MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

SIERRA HEARING ROOM

1001 I STREET

SACRAMENTO, CALIFORNIA

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JAMES F. PETERS, CSR, RPR
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APPEARANCES

PANEL MEMBERS

John R. Froines, Ph.D., Chairperson

Jesús A. Araujo, M.D., Ph.D.

Paul D. Blanc, M.D.

Alan R. Buckpitt, Ph.D.

Ellen A. Eisen, Sc.D.

S. Katharine Hammond, Ph.D.

William W. Nazaroff, Ph.D.(via teleconference)

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, Scientific Review Panel

Mr. Peter Mathews, SRP Support Administration

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Robert Blaisdell, Supervisor, Environmental Modeling Section

Dr. Joseph P. Brown, Staff Toxicologist

Dr. Daryn Dodge, Staff Toxicologist

Mr. Brian Malig, Research Scientist

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

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

Dr. Aijun Albert Wang, Staff Toxicologist

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PROCEEDINGS

CHAIRPERSON FROINES: Is Bill on the line?

PANEL MEMBER NAZAROFF: Bill is on the line.

CHAIRPERSON FROINES: Good morning, Bill.

PANEL MEMBER NAZAROFF: Hi. Who's this?

CHAIRPERSON FROINES: This is John Froines.

PANEL MEMBER NAZAROFF: Hi, John. How are you?

CHAIRPERSON FROINES: Good.

We are about to begin.

So let's say that the Scientific Review Panel meeting of October 31st is -- currently is in session.

And the first speaker -- the first issue will be caprolactam, and the first speaker will be Melanie Marty with OEHHA.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: My name is Melanie Marty. I'm Chief of the Air Toxicology and Epidemiology Branch at OEHHA.

And the first item today is caprolactam. So I'm going to just run quickly through the most recent activities and then hand it over to my staff.

So as you'll recall, the Panel has met twice on this Reference Exposure Level document, in January and May. We prepared revisions in response to public comment and to comments from the Panel.

Then we had a meeting scheduled August -- at the

end of August. But industry representatives sent comments directly to the Panel, which we were asked to respond to by the Chair. So we developed responses to the technical comments, and then the meeting was postponed until today.

So that's it in a nutshell.

Daryn Dodge -- Dr. Dodge is going to give the presentation, go through the REL, through the changes we made, and responses to the key industry comments. And to Daryn's right is Brian Malig. Brian is an OEHHA staff person. And then Robert Blaisdell also.

So, Daryn, take it away.

PANEL MEMBER BLANC: Paul Blanc here.

Could we just clarify --

CHAIRPERSON FROINES: Paul, turn your mic on.

PANEL MEMBER BLANC: -- clarify for people -- just clarify for people that the revised document that people have received does not include certain revisions that may be referred to in the comments that are about to come up. I think that wasn't as explicit as you might want.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay, yes.

The document that you all received to review we sent in July -- the end of July. So we subsequently responded to industry comments that were sent to the

Panel. So there are a couple of revisions that we're going to bring up in the slides that we need to have a little bit of discussion of anyway. And it's related -- it's around statistical issues.

PANEL MEMBER BLANC: Revisions that you propose will be reflected in the final document?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: So that there are -- are you going to address issues, for example, of neurologic changes?

PANEL MEMBER BLANC: No, those are relevant to the revision that you already have.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

CHAIRPERSON FROINES: And then you're not going to review that?

PANEL MEMBER BLANC: I'll comment on that as lead. In other words, there needs to be comment on the revisions that were made in response to our discussion.

CHAIRPERSON FROINES: Okay, okay.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Daryn.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA STAFF TOXICOLOGIST DODGE: Thank you, Melanie.

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OEHHA STAFF TOXICOLOGIST DODGE: Okay. I'll just give a brief recap what happened at the last SRP meeting in May.

We presented draft 8-hour and chronic RELs. These were based on a subchronic exposure study.

CHAIRPERSON FROINES: Excuse me. By sitting here, am I blocking anybody's view?

PANEL MEMBER BLANC: No.

CHAIRPERSON FROINES: No, okay. Thank you.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. At the last meeting we presented draft 8-hour and chronic RELs. This was based on a subchronic exposure study in rats by Reinhold, et al. And the endpoints were lesions in the nasal and larynx epithelium.

At the last meeting we didn't have an acute REL. We were still attempting to get the raw data from an acute human study by Ziegler, et al. And we felt that the published report had more information there. And there wasn't enough there for us to establish a REL. But if we had the raw data, we could take a look and see what there was.

Subsequently, after the meeting in May, about a

week or less, we did obtain the raw data from Dr. Ziegler.

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OEHHA STAFF TOXICOLOGIST DODGE: This is an overview of the changes to the documents. We did get the raw data, as I said. And we derived an acute REL based on that raw data. And that's in the major change in the document.

We added in response to the Panel an appendix of detailed benchmark concentration modeling results of the Reinhold 13-week rat data. That's Appendix A.

We added a Korean case report of neurotoxicity for heavy worker exposure, and we had it translated by one of our scientists. In the process of doing that we found another Chinese report that found the same endpoint, neurotoxicity with heavy worker exposure. So we also had a scientist who could translate that article and we put summary of it in the current draft REL.

And in the process of that we found four Chinese caprolactam occupational studies, and we had those translated. And we have summaries of those in the draft REL report.

CHAIRPERSON FROINES: Can I ask you a question?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah.

CHAIRPERSON FROINES: I have the mic on. I have a cold.

The Chinese and Korean case reports of neurotoxicity with, quote, "heavy worker exposure," is there any way to say more about what that exposure reflected? Because "heavy worker" doesn't -- is not as clear a statement -- not as clear characterization as one might prefer.

PANEL MEMBER BLANC: Can I make just a process suggestion. And, again, Melanie, this is why I asked you the question at the beginning. We seem to be mixing two things: One is a presentation regarding the changes that are reflected in the document that we have; and then comments that are going to be forthcoming regarding the response to the -- response to the document, right?

So it would seem to me the most logical thing would be, since -- I assume what you want us to do is discuss all of it as a package, both the revisions and then the responses.

So, John, what I think we should is just hold off, let them present this --

CHAIRPERSON FROINES: No problem.

PANEL MEMBER BLANC: -- and then we can go systematically through, first, the revisions that we have had and then the more immediate issue of what their responses were to the comments on the revision. Otherwise it's going to be like one of those Russian dolls that we

keep opening up and there's one inside another.

CHAIRPERSON FROINES: That's fine. We'll do that. Keep in mind what I just asked you, however.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

We also added in response to the Panel a couple case reports of contact dermatitis resulting from dermal exposure to caprolactam.

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OEHHA STAFF TOXICOLOGIST DODGE: We also added summary tables of acute and chronic exposure results in animals and humans.

And then a couple of new tables are in there to -- one is to help clarify the 13-week exposure endpoints. I separated that into a 13-week exposure table; and another part of that same study, 13-week exposure plus 4-week recovery. I tried to combine both of the major endpoints from both of those parts of the study, and it led to a bit of confusion.

Now, a new table in the report is based on the daily and weekly observations of the 13-week rat study. And the numbers I got for this able are from the industrial study. It wasn't in the published report by Reinhold, et al.

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OEHHA STAFF TOXICOLOGIST DODGE: Okay. Now, I'd

like to go into the human chamber study on which the acute REL is based on -- the draft REL.

