, so we're still
in the process of developing the REL information we
currently have.

CHAIRPERSON FROINES: Doing what?

OEHHA STAFF TOXICOLOGIST WINDER: We're in the
process of continuing with the manganese development.
These models are not available, not published yet.

PANEL MEMBER BLANC: So does that mean the
four-part series of articles on pharmacokinetic model
in manganese in the rat based upon IV exposure, not
inhalation data, those weren't relevant because that
was IV?

OEHHA STAFF TOXICOLOGIST WINDER: Pretty much.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: No, we didn't use -- they -- the folks who
commented submitted rafts of their PBPK modeling, but
they're not published yet, so they haven't been
peer-reviewed.
PANEL MEMBER BLANC: That's appropriate. But the other, since there is this raft of pharmacokinetic modeling articles, I mean those aren't really referred to, even to say that because they're IV they're not appropriate to our needs.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah. I haven't addressed that at all. I was only looking for inhalation-related exposures in modeling.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We didn't comment on those.

OEHHA STAFF TOXICOLOGIST WINDER: But you're right.

PANEL MEMBER BLANC: Because, for example, I would suggest to you that an article entitled Pharmacokinetic Modeling of Manganese in the Rat IV: Assessing Factors That Contribute to Brain Accumulation During Inhalation Exposure is somehow relevant to your work.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Is that one that hasn't been -- I'm not sure what you're --

OEHHA STAFF TOXICOLOGIST WINDER: Who is the author of that?

PANEL MEMBER BLANC: Holding it in my hand. It's Nong, Andy Nong, but it's from that whole --
OEHHA STAFF TOXICOLOGIST WINDER: Yeah, it's from the --

PANEL MEMBER BLANC: -- Dorman industry.

OEHHA STAFF TOXICOLOGIST WINDER: -- Dorman.

PANEL MEMBER BLANC: I'm going to return to this issue in a more generic form.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. That's the extent of the slides we had.

PANEL MEMBER BLANC: Okay. Then with the Chair's permission, then, maybe I should just continue.

CHAIRPERSON FROINES: Yes.

PANEL MEMBER BLANC: This is a particularly challenging subject area because there's such active research going on, and you could find yourself in a blind loop where no matter what you do it's going to be new stuff coming out.

And it was really the driving factor in me asking the question about how you're going to handle what the cutoff time is going to be for your work.

But just so I'm clear, what is the cutoff time for what we have before us now? When did you stop looking at the literature?

OEHHA STAFF TOXICOLOGIST WINDER: We have been reviewing the literature up to, I believe, prior to the last meeting.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: April.

PANEL MEMBER BLANC: April. Okay.

Something that struck me as I started to read this and then started to try to look at what was out there was that, given the sensitivity and hotness of this topic, I thought the literature review was really -- really did yourselves a disservice for this REL.

And if you look at some of your other RELs, you have three or four times as many citations for some of the other ones. Now some of the other ones are about on this level, but may not be as germane. But certainly the arsenic, as an example, has far more literature that's invoked.

And I think that you're obliged in an area where there is so much active research to have more citations.

And in particular, I think that there is animal -- there is primate data that is relevant as a backup data to your chronic REL discussion.

I was really flummoxed by the nature of the animal data that you cited which was ingestion data as the corollary to your chronic REL. It wasn't inhalation -- it wasn't animal inhalation data,
particularly. It was an awful lot of animal dietary exposure data.

OEHHA STAFF TOXICOLOGIST WINDER: A number of the studies, especially the Dorman comparing dietary with inhalation and the effects of dietary on inhalation and vice versa.

PANEL MEMBER BLANC: There is some of that. But I think that there is a very important 2007 paper from the Dorman group which is called Manganese Inhalation by Rhesus Monkeys is Associated with Brain Regional Changes in Biomarkers of Neurotoxicity.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I haven't included that.

PANEL MEMBER BLANC: That paper suggests a fairly low LOAEL, even though they, you know, sort of discount their own findings. But it's -- I think it's 60 micrograms per meter. And they definitely see effects which I would interpret as being biomarkers of localized important effects.

And of course -- I mean I'm going to give you all this stuff -- but just in my own, you know, my own view of this, I mean I think you've systematically undercited that research group. Or you could be misinterpreted as systematically underciting them.

Now I think it's important to state that
they -- much of their work is funded by the corporate
interests with the main interest in -- with a major
interest in manganesic air pollution effects, and
I'm -- I think it would be appropriate to state that if
you wish without any implications per se, but just to
acknowledge it.