The exposures in the study was 0, .15, .5, and 5 milligrams per cubic meter caprolactam. The subjects were exposed for six hours total at each of these concentrations. There was 20 participants.

Endpoints they were looking at? They were looking -- the time points were zero, or just after entering the chamber, one, three, and six hours of exposure. And those endpoints included eye blink frequency; eye redness; nasal resistance, which actually was only measured at the end of the 6-hour exposures. And they filled out subjective symptom questionnaires at each of those four time points.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, the statistical analysis was we used the Page's trend test. This is a applied to non-normally distributed data, takes into account measurement of the same subjects at different exposure times, and takes into account the ordering of the doses.

Now, we had a couple of other statistical tests in the draft REL, including Friedman's and a repeated measures ANOVA.

Ultimately it was decided by Dr. Haseman, who was

the representative from the stakeholders who did the statistical analysis for them, the raw data, and Dr. Stan Glantz, that the best test really is the Page's trend test, and we'd just rely on that. I'll go into that a little bit more later on in another slide.

But, anyway, in the Page's trend test sees a significant trend, we then use the Wilcoxon sign-rank test to see where the differences among the dose groups are.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, among the objective measures we looked at one hour of exposure. And we chose the one hour because that's the duration of our acute REL.

We saw no statistically significant trend for eye redness or nasal irritation -- or nasal resistance. However, we did see a statistical significant increasing trend with increasing dose for eye blink frequency. And the difference from the control was the high dose, which was 5 milligrams per cubic meter.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, among the subjective symptom results, there was 29 questions placed into 7 subgroups. The most important subgroups were eye irritation, which had 7 questions; nasal irritation, which had 5; and odor, which had 4.

So odor naturally, as I explained at the last meeting, there was -- there was recognition among the subjects that there was an odor there. So that was statistically significant. However, we also found eye irritation by the Page's trend test was significant.

And the sign-rank test found the difference from the control group at the highest level, the 5 milligram per cubic meter.

Now, interestingly, there was no trend or difference from controls for nasal irritation even though the subjects recognized the odor. So they were able to differentiate between irritation and odor.

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OEHHA STAFF TOXICOLOGIST DODGE: So for acute REL derivation, the critical effect is increased eye blink frequency.

The LOAEL, or lowest observable adverse effect level, was 5 milligrams per cubic meter, the high dose.

So our NOAEL is .5. And that's the point of departure; that's the mid-level dose.

There's no time adjustment for the derivation because it was one hour exposure, which is the duration of our acute REL.

No interspecies adjustment since we have human data.

And for intraspecies uncertainty factors, we had a toxicodynamic uncertainty factor of 10 for human variations since the study was in normal humans. No sensitive humans, in other words.

The cumulative uncertainty factor is 10. So divided by the NOAEL, or point of departure, of .5 gives us an acute REL of 50 micrograms per cubic meter.

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OEHHA STAFF TOXICOLOGIST DODGE: I want to discuss a little bit about our new summaries that are in the draft REL document.

The added Chinese and Korean case reports have heavy exposure -- heavy exposure led to seizures in these workers. Now, this supports the Tuma case report which is in the previous draft, in which they saw the same thing, seizures with heavy caprolactam exposure. Since these are case reports, they really had no idea after the fact what those concentrations were. But I did the best I could explaining how the exposures occurred or what they looked like when they came into the emergency rooms with seizures.

In a few cases they were pretty much covered in the material, in caprolactam. And they did get blood samples from one of these studies. I forget if it's the Chinese or Korean report, but they found high levels of

caprolactam in their bloodstreams.

The seizures that they see in the workers support the use of an intraspecies uncertainty factor of 10 for child sensitivity issues to neurotoxicants.

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OEHHA STAFF TOXICOLOGIST DODGE: Okay. We added some Chinese occupational study summaries, four of them, which we had translated from Chinese to English, thanks to one of our colleagues.

Now, there was a whole array of symptoms like in some of the early studies that were English -- that were England or U.S. reports. These included dizziness; insomnia; nausea; nosebleed; dermal lesions; nasal symptoms, including dryness, rhinitis, sinusitis.

And then there was one female -- or one study in female workers. They saw dysmenorrhea, primary infertility, and pregnancy hypertension.

You know, a problem with these studies is that there was also co-exposures to other chemicals, and they noted this in a few of the studies. And the methodology and results sections were unfortunately too brief and lacked details for us to use as a basis for chronic REL.

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OEHHA STAFF TOXICOLOGIST DODGE: That's my presentation for the new material.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So, Paul, would you like some discussion of the existing draft, or should we go on to the comments received from industry and our response to those?

PANEL MEMBER BLANC: Well, I think you have to go on to that first, because the presentation we just heard mixed in fact your response to the critique already. So you've already brought that up. So since that was already partially alluded to, I don't think it makes sense to have the discussion till you finish that presentation.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BLANC: Is that correct?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yep.

PANEL MEMBER BLANC: Otherwise I think people will be extremely confused.

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OEHHA STAFF TOXICOLOGIST DODGE: Okay. Material was sent to the Panel recently. This involved comments from the industry stakeholders. Much of the material was reiterated comments from previous meetings regarding the chronic REL and how that was derived -- chronic and 8-hour RELs.

So we are going to primarily concentrate on the

new comments, which is in regard to the draft acute REL.

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OEHHA STAFF TOXICOLOGIST DODGE: One of the main comments is here: "OEHHA is 'cherry-picking' from the raw eye blink data to show a statistically significant increase in blink frequency.

"OEHHA used 1-hour data from the manual 'lights-off' approach that was statistically significant and ignored 1-hour data from the semi-automated 'lights-on' approach that was not statistically significant."

Now, Dr. Ziegler in his published study looked at eye blink rate using two different methods: There's one sort of a standard traditional approach, in which videotaped -- the faces of the -- or the eyes of the participants are videotaped during exposure. And then this videotape is looked at by researchers later on in a double-blind approach and they just manually count the eye blinks.

Now, the semi-automated approach is new. I don't believe it had been used before in this fashion. And this is where they had a neon light shining on the faces of the subjects during the exposures, and there was a detector that noticed a change in light when they blinked.

And so this was counted on later on, I guess

manually, the change in light from this detector.

Now, actually both of these recordings methods show a statistically significant increase trend in blink rate, just not all at the same time points.

In addition, Dr. Ziegler in his "Discussion" section of the published study noted that the lights-on method needed to be verified before it would be used by researchers as proof of an eye blink rate increase.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, this is the results here from the eye blink data where we applied the Page's trend test. So we have our traditional lights-off manual count method in the first column here. There was no statistically significant trend at zero hour when they first entered the chamber, but there was at one hour for a reason not totally clear to me, they only had four to eight subjects for the 3-hour and 6-hour time points. And this was not enough to determine -- or to use for a Page's trend test, so we had not enough data at those time points.

However, with the semi-automated neon light method, they saw -- there was no -- when we applied the Page's trend test, we saw no statistical significance at zero and one hour but we did at three and six hours.

PANEL MEMBER EISEN: I have a question.

I don't understand how there were enough subjects to do the Page test for the semi-automatic method and not for the manual method. Wasn't it the same data, just different counting?

OEHHA STAFF TOXICOLOGIST DODGE: Well, they had 20 subjects for all the time points -- I'm sorry -- for all the doses at zero hour, at one hour, to look for trends, 20 subjects at each of the four doses at one hour and at zero hour for the dim light or manual count method.

However, for the three hour and six hour time points, they only had four to eight participants at the various doses.