But I think to not review that literature
makes it seem like you don't know what the current
literature is, and therefore it undermines your
argument.

Plus I think there's going to be information
here, aside from that, which is going to be quite
useful to you.

So I think without doing that this document is
not adequate.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: I don't think we systematically undercited the
work by Dorman's group.

PANEL MEMBER BLANC: Well, there's nothing
after 2002 that you cited, seems like. And they've
had -- or virtually nothing after 2002. And there is

Another paper that I think you're going to --
another epidemiological study that I think you're going
to be forced to summarize, even though I don't think
it's going to affect your judgments, it has to be the Bowler study on the bridge welders.

I mean we're sitting here looking at where that study happened. And, you know, it has a myriad limitations, but I think you're going to have to summarize it and deal with it in some way.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I have a hard time trying to decide what to do with the welder data. There are a number of studies that deal with effects on welders. Unfortunately, there's a lot of mixed exposures there, and it's kind of hard to sort that one out.

PANEL MEMBER BLANC: Yeah, but since this was not published as an exposure to welding fume but exposure to manganese fume, I think you're obliged. You can critique it by saying there were other concomitant exposures and, you know, but it is a paper with manganese levels and neuropsych effects and, you know --

PANEL MEMBER HAMMOND: And any of those welder exposures are not -- how many of those are neuropsych effects?

CHAIRPERSON FROINES: Are what?

PANEL MEMBER HAMMOND: The other exposures associated with welding are not all having
neurobehavioral effects, neuropsych.

PANEL MEMBER BLANC: Yeah, this one I think you're just, just -- you just have to deal with it.

OEHHA STAFF TOXICOLOGIST WINDER: Sure. Okay.

PANEL MEMBER BLANC: Now, that's a sort of a general comment. But there are some other things as well.

And let me just ask you when you -- again, this is a somewhat different situation than many of the materials you're dealing with RELs with, you know, of the five because you're forced to have to deal with not only elemental manganese but some of the important species.

How did you determine what you wanted to include and not include in the list on table 2.1? You have manganese, manganese oxide, manganese tetroxide, you have manganese chloride. So it's not just element and oxide. You decided to include manganese chloride.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, that's primarily based on what gets emitted from facilities in the hot spots program.

So it could be other manganese compounds too that this would apply to, just apply to the manganese fraction of those salts; but there's other salts too, and they were --
PANEL MEMBER BLANC: The reason I ask is because --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We would apply this REL to all inorganic manganese compounds.

PANEL MEMBER BLANC: Okay. Well, so there are some inorganic manganese compounds which are going to become issues as you go through since a lot of the animal studies are with manganese sulfate.

OEHHA STAFF TOXICOLOGIST WINDER: Sulfate.

PANEL MEMBER BLANC: I think if you don't include manganese sulfate in your table you should at least say something about manganese sulfate because so much of the data are going to be there.

And I think that you're obliged somewhere to talk about permanganate. And I'm going to come back to that a little bit in roots of exposure. But I think that's a kind of a critical player in certain outbreaks and case reports, so it shouldn't be ignored.

But when you talk about occurrence and major uses in Section 3, really at the very beginning, the notion that nowhere is alluded to the fact that the breakdown of organic manganese compounds could become a major source of inorganic manganese in the air is a critical oversight in this document.
I mean we have a major national and international debate on MMT. There's no way you could know that from anywhere in this document.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. So we'll include and expand.

PANEL MEMBER BLANC: And as another minor point, in welding, the exposure to manganese oxide, yes, can occur from base metal that's being welded. But I think if you look at the literature, you'll find that the welding rods are the major contributor to manganese exposure. Would you agree with me on that?

PANEL MEMBER HAMMOND: Absolutely.

PANEL MEMBER BLANC: And the welding rods are not mentioned at all. That sort of suggests a lack of familiarity or a superficial view of the exposure literature that could give the wrong impression.

And the same thing is true in the next sections when you talk about how manganese can enter the body. From a health point of view -- I mean you've got one hat on, which is a sort of public health, air pollution, and environmental thing; but since you end up -- one ends up deriving information from other sources, I think it should be acknowledged that parental exposure to manganese has been quite important.
in human health in terms of the recent outbreak of manganism in IV drug abusers who have used potassium permanganate to generate modified sympathomimetics.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Ephedrine.

PANEL MEMBER BLANC: Yeah. I think it has to be, I mean, an internal article, you know, that kind of outbreak needs to be alluded to, at least in passing.