PANEL MEMBER EISEN: But why can you -- why is there enough data to do a test for the last --

OEHHA STAFF TOXICOLOGIST DODGE: Well, they had all 20 for every dose.

PANEL MEMBER HAMMOND: Aren't the lights-on and lights-off, so to speak, experiments -- separate experiments? They're not the same experiment.

OEHHA STAFF TOXICOLOGIST DODGE: Well, what they did is they did the traditional approach first and then immediately did the semi-automated right afterwards, like five minutes later. And these would be the --

PANEL MEMBER HAMMOND: Oh, so those people were actually obviously present because they had the

lights-on --

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: I think he's explaining it poorly. They didn't do the traditional measurement for all the subjects at the higher doses. They only did it for a subset.

PANEL MEMBER EISEN: I see.

PANEL MEMBER BLANC: Whereas they did the nontraditional method, which they themselves said was not really ready for prime time in all the subjects at the higher dose.

PANEL MEMBER EISEN: Um-hmm, an investigator decision.

PANEL MEMBER BLANC: That's correct.

PANEL MEMBER EISEN: Unfortunately.

PANEL MEMBER BLANC: So the data don't exist.

Is that a safe way of saying it?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah.

PANEL MEMBER BLANC: That's how I understood your written comments.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, that's correct.

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OEHHA STAFF TOXICOLOGIST DODGE: Okay. The next comment came in, and this was from Dr. Haseman. In fact,

most of these comments are from Dr. Haseman, who was the statistician that was employed by the stakeholders to look at the raw data from an acute study.

He states he prefers the Page's trend test because it takes the ordering of the doses into account.

The Friedman test ignores the ordering of the doses, and the repeated measures ANOVA assumes normality and also ignores the ordering of the doses.

And we had the Friedman test in there as a comparison or companion test with the Page's trend test. And we found with a couple of the tests we could probably use the repeated measures ANOVA because it looked like there was a normal distribution. But it could have gone either way.

Now, OEHHA agrees with the recommendation and proposes to the Panel that we only use this statistical analysis with the Page's trend test in the final REL document.

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OEHHA STAFF TOXICOLOGIST DODGE: Next comment here regards the day effect as a confounding factor. This was a hypothesis proposed by Dr. Haseman, and it took up quite a bit of --

CHAIRPERSON FROINES: May I ask you a question?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah.

CHAIRPERSON FROINES: I'm sorry.

OEHHA STAFF TOXICOLOGIST DODGE: Your mic, I think you turned it off instead of on.

CHAIRPERSON FROINES: The issue of normality seems not trivial. Can you say a little bit more about the fact that it appeared normal but not quite appeared normal. I mean I'm not sure what you're saying. Because it makes a difference.

OEHHA STAFF TOXICOLOGIST DODGE: Well, for a couple of the objective tests I believe Dr. Ziegler in the original paper assumed normality. And so we applied the repeated measures ANOVA test to that same data.

CHAIRPERSON FROINES: I understand.

OEHHA STAFF TOXICOLOGIST DODGE: However, it appeared it could go either way. It might have been non-parametric.

PANEL MEMBER BLANC: I'll be happy to comment on that as --

OEHHA STAFF TOXICOLOGIST DODGE: Dr. Blanc.

PANEL MEMBER BLANC: I said I'll be happy to comment on that more as lead when we get to this.

CHAIRPERSON FROINES: This is getting so that I have to ask Paul every question.

PANEL MEMBER BLANC: No. I mean why don't we just wait, unless it's really -- I understood your

question because it was like not decipherable. But in terms of, you know -- I think I'll be able to address your question.

CHAIRPERSON FROINES: Okay. That's fine.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. We have a comment here on the day effect. And I'll go into the next several slides regarding this confounding factor proposed by or hypothesized by Dr. Haseman. And it goes like this. The comment was: "Eye blink data suggests subjects become increasingly familiar with tests during the week of exposures resulting in increased blink frequency on successive days of testing," i.e., the so called day effect.

And the exposure study design by Dr. Ziegler, the published study, was unbalanced, leading to the day effect.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, by unbalanced, Dr. Haseman is referring to the way Dr. Ziegler set up his study. There was four participants exposed during each of the exposure weeks. And the dose that they were exposed to on each day during that week was randomly selected. So in other words, this led to too many of the high dose exposures occurring during day 3 and 4. As you can see, about four out of five is occurring at

the last two days of exposure. And the low dose, there's too many low doses in the last three or four days. There's three of them actually on day 3.

And, you know, since there was a lot of the low and highs in the day 3 and 4, that left the control and the mid-dose range too many in the day 1's and 2's.

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OEHHA STAFF TOXICOLOGIST DODGE: Dr. Haseman proposes that a more balanced study design would have none of the same doses on any one -- or doubled on any one day.

This is a nice balanced design. But I'm not sure from Dr. Ziegler's methodology if he could stuff another -- a fifth person into the chambers each week. It was probably at the maximum of four.

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OEHHA STAFF TOXICOLOGIST DODGE: So to correct for this day effect, Dr. Haseman had days 1 and 2 essentially equivalent in terms of eye blinks. But on days 3 and 4, he saw an increase of 5.5 blinks.

So to compensate, he added 5.5 blinks to all day 1 and 2 data, regardless of dose, to level the playing field, as he called it, and eliminate the confounding day effect.

Now, when he did this, he found no statistically significant increase in eye blink rate, except there was

still -- there's still a significant trend at the three hours using the semi-automated counting method. All the others were not significant.

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OEHHA STAFF TOXICOLOGIST DODGE: Now, we have several points we want to cover here in responding to this confounding factor.

The day effect relies on the subjects 1 to 4, for example, exposed during week 1. Now all the subjects were labeled -- or given a number 1 through 20. So the assumption here is that subjects 1 to 4 were exposed during week 1, subjects 5 to 8 were exposed during week 2, and so on. But it's not clear from Ziegler's study that -- in his methodology section, that this is how the subjects were exposed.

We also observed a decreasing rather than an increasing eye blink trend during 6-hour exposures. This occurred at all control and caprolactam exposures except for the high dose. So if a day effect exists at all, you would expect it to be a decreasing eye blink trend rather than an increasing.

PANEL MEMBER BLANC: No, you just said the opposite -- you just said the opposite of what you meant.

He argued that people increase their eye blink over time.

OEHHA STAFF TOXICOLOGIST DODGE: Right, right.

PANEL MEMBER BLANC: And your argument would be if that were the case if you were exposed for six hours, then over the six hours you should have a decreased amount of blink compared to just a 1-hour exposure.

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: And you saw that it decreased, didn't increase. Because you had said the opposite levels --

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, I'm sorry. Yeah, that's correct.

PANEL MEMBER BLANC: Did everybody follow that?

Okay.

OEHHA STAFF TOXICOLOGIST DODGE: So this is the statistical analysis of the eye blink trend during the 6-hour exposures.

You saw a significant decrease at 0, near significant at .15, significant at .5, and no trend observed at 5, which is where we saw the difference from the control in terms of increasing eye blink rate.

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PANEL MEMBER EISEN: Can you go back to that slide.

OEHHA STAFF TOXICOLOGIST DODGE: Sure.

PANEL MEMBER EISEN: So can you say what this is

again now? Can you say what's -- how many observations that each of those held?

OEHHA STAFF TOXICOLOGIST DODGE: There's four.