And certainly historically, parental feeding of manganese and it's an important model because it demonstrates how critical the normal homeostasis is.

OEHHA STAFF TOXICOLOGIST WINDER: We refer to parental exposure primarily to show that some of these studies indicate that the effects of high levels of manganese are derived --

PANEL MEMBER BLANC: But in fact, a sentence says manganese can enter the body both by oral and inhalation routes. Well, and obviously by parental means, and that's been important.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Environmental manganese.

PANEL MEMBER BLANC: Well, if that's what you mean. Although we would acknowledge that parental exposure has been important in human disease, or something like that.

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MARTY: Yeah.

PANEL MEMBER BLANC: As well as subcutaneous, by the way, I think when you say it's -- external absorption of manganese is insignificant through intact skin but, you know, for example use of potassium permanganate on wounded skin, you know, may be not such a trivial thing.

And there is stuff here on -- again, this is where you start to get into -- it started to be confusing to me about the olfactory absorption. And when you use the term inhalation, sometimes you mean inhalation to the lung, and sometimes you mean airborne exposure that could lead to upper as well as lower airway tract exposure.

And so I think you need to go back and be meticulous when you say what it is you mean when you say certain things because I think it's really, really important for this compound.

OEHHA STAFF TOXICOLOGIST WINDER: So distinction between nasal intake versus pulmonary.

PANEL MEMBER BLANC: Yeah, just be careful of your wording.

And do you feel that you're obliged to acknowledge and then discount this whole thing about
aerosol generation of manganese in showers from -- you know how there was this whole little brouhaha about what is the theoretical exposure to people if they have high manganese water --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: In the water.

PANEL MEMBER BLANC: -- that they generate aerosol?

OEHHA STAFF TOXICOLOGIST WINDER: Seemed like in the literature that was pretty effectively discounted there, and that's the reason it wasn't included here.

PANEL MEMBER BLANC: That's the kind of thing again where, depending on your desires or needs, you can say although this has been raised it has been subsequently discounted, rather than just not mentioning it at all. You know, if in fact that's what you think.

And again, I would call your attention to the paragraph on page 5 that deals with the nasal issue, and I want you to go back over that and think about what you're trying to say, what the issues of particle size are.

One of the papers you cite has to do with, I think, small particles, but it's not at all clear to me...
that large particulates can't be taken up by the nose as well. So you need to go back to the papers you cited and really see.

Now your decision to not make any acute manganese REL, even though it might be a pretty high REL, is because the data on pulmonary acute lung injury from high-level manganese inhalation which is often alluded to in the literature, there's such poor case reports and so limited. Is that right?

OEHHA STAFF TOXICOLOGIST WINDER: That's part of it. And the information seems to suggest -- the pulmonary response associated with acute exposure doesn't seem to be unique to manganese.

PANEL MEMBER BLANC: Well, I didn't understand that at all. Your line that -- okay: However, a pulmonary inflammatory response is also associated with inhalation of particulates in general and does not appear to be dependent on the manganese content.

OEHHA STAFF TOXICOLOGIST WINDER: So --

PANEL MEMBER BLANC: I don't believe that's true at all. And I don't support that statement.

OEHHA STAFF TOXICOLOGIST WINDER: I haven't seen data to suggest that the manganese content there was shown to be --

PANEL MEMBER BLANC: I haven't seen data that
support a generic effect from particulates causing pulmonary edema.

PANEL MEMBER HAMMOND: Pulmonary edema?

PANEL MEMBER BLANC: Yeah. So I don't know what it is you were trying to say there, but I don't agree with it, and -- or I don't think it was clear. Or I'm disagreeing with something that you didn't mean to say.

CHAIRPERSON FROINES: Where is that?

PANEL MEMBER BLANC: Point 5.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That sentence doesn't seem to follow anyway. It doesn't follow the sentence before it. So I'm not sure if it's left over from an earlier version or what.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Sounds like we need to rework that one.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We need to take the sentence out. I think a more pertinent issue is the lack of dose response formation to generate an acute REL.

PANEL MEMBER BLANC: Well, you have this -- one is a two-hour exposure of mice to manganese oxide aerosols that resulted in a NOAEL of 2.91 milligrams per meter based on pulmonary edema.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: We can relook at that to see if it's worth it.

PANEL MEMBER BLANC: Okay. Because it doesn't hold together, just the way -- God knows you've found acute RELs on less. I don't know.

I also wasn't that comfortable with you guys citing at certain key places ATSDR as your source for -- because that in itself is a review.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: I think you should avoid doing that if you can.