PANEL MEMBER EISEN: Four observations?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah. For example, at 0 milligrams per cubic meter they did measurements just after the participants entered the chamber, which they called 0 hour. Then they measured eye blink again at 1 hour and then at 3 hours, and then at the end of exposure at 6 hours.

PANEL MEMBER EISEN: And these are the same four people -- I don't understand why there's --

PANEL MEMBER BLANC: No, he didn't answer the question correctly.

There's four observations per person. At the 0, there are 20 people, at the --

PANEL MEMBER EISEN: So there's actually 80.

PANEL MEMBER BLANC: No, because that -- this is the manual eye blink, so they don't have as many subjects I think at the higher -- are you using your automated?

He's using the automated, so he has everybody. So you're correct, there are 80, or there should be.

PANEL MEMBER EISEN: So there are 80 observations in each of these rows?

PANEL MEMBER BLANC: Eighty persons with four

observations each.

PANEL MEMBER EISEN: I thought it was 20 people.

PANEL MEMBER BLANC: Twenty people - I'm sorry - with --

PANEL MEMBER EISEN: -- four observations each. There are 80 people. Each of the 80 people are exposed --

PANEL MEMBER HAMMOND: 20 people.

PANEL MEMBER BLANC: Twenty people studied four times.

PANEL MEMBER EISEN: Are exposed -- this is during just for six hours, you have 20 people exposed at 0 --

PANEL MEMBER BLANC: -- for six hours.

PANEL MEMBER EISEN: -- for six hours four times?

PANEL MEMBER BLANC: Observed over four times during the 6-hour period.

So all these people have six hours worth of exposure and all of them are measured at four points during the six hours, is that correct?

OEHHA STAFF TOXICOLOGIST DODGE: Right, during -- yeah, just after just after entering the chamber, at one hour of exposure, at three and at six.

CHAIRPERSON FROINES: And we're talking about 20 people?

PANEL MEMBER EISEN: And were talking about 20

people.

OEHHA STAFF TOXICOLOGIST DODGE: And 20 people.

CHAIRPERSON FROINES: Per dose?

PANEL MEMBER BLANC: Per dose.

PANEL MEMBER EISEN: Per dose.

PANEL MEMBER BLANC: And so what this table shows is that over time at any given dose of the three lowest doses, people do not blink more over time, they blink less over time in a non-random -- in a way that's not likely to be due to chance. Except for the highest dose, where you continue to blink as much as you did over the six hours.

So the hypothesis that the more you measure someone, the more they blink, just by virtue of being studied more often -- so I've come into the lab four times this week, so by the end of the week I blink more, this is indirectly addressing that, right? This is on single day. But if you were to argue that there'd be an effect over multiple days, there should be an effect over many hours, since the other levels in total -- and one of these exposures you are exposed more than you are for the 1-hour exposure where you're in the lab for one hour a day for five days.

So, again, if there was a systematic confounding of increased blinking with increased number of observations that should --

PANEL MEMBER EISEN: Time over the day. It's time over the day. That's where it's --

PANEL MEMBER BLANC: Well, time over -- you should see the same effect with time over the day if it was going to be multi-days per week, and you don't.

Does that make sense?

PANEL MEMBER EISEN: No, not really.

Is this pooled across days?

PANEL MEMBER BLANC: This is --

PANEL MEMBER HAMMOND: It has to be.

PANEL MEMBER BLANC: No, because this is for a single day that you have a 6-hour exposure.

PANEL MEMBER EISEN: But aren't there multiple days where --

PANEL MEMBER BLANC: Not at different numbers of hours. So you'd be exposed for six hours on one day and on another day you would be exposed --

PANEL MEMBER HAMMOND: But for all 20 people it would have to be, Paul, I think. In other words, if you take the .15 dose for the 20 people, they were on --

PANEL MEMBER BLANC: Oh, they were on different days, is that what you mean?

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER BLANC: They were pooled days from that sense.

PANEL MEMBER EISEN: Yes, you would --
PANEL MEMBER BLANC: I'm sorry.
PANEL MEMBER EISEN: Day is being ignored.
PANEL MEMBER BLANC: Yes, that's correct.
PANEL MEMBER EISEN: No matter what day you were -- whether it was a first, second, third or fourth days, it would --
PANEL MEMBER BLANC: Yes, yes, yes, yes.
PANEL MEMBER EISEN: Ignoring it.
PANEL MEMBER BLANC: Yes.
OEHHA STAFF TOXICOLOGIST DODGE: So what we're trying to do here is show that the exposures over six hours is a decreasing trend, so you'd expect the same thing to happen over days because there's four subjects exposed each day, Monday Tuesday, Wednesday, Thursday, at randomly selected doses.
Does that make sense?
(Laughter.)
PANEL MEMBER EISEN: No. Could you say it again.
OEHHA STAFF TOXICOLOGIST DODGE: Well, we can come back to it.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Okay. Another response we have regarding the day effect.
Blink rate trend with caprolactam exposure dose

level is more pronounced than the day effect. So at the 1-hour time point with the dim light or lights off method, we found a -- by the Page's trend test, a significant trend. But when we looked at the day trend with the Page's test, it was not.

Now, the other time points that were significant with the Page's trend test, both the dose trend and the day trend was below .05. But in all cases the dose trend was more pronounced than the day trend.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: And finally, we did not encounter any evidence or discussion of a day effect by other researchers using similar study protocols. In other words there's other eye blink studies -- eye blink rate studies out there using chemical irritants. But nobody discussed this sort of hypothesized confounding factor.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: So in summary, the hypothesized confounding by experimental day of exposure is not consistent with the study data. There's no precedent from other published studies supporting the proposed reanalysis by Dr. Haseman. So the rationale for such an effect is not convincing.

PANEL MEMBER EISEN: So one more -- can I go back

and ask a question?

Or should I wait, Chairperson? Do you want questions now or not?

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER EISEN: Can you go back to the day effect slide.

So --

PANEL MEMBER BLANC: The day effect slide?

PANEL MEMBER EISEN: That's it.

PANEL MEMBER BLANC: Oh, that's the one you want?

PANEL MEMBER EISEN: That's the one I want.

Yeah, isn't that the day effect? You're trying to look whether within dose levels you see a day effect?

OEHHA STAFF TOXICOLOGIST DODGE: Within the dose -- yeah.

PANEL MEMBER EISEN: -- levels do you see a day effect?

PANEL MEMBER BLANC: No, this is a 6-hour exposure -- is there a 6-hour exposure effect?

OEHHA STAFF TOXICOLOGIST DODGE: I'm sorry. Yeah, within the 6-hour exposure.

PANEL MEMBER EISEN: -- that was in each of these dose levels people were measured multiple times during the six hours, and you're trying to see whether it's increased.

PANEL MEMBER BLANC: Yes. Yeah, but not during -- it's not an experimental day effect. I'm sorry, maybe I didn't understand your question. There are two separate questions. The critique argued that there's an overwhelming confounding -- a hundred percent confounding essentially of the day of the week upon which you have the effect and the exposure level. Which there are earlier slides showed it's not a completely balanced design but it's certainly not a hundred percent overlap. And therefore, if I -- this will spell out what the critique was that they're responding to. Therefore, in fact, you were so confounded by the day of the experiment that you can't measure the dose response; you have to substitute a variable or adjust for a variable, which is the day of the week upon which the experiment occurred. And that was argued to be because over the week you tend to blink more. So they asked the question, well, if you're supposedly blinking more over the week, if you were in the chamber for six hours, would you blink more over the course of the day?

PANEL MEMBER EISEN: So that seems to me to be mixing apples and oranges. I mean so there's a day-of-the-week effect and there's time-of-the-day effect. And I don't understand which --

PANEL MEMBER BLANC: It's a fatigue or an

adjustment or a luring effect.

PANEL MEMBER EISEN: Over the course of a day or over the course of a week?

PANEL MEMBER BLANC: Well, the argument that they're making -- it's only part of their argument. But the argument they're making is if there were such an effect over a week, you would see it over a day as well. Okay? So it's an indirect argument. That's why I used that term. So that's what this addresses.

PANEL MEMBER EISEN: This is looking at over a day though.

PANEL MEMBER BLANC: This is looking over the day.

PANEL MEMBER EISEN: Right.

PANEL MEMBER BLANC: And then their next slide --

PANEL MEMBER EISEN: And that suggests that there is a decrease.

PANEL MEMBER BLANC: The opposite, because they argued that it was an increase over the day, over the week.

PANEL MEMBER EISEN: Okay. So that suggests a decrease.

PANEL MEMBER BLANC: An opposite effect of what they're arguing, if there is one.

PANEL MEMBER EISEN: Okay.

PANEL MEMBER BLANC: Except it's not present in the highest dose anyway.

PANEL MEMBER EISEN: That's okay with me. That's fine.

PANEL MEMBER BLANC: Okay. So exactly the opposite.

PANEL MEMBER EISEN: Three out of four.

PANEL MEMBER BLANC: Okay. And then this is a more direct -- just ask --

OEHHA STAFF TOXICOLOGIST DODGE: See, there's a more direct comparison of the trends.

PANEL MEMBER BLANC: This is a question. Is there a trend over the week and is there a trend over the dose? And the time period that they looked at was one hour, was what they were concerned with. And for the 1-hour exposure, which is the one that they based their REL on, in fact, there is again a dose response for trend. That's why they -- from Page's test, which that's already in the document as we have it, but they adhere, is there a trend over experimental day? And there is not a statistical trend over experimental day at the dose level that they're using.

So the second -- the lower part looks to see what about for the higher doses -- I'm sorry -- what about for the longer duration of exposures which they don't use in

the REL? And you do see that there's a difference by experimental day at the doses they're not using for the REL. But this begs the question as to whether that is a confounder for which you should adjust -- this is not a multi-variate comparison. This is looking separately at the trend for dose and the trend for day.

So at the higher -- at the -- I'm sorry -- the longer hours of duration experiments, yes, there is a relationship with day of the week numerically, that it does presume that the data subject number corresponds to which weeks they were in they're not sure of. And then you're left with the question, if you believe that, would you also apply the same logic to the 1-hour time frame which they are using, for which there isn't such a trend, and then would you do the kind of adjustment that the critic was suggesting?

So does that all make sense? And I'll return to that in my own comments. I'm just trying to answer your question.

PANEL MEMBER EISEN: I mean barely. I mean a little bit. I understand a little bit. Do I understand perfectly? No.

PANEL MEMBER BLANC: I think you'll find the written comments that they wrote are a little bit more helpful than this oral presentation.

PANEL MEMBER EISEN: Okay.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Can I say something?

I think it needs to be put into perspective. Caprolactam is an irritating substance. We already know that. If you hypothesize it's just the day effect, you're ignoring the fact that caprolactam is an irritating substance. That's one issue.

The other issue is, if you look at the reference exposure level derivation, we looked at 5 milligrams per cubic meter, which was statistically significant compared to controls. And that's what we identified as a low observed adverse effect level. That would be standard methodology.

So, you know, I just don't think that there's a whole lot of substance to the argument and that we, you know, need to spend tons of time on it. My opinion.

CHAIRPERSON FROINES: I think, Melanie, I agree with you, and I agree with what Paul has been saying. But to the degree that there isn't -- it's not written out in a process that ends up with clearly defined conclusions, that might be advantageous to have it a more structured kind of process.

PANEL MEMBER EISEN: Can I ask another question?

But isn't this an acute study, Melanie? Aren't

we looking at Ziegler as a study of an acute effect? So you're saying you can't do a study of acute effect in this manner where you're looking at repeated days and repeated times over the day?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, no, that's definitely not what I'm saying.

PANEL MEMBER EISEN: Okay.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: You know, it is an acute study of an acute effect. So, you know, I just think -- and we chose one hour because that is the duration --

PANEL MEMBER BLANC: You know, I'm holding off on -- I'm a lead, I reviewed this -- I read this -- how many people that -- oh, I won't ask how many people have read this painful response. But I have read every word of it. So, you know, let me do my job after you do your job and then let's see what people have to ask.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: I think everybody's read it. I think --

PANEL MEMBER BLANC: Well, he hasn't finished yet.

CHAIRPERSON FROINES: Well, I understand that.

But I think everybody at this table has read it, and I don't think that's an issue and shouldn't be brought up as an issue. They can finish.

PANEL MEMBER BLANC: I apologize.

CHAIRPERSON FROINES: They should finish.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Okay. So with regards to a separate issue now. Another comment came in. This is from Dr. Haseman again where he says, "The subjective eye irritation variable is confounded by odor. The overall odor and eye irritation responses in both the mid and high dose caprolactam groups show a significant correlation by the Spearman test."

Now, our response is that we concur that some component of the statistically significant eye irritation trend may be due to odor. This is one reason why we base the acute REL on the objective eye blink frequency increase with increasing dose.

The other point we want to make is that even given that there might be some confounding by odor for eye irritation, we did see no confounding -- or we saw no nasal irritation trend in the data, although odor was recognized by the participants. You would expect that nasal irritation would be a more sensitive indicator. But the subjects were able to tease out the difference between

nasal irritation and odor.

So this in a way supports eye irritation as a real effect.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: The next comment, no correlation between eye blink and eye irritation. Dr. Haseman then went on and found that blink frequency and eye irritation were not correlated in the Ziegler study, contrary to what would be expected if these are real caprolactam effects producing irritation.

Now, Haseman's application to the Spearman correlation test does not take the high individual eye blink variability, which is natural, into account. This also occurs with eye irritation and natural high variability in response, but less so.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: So in our response we did another statistical evaluation. To account for the variability, we ran a Spearman test of the relative eye blink increase versus the absolute eye irritation increase at one hour. And we found a correlation at .01 between these two variables, the eye blink and eye irritation. Haseman says that there is no correlation. But we found a correlation when we tried to account for high variability of the base line in eye

blink.

Applying the same procedure for odor, we also examined relative eye blink versus absolute odor change at one hour, and we found no correlation there.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: This comment regards eye redness test. There is clearly no caprolactam effect on eye redness, as would be expected if blink frequency and eye irritation effects are real due to irritation.

And our response is that eye redness is an inflammatory response, while increased eye blink frequency is an irritant response and may or may not include an inflammatory comment. And in support of that is a recent study in formaldehyde which at irritant levels produced increased eye blink in one test and no eye redness. But then they tested again with a masking agent and they did not see a correlation.

So it's inconsistent, this response, to eye redness. Expecting to see eye blink and eye redness increase at the same time, it's inconsistent with some other studies.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: This final comment regarding the acute REL. Increased eye blink rate

not biologically important.

CHAIRPERSON FROINES: Can I ask you -- and Paul's going to address it, so I won't -- I just want to make sure. Is there only one study that addresses eye irritation and redness? Is that the full literature? I mean -- or it seems that there should be more on this topic.