CHAIRPERSON FROINES: I think as a matter of policy, in general, I think we should use primary references and not secondary sources.

I don't necessarily have -- put great stock in ATSDR documents, and it would be better to use the primary references. Just as a general point.

Can I ask one question, Paul, before you go on.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: Do you know for a fact, do you have any evidence from electrochemical potentials that manganese would undergo Fenton reactions with hydrogen peroxide?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: We have not explored that issue.

CHAIRPERSON FROINES: We know iron does. We know copper does. We know metals with a valence state of 2 undergo Fenton reactions and create reactive oxygen, hydroxyl radicals. So it would be worth at least knowing that E0 is not right for that reaction.

PANEL MEMBER BLANC: If you go to 6.2.1 on page 12 which is your potential for differential effects in children section. And this comes back to the discussion we just had and the response to the critic. And in fact, it may have been this that generated -- unnecessarily generated some of the response that you got.

I don't find this a particularly well-argued bullet point section, and it seems as if they were all toxicokinetic arguments without any toxicodynamic arguments.

OEHHA STAFF TOXICOLOGIST WINDER: It's true; they largely are.

PANEL MEMBER BLANC: But yet I would say the compelling thing to me would be toxicodynamic -- or as compelling, at least, in this kind of neurotoxin.

So I think you need to go back through there, and if there are things, first of all, which are really sort of not so important, I'd just get rid of them, if
you think they're more controversial than not, and try

to have a balanced argument.

Then if you -- just to underscore what I said

about the animal studies and how I was a little bit

surprised and taken aback, when you get to a section on

animal studies of chronic toxicity, you start with an

oral study -- which I couldn't figure out why you were

starting with that -- then you do go to a study with

four rhesus monkeys from 1984, and then you go to an

injection study.

And that's what made me go look at PubMed. I

said really? There is no -- this is all this is for

inhalation study? I thought there was a lot of primate

stuff going on. What's happening? So that was really

weak.

And I know you showed that figure -- I mean on

the diet. I think that's a -- I think what I would do

if I were you is get rid of that figure and make your

key point in a couple of sentences.

But the figure -- first of all, the legend is

not interpretable as it is. I didn't know the upper

limit to what, you know. But I think it's really kind

of an obscure -- it's not straightforward to me at all.

And I think some of the other things we've

talked about as we've gone through.
So I think that this document which is --
could emerge as a major public health protective issue
in the State of California, were we to see the
introduction of organified manganese into our breathing
zones, I want to see this particular document be as
strong as it can be.

And I think, you know, for better or for
worse, you have to respond to a series of -- you know,
a very long critique which really wasn't to the -- very
much to the point, so then that diverted you to respond
to things that ultimately didn't make the document
stronger one way or the other because they were sort of
off the mark anyway.

OEHHA STAFF TOXICOLOGIST WINDER: Okay.
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF
MARTY: Sounds like we have some additional work to do
on this REL summary.

PANEL MEMBER BLANC: And given your expertise
in primate exposure stuff, I think that you could maybe
be a resource for them looking at some of these
studies. The animal stuff is the first example we've
had of a rich data set of primate data.

PANEL MEMBER PLOPPER: Sure. That's true.
PANEL MEMBER BLANC: That's it.

CHAIRPERSON FROINES: I'm sure they'll
consider that enough.

PANEL MEMBER PLOPPER: Good start.

CHAIRPERSON FROINES: Is there a motion to --

I don't think there's anything else that I know of.

PANEL MEMBER GLANTZ: Did anybody else have

anything they wanted to say? I don't.

PANEL MEMBER BYUS: I think the document is --

the parent document is very good. I think it's very

nicely crafted and put together, and most of the REL

calculations are also very good. And I think it's

going to be a really nice addition, and you did a nice

job on it.

CHAIRPERSON FROINES: Melanie?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Okay. We need another meeting, obviously, for

this document. So I was talking with Jim earlier.

What we could do is have a meeting, September's time

frame, to finish the REL summaries, and also at that

time introduce the cancer risk assessment changes.

That document is going out for public review

starting next week for a 60-day review which might end

up being longer, so you won't have in September the

public comments and our responses.

But we could have a meeting to finish this off

and introduce the Panel to the changes that are now
being proposed for cancer risk assessment.

So just putting that out there.

CHAIRPERSON FROINES: So I think, Peter, we're
talking about September. We're not talking about
anything sooner than that. And then school starts, so
that everybody gets pretty busy, so September is
probably the best time that I can think of.