OEHHA STAFF TOXICOLOGIST DODGE: There are a few studies out there that looked at --

CHAIRPERSON FROINES: Just a yes or no.

OEHHA STAFF TOXICOLOGIST DODGE: -- that looked at both endpoints, yes, but not a lot of them did.

CHAIRPERSON FROINES: Okay. Let's wait for Paul.

OEHHA STAFF TOXICOLOGIST DODGE: Any other questions?

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Commenter here says he does not view the high dose caprolactam effect in overall blink frequency or the mean eye irritation as being biologically important responses.

Now, in other studies, which are in our response to comments, statistically significant increase in eye blink rate in those other studies are in the same region as what we found with this caprolactam study. In other words, you know, around nine blinks per 90 seconds.

Now, the eye irritation trend is not as strong a response, and this is found in other studies too in which they had -- they were looking at both endpoints, eye blink rate and eye irritation -- subjective eye irritation.

Generally eye irritation is not as strong a response. And this is in part why we did not base the REL on this endpoint, because it appeared eye blink frequency increase due to caprolactam exposure is a more sensitive endpoint.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Now, we have a few comments -- new comments regarding the 8-hour chronic REL. And this is based on the 13-week rat exposure study.

And these comments regard a new table I have in the REL document. And this is a -- this is from the industrial study on which the Reinhold, et al., published study is based on.

In this industrial study, they actually had numbers for the various observations they made while these rats were being exposed.

In the comment here, the incidence of labored breathing in animals outside the chamber was very low, sporadic, and did not reflect a dose response. Labored breathing does not constitute an organ dysfunction or adverse effect.

One of the other observations. Secretory observations included red facial stains and clear nasal discharge, and these are common findings in whole body inhalation studies.

Staining and discharge do not represent adverse function of the respiratory tract and cannot be considered as adverse findings.

Now, first off for our acute REL derivation, if these effects occurred in humans during exposure caprolactam, we would indeed consider them adverse effects.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: I want to show the table, the new table we have now in the REL document. These are the observations during the exposures, and I tabulated them. Again, this is from the industrial study where I got these numbers.

PANEL MEMBER BLANC: Do you want to tell us which table, so that we can follow.

Is it table 8 on page 35? No.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's Table 7 on page 34.

OEHHA STAFF TOXICOLOGIST DODGE: So what you see here is -- for general animal condition, we see a trend with higher exposure. The animals are in worse shape,

with red facial stains. There's a trend -- increasing trend with increasing dose. And the same with clear nasal discharge.

In terms moist rales, that was seen at the two highest dose levels.

Now, this information here is at week 13, at the end of the study. However, there was quite a few more animals showing moist rales in the highest two doses around week two or three.

Now, the in-chamber observations, 6th to 26th exposure, this is presented in a percentage of animals exhibiting symptoms. That's because the observations for this particular endpoint was inconsistent. In other words, not all animals were looked at every day for labored breathing. Sometimes there was only 20 of the animals looked at, sometimes 40. And they didn't tell me -- or tell us which 20 were looked at if they only looked at half of the animals.

So I presented it as percentage, and didn't feel comfortable enough trying to do any sort of statistical trend analysis with this data.

However, we could run our benchmark dose modeling program on the in-life physical exam findings, the general animal condition, red facial stains and clear nasal discharge. And that's what's at the bottom of this slide,

running our benchmark dose modeling program. For red facial stains the point of departure was 4.3, for clear nasal discharge was 6.2, and general animal condition was 3.2 milligrams per cubic meter. And the point of departure is the 5 percent response -- is the upper confidence -- upper 95 percent confidence limit at the 5 percent response rate.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's the lower.

OEHHA STAFF TOXICOLOGIST DODGE: It's the lower?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: On dose.

It's the upper bound on the slope but it's the lower bound on dose.

OEHHA STAFF TOXICOLOGIST DODGE: So we also did a benchmark dose analysis, if you recall, on the pathology results of the upper airways in these animals. Using the same modeling technique, the point of departure was the same. It was around 3 to 4 milligrams per cubic meter.

So here we have the observations and the pathology results coinciding with the same point of departure.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: The final comment here that we'll discuss is regarding the Reinhold

rat study vapor component of the exposure.

Now, the original industrial report states that there was an unquantified vapor component to the exposure. And the commenter here says if the caprolactam atmosphere presented to the study rat was at saturation level (13 milligrams per cubic meter), then the actual caprolactam exposures were 37, 83 and 256 rather than 24, 70 and 243 as presented in the paper.

So the assumption here is that the additional 13 milligrams per cubic meter of vapor was not analyzed by their detection equipment.

Now, in the study caprolactam was dissolved 1 to 1 in water and aerosolized. And the Henry's partition coefficient is very small for caprolactam, which suggests that it's hydrophilic and that it wants to stay with the water particles. It doesn't want to partition into the vapor form.

So we suspect that it's -- this number is quite a bit smaller, this vapor component. And in fact in the original industrial report, they don't really address it, probably because it was inconsequential.

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OEHHA STAFF TOXICOLOGIST DODGE: Any other questions?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH

CHIEF MARTY: So that's the end of the presentation from staff on caprolactam in the response to comments.

So if there's additional issues, we should bring them up now.

PANEL MEMBER BLANC: Is this where you'd like the comments from the leads?

CHAIRPERSON FROINES: I believe that -- unless Bob's going to say something -- no. Or the person, whose name I don't -- Ryan --

OEHHA RESEARCH SCIENTIST MALIG: Maybe in the context -- maybe during the discussion.

CHAIRPERSON FROINES: Then it seems to me that what we've all been waiting for is to hear from Paul.

(Laughter.)

PANEL MEMBER BLANC: So, as you know, I'm co-lead on this along with Dr. Stan Glantz, who cannot be here today. But he and I are at the same institution, so we've had an opportunity to discuss together his comments. And most of his comments relate to issues raised in the OEHHA response to the public comments.

So I think it would make sense to first deal with the revisions that are in the draft that everyone has, and then move on to the responses that -- our responses to this document that they then responded to.

Does that make sense as the way to go?

CHAIRPERSON FROINES: Um-hmm.

PANEL MEMBER BLANC: So I think there were three main areas of -- or four from the Panel at the last meeting. And two of them were the more substantive and two were perhaps less substantive.

One area I'll critique was that the document as it existed prior to this revision was not inclusive enough of relevant human case report data, in particular case report data relevant to neurological endpoints and to sensitization endpoints as reflected in contact dermatitis case reports. I think that's fair. I think that you and I were the main people bringing that up.

And so I think that this revision is effective in utilizing and putting in context that case report literature. And, in addition, as lead, I gave them feedback on where the dermatitis -- contact dermatitis cases were most effective to be discussed. And in my view they had relevance to an acute response, since once one is sensitized, one responds acutely, and they responded to that critique.

I think the only -- and I note gladly that that also led them to find some occupational exposure literature that's more relevant to chronic exposure as well.

I do note that in the document it indicates where

the chronic-related occupational studies from China were translated for the purposes of this document. That is not consistently indicated. And till your oral comments I actually didn't realize that the Korean and Chinese case reports needed to be translated. So for consistency, I think you should parenthetically indicate that in the text where appropriate. It would be just to use the same language that you used for the other.

So that was one area. And I believe that the revision is responsive and is a better document on that basis.

The second and even more substantial critique from the Scientific Review Panel at the last meeting was dissatisfaction with opting out of an acute level -- reference level acute exposure, REL. I think there was a consensus or a strong point of view that the single occupational study was inappropriate but that the Ziegler human exposure data were more desirable and that the optimal scenario would be obtaining the raw data and analyzing it appropriately.

And I think there was -- the revised document was responsive to that request. And I'll come back to then the critiques that were made in your responses in terms of the analysis.

The third request from the Panel I believe was to

have some additional tabular data related to the animal studies from which the chronic REL was obtained, that you went over that sort of late in your presentation. And I think you were responsive in providing that additional data. I believe there may be some appendix to data as well. So that was responsive.

And then the fourth area was a more general sense that there were areas of the document, multiple places in the text where the text could be corrected, tightened, improved, to have a more consistent tone, consistent with other OEHHA documents. And I think that there's been an effort to edit the document accordingly and to clarify certain technical points that had to do with uses of terminology, for which there was confusion in the way the material that you were forced to use reported their data, because this is a substance which -- which precipitates out of a gaseous phase into a solid, and so people talk about flakes and particles and vapor and all kinds of things.

OEHHA STAFF TOXICOLOGIST DODGE: Dust.

PANEL MEMBER BLANC: And you tried to be -- I think you tried to address some of that.

So I think on all counts, you were appropriately responsive to the revision inputs in terms of this revision. So that would be my assessment of the revision

as you've done it.

And, now, I can move -- so perhaps if you want to do it in two steps, we could talk about that piece of it first and then talk about the industry questions and their response.

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER BLANC: I mean would you rather -- I mean should I just keep going?

CHAIRPERSON FROINES: I think once you've got the floor, you should stay with it.

PANEL MEMBER BLANC: All right. So then in terms of this response and your presentation of it, I'm sympathetic to what --

CHAIRPERSON FROINES: Wait, wait, Paul. Just one thing.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: You've just gone through a fairly extensive discussion. And let me just say, you asked the rest of the Panel --

PANEL MEMBER BLANC: Yes, please.

CHAIRPERSON FROINES: -- if they have comments as to what Paul said or OEHHA, that we might just talk about that briefly before you go ahead.

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: So, Alan, do you want to go

ahead?

PANEL MEMBER BUCKPITT: I'd have to agree with Paul. This is a much more complete document than what we saw two times ago. And there's still some writing issues, but I think they're minor in comparison.

PANEL MEMBER EISEN: (Shakes head.)

CHAIRPERSON FROINES: Okay. Kathy.

PANEL MEMBER HAMMOND: I'm very pleased with the revision, particularly having the occupational pieces added. But they actually raise some concerns. You know, I'm just worried about some of the things that have been reported. And we haven't really talked about that. I don't know if you were going to talk about that.

CHAIRPERSON FROINES: So do you want to hold that till Paul goes through the next phase?

PANEL MEMBER HAMMOND: Sure, yeah. I just didn't know where Paul was.

PANEL MEMBER BLANC: No, I mean you could bring it up now, because they don't relate to their response to their analysis of the Ziegler data.

PANEL MEMBER HAMMOND: Right, right, right. Yeah --

PANEL MEMBER BLANC: So I felt it was stronger for having it. But I didn't feel that it made me want them to change the uncertainty factor, for example, or,

you know, add another factor of 10 because of data lapses or in some other way change their conclusions. And I felt that where it was placed in the document was appropriate in terms of being chronic. And so I didn't -- and I felt they were detailed enough presentations that I didn't -- I wouldn't do something differently with it. But, for example, if based on their translation you feel that there must have been a piece of data in the report that's missing, or in their synopsis, then you should address that so that they can provide that if it exists in the Chinese -- the two -- you're referring to the two Chinese studies, I assume. Or are you referring to the case reports?

PANEL MEMBER HAMMOND: The case reports.

PANEL MEMBER BLANC: Of neurological toxicity?

PANEL MEMBER HAMMOND: Um-hmm.

PANEL MEMBER BLANC: So you should refer to the page of the document where --

PANEL MEMBER HAMMOND: Well, I was -- I mean the summaries on page 32 and their comments about some of the translations. First of all, about the exposures that were measured. The comments made about the wide variability in those exposures and how that makes it difficult for the people who are exposed to, that's common in occupational settings. That's not unusual. So it's not an unusual

variability, just to be aware of that. I mean that doesn't surprise me.

I think, like you all, I'm a little concerned about how they measure things. It appears to me in the zoo study where they just measured by weighing filter paper, that they're weighing particulate matter than assuming it's all caprolactam. I think that's what that means.

But if one does that, you could say that's an upper level of caprolactam. But it could be much lower. Obviously the vapor level can't be higher than the saturated vapor level, and it's not likely to be saturated. So that's another upper point to what those exposures are.

So I think that that's important -- I actually think those are important points there in this whole discussion about like where have effects been seen in people. I understand we don't know what levels they were exposed to. But it was lower than these various levels that have been mentioned in the text.

I personally was quite concerned about the seizure issue. And I'm concerned particularly about -- to be really honest, about the idea of a child crawling on a carpet, and what does this tell us about the neurologic effects? And I don't -- I know that's a stretch from

where we are.

PANEL MEMBER BLANC: Not at all. And that's why there's a tenfold within human factor.

PANEL MEMBER HAMMOND: I don't think tenfold is enough if you're going from adults having seizures to a child. First of all, there's a tenfold right there. And then we're talking about -- I don't think we want -- or you'll want to protect just from seizures in children, but developmental problems neurologic. So I guess that's my concern.

PANEL MEMBER BLANC: Well, okay. Let me see if I -- you're making the argument there should be another tenfold factor, that it should be a hundredfold because of uncertainty -- extreme uncertainty in the -- or are you arguing that the deviation -- there are two ways that that can be approached, I guess: One is that in a benchmark calculation, they could use something other than .05. They could use .01. Or you could argue that there should be another tenfold additional factor because of extreme uncertainties in the database.

But you can't purely argue it, I don't think, to be consistent - unless that I'm confusing matters - the argument that because it's children and it's serious isn't on its face an argument for using something other than ten for intraspecies.

CHAIRPERSON FROINES: Can I just ask Kathy to clarify.

You were concerned about the seizure issue and you were concerned about the children's issue. Can you -- in terms of, say, safety factors, can you say precisely what the safety factors -- how you would name them?

Do you see what I mean?

PANEL MEMBER HAMMOND: Right. I had actually intended that as a question rather than a statement. I wanted to ask OEHHA how they thought about it rather -- I didn't come here with a strong statement, but rather just to say, have you carefully considered this aspect, looking at the grand seizures, saying those are in adults and what -- to what degree have you considered protection of children from neurologic effects in the development of the acute -- of the chronic REL?

CHAIRPERSON FROINES: I think the other question that Paul raises needs to be answered as well. And that's the value one selects for the benchmark dose.

PANEL MEMBER HAMMOND: I totally agree, but this is --

PANEL MEMBER BLANC: It's all folded into that, I think.

PANEL MEMBER HAMMOND: Yeah.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH

CHIEF MARTY: This is Melanie.

I think that when we saw the neurologic effects, we did sit up and take notice because that's one of our red flag endpoints for increased sensitivity to the developing fetus. So I think what we decided was it provides additional support for the tenfold toxicodynamic intraspecies uncertainty factor that we utilized based on respiratory sensitivity.