PANEL MEMBER HAMMOND: School starts in August
for me.

CHAIRPERSON FROINES: Is Davis quarter or
semester?

PANEL MEMBER FLOPPER: Quarter.

CHAIRPERSON FROINES: So Charlie and I are
okay.

PANEL MEMBER BYUS: Medical school has blocks.

CHAIRPERSON FROINES: Okay. Anything else
from OEHHA today?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I'm sorry?

CHAIRPERSON FROINES: Do you have any other
issues.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: No, just that one.

CHAIRPERSON FROINES: Good. Anybody else on
the Panel have comments? Joe?
PANEL MEMBER LANDOLPH: Is Roger going to come back to us someday, or do we know?

CHAIRPERSON FROINES: Jim, do you want to give a report?

MR. BEHRMANN: Jim Behrmann, liaison to the Panel.

In my several conversations with Roger, he expressed his willingness to continue providing assistance to ARB and OEHHA and DPR but feels that he cannot easily travel at the moment given his wife's condition.

She was coming back from very serious surgery, and there were some complications, as I understand it. So he felt that he wanted to be -- he did not feel it was easy for him to travel, so he felt the need to step down from the Panel.

CHAIRPERSON FROINES: So the next step is to get a list of names from the university.

MR. BEHRMANN: What the next step will be is that we request an updated list from the president of UC. They create a pool of nominees, and that particular category is appointed by the secretary of Cal/EPA.

So once that pool of nominees is created, then a decision will be made by Secretary Adams, and an
appointment will be made. So we're just initiating that process right now.

PANEL MEMBER BYUS: Are you going to ask Roger who he would recommend?

MR. BEHRMANN: Yes.

PANEL MEMBER BYUS: Very good. I mean that's who I'd ask.

CHAIRPERSON FROINES: Well, I think it's important for the Panel to give you input about -- I mean I have rather strong feelings about what our needs might be, but I think that why don't we let people communicate with you?

MR. BEHRMANN: Please, if you have names, please do submit them to me, and we can pass them on.

As you know, the UC president's office runs its own process, and they run a very careful process in terms of vetting candidates and the like. But I'm sure they would be open to receiving names from us as well.

CHAIRPERSON FROINES: Well, we have one, two, three, four people who we would classify as toxicologists, I think. And Stan is a statistician and Kathy is exposure assessment, and Paul's a physician toxicologist/exposure assessor --

PANEL MEMBER GLANTZ: Curmudgeon.

PANEL MEMBER BYUS: Curmudgeon.
CHAIRPERSON FROINES: Just the thing that's important is the data that we review tends to fall into three categories: Epidemiologic data, exposure data, and toxicologic data.

So my view is that we need somebody who would help in the exposure area, exposure assessment area.

PANEL MEMBER HAMMOND: In particular, I think Roger brought an understanding of atmospheric chemistry.

MR. BEHRMANN: That actually is the category in the law that he fulfilled.

CHAIRPERSON FROINES: I would argue that I would prefer somebody who had a little bit more understanding of some of the exposure issues that relate to epidemiologic studies.

PANEL MEMBER HAMMOND: Oh, I'm not saying it's not important, but I think it shouldn't just be exposure assessment that doesn't know atmospheric chemistry.

MR. BEHRMANN: By law they would have to also be an atmospheric chemist or be trained in that field.

CHAIRPERSON FROINES: We would like to convince ARB to take up some atmospheric chemistry issues, because that hasn't happened in 20 -- how many
years?

MR. BEHRMANN: The Panel --

CHAIRPERSON FROINES: 25 years, has not happened.

MR. BEHRMANN: I'll communicate that to the Air Resources Board, or I can pass this message on.

PANEL MEMBER BLANC: I think they should have a Scots accent.

CHAIRPERSON FROINES: What did he say?

PANEL MEMBER BLANC: They should have a Scots accent because I miss that.

CHAIRPERSON FROINES: Anybody want to make a motion to adjourn?

PANEL MEMBER BYUS: I move we adjourn.

PANEL MEMBER BLANC: Second.

CHAIRPERSON FROINES: All in favor?

(Ayes)

* * *

(Thereupon the California Air Resources Board, Scientific Review Panel meeting adjourned at 3:29 p.m.)
CERTIFICATE OF REPORTER

I, LINDA KAY RIGEL, a Certified Shorthand Reporter of the State of California, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, Linda Kay Rigel, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this June 30, 2008.

LINDA KAY RIGEL, CSR
Certified Shorthand Reporter
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