In this case the concern is that irritants can exacerbate asthma. So we already had the tenfold in there. And I think the environmental exposures in the ambient setting probably are pretty -- a lot lower than what was experienced by the workers.

The other issue is there were some reproductive and developmental toxicity studies in animals, and they did not find neurotox, which is interesting.

CHAIRPERSON FROINES: To what degree did you analyze the study design in those investigations? Because people do pretty terrible neurologic testing, as you well know. So to say that it wasn't found doesn't mean that it was a properly designed study.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I realize that. And if -- you know, probably if you did the study now, you would, you know, run it differently, because they're -- the studies were

done in the eighties basically. So we understand that.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. Just to add the Reinhold study on which the chronic and 8-hour REL was based on - that's the rat study, 13-week - there was a neurological component and behavioral component to that study, and they saw no effects.

PANEL MEMBER HAMMOND: Let me -- sorry.

OEHHA STAFF TOXICOLOGIST DODGE: Well, the most sensitive endpoint there was the upper respiratory injury to the epithelium.

PANEL MEMBER HAMMOND: So my question remains still. Do you feel confident, given that we have the data from the case reports on occupational, which I understand they're at much higher levels -- do you feel confident that you are protecting both working women who are pregnant and their offspring from neurodevelopment effects and that you're protecting infants crawling on carpets that -- and the answer could be yes. But I just want to make sure that that is included in this document and that you feel that there have been sufficient protections for that.

OEHHA STAFF TOXICOLOGIST DODGE: I believe there is definite protection there built into the REL.

OEHHA ENVIRONMENTAL MODELING SECTION SUPERVISOR BLAISDELL: We're always limited by the data that we have.

But within the limitations of the data, yet.

CHAIRPERSON FROINES: Can I go back to my question?

No, I'll come back. Go ahead.

OEHHA STAFF TOXICOLOGIST DODGE: Well, I also wanted to say there was a number of repro developmental studies in animals with caprolactam. And we ran through the whole derivation process based on those endpoints we saw in the fetuses. And after we did that, the most sensitive endpoint by a significant margin was the respiratory irritation endpoint.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So that analysis is on page 45.

CHAIRPERSON FROINES: Can I just reiterate my question. Then you can put it to bed.

And, that is, when you said that there were no neurologic findings in the study you were talking about, was it a properly designed neurologic study? Did you -- what was your critique of the study design?

OEHHA STAFF TOXICOLOGIST DODGE: It looked pretty good. I mean it's --

CHAIRPERSON FROINES: I mean we had to live through this methyl iodide and we saw some pretty inadequate studies.

OEHHA STAFF TOXICOLOGIST DODGE: Now, I'm not

expert, you know, in this particular field, but they followed the protocol at the time that was standard for these kinds of tests.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER HAMMOND: But That protocol has changed, I think. And I certainly know that the accepted -- what we learned again in the methyl iodide work was that there's a need for longer time follow-up and had been done in the past. And so I guess that those are the questions that John was asking.

CHAIRPERSON FROINES: Yes, exactly.

PANEL MEMBER BLANC: I would say that my point of view on this is that, first of all, the human case report literature, which I championed them including, is relevant in my mind to the acute exposure effect, the seizures that were observed. And suggest that an acute high-level exposure of the central nervous system is an endpoint of toxicity.

I wasn't convinced from the descriptive occupational studies, particularly that in chronic exposure the CNS was the target organ of toxicity. What I think would be -- and therefore I think the issue is more -- or is first and foremost relevant to the acute exposure REL derivation. And, you know, in light of this discussion, what might be the most useful is to have an

explicit sentence in the document, or two, that says, "Although we were concerned with the neurotoxicity, we do not" -- and this clearly supports the tenfold intraspecies variation -- "we did not choose a lower point for the benchmark derivation at the .01 level and stuck with the .05 level," if that's what you did. I mean I think there was a benchmark.

I'm not confusing the two, am I? In the acute there was a benchmark calculation as well?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, the acute --

PANEL MEMBER BLANC: It didn't. There was only the other that you did a benchmark.

OEHHA STAFF TOXICOLOGIST DODGE: Correct, just the 8-hour and chronic.

PANEL MEMBER BLANC: So I think then you should have to say that you did not feel it raised enough questions for you to apply a hundredfold rather than the tenfold, just so that it's clear that you took seriously and considered it so it's documented there.

CHAIRPERSON FROINES: What I would -- I would add basically what Kathy said - and this doesn't contradict Paul - I would add a sentence or two that says, "Studies done in the future should take into consideration design issues that are up-to-date." And so it's just -- so

you've just acknowledged the fact what -- exactly what Kathy said.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Just of note, they did run a functional observational battery in the Reinhold rats. And that's based on -- they cite Moser 1989. So it might have changed a little bit since then, but they did do that.

CHAIRPERSON FROINES: Well, don't -- I mean don't put something in if it's not appropriate.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. Thank you.

PANEL MEMBER BLANC: I think we're still going around the table to talk about this revision.

CHAIRPERSON FROINES: Jesús.

Or, Kathy, are you finished?

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER ARAUJO: Yeah. I am pretty much in agreement with all the comments. And I especially commend again the effort in looking at all these studies.

And in relation to the concern of the neurotoxicity, I have to share -- I have to say that I share some of the same concerns. And I wondered whether there is something else that is still within our reach that we could do.

So I noticed that out of the three occupational exposure case reports that you cite and that you translated -- I appreciate, by the way, that you sent the translations to us, and I could have primary access to those -- two of them don't show any levels. But one of them, the study from Chen in 2002, did show the concentration of caprolactam in urine, 2.9 to 3.7 grams per liter. And I am reading the translated paper that you did -- that you sent. And there are specific conditions in that paper that says that they exposed -- there was an acute exposure from all three individuals from 8 a.m. to -- it was higher to work from 8 a.m. the 3 p.m., and they started feeling symptoms at 1.M. And apparently the rest of the symptoms happen even after 5 p.m. So we know that there was an exposure of at least five hours, probably in between five to eight hours. And because of that, so they developed all the systemic and convulsions -- symptoms.

So I wondered whether, based on the pharmacokinetic or pharmacodynamic in data that may be available from other studies, so whether we could or somebody could estimate a blood level that could give rise under those conditions to a urine level of this concentration. And at least have that as perhaps the only concrete or objective data in terms of relation from in

between blood levels and neurotoxic effects. And whether an estimate of the level of exposure, the dose of exposure that could give rise to these blood levels. So from that regard, so we could in a more precise fashion get to the idea of whether this tenfold factor is sufficient to be protective or to feel comfortable or whether we should even go into higher or lower concentration. I mean a factor -- a higher factor for the protection of susceptible people.

PANEL MEMBER BUCKPITT: I haven't read the Chen study. But were they measuring parent compound on the urine? When they say that they had 2.9 to 3.7 grams per liter, is that parent compound?

OEHHA STAFF TOXICOLOGIST DODGE: You know, I had a difficult time with that too. I assume it was the parent compound. But it's possible they might have been measuring --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Daryn, Albert's here. He can read it.

OEHHA STAFF TOXICOLOGIST WANG: This is Albert Wang. I'm staff toxicologist in the same branch. I translated these case reports basically word by word -- verbatim.

In the urine the concentration of caprolactam. So, yes, it's the parental compound.

PANEL MEMBER BUCKPITT: Okay. So if we go back to the studies that Peter Unger published in the early eighties, only 2.3 percent of the compound comes out as parent compound in the urine, which must mean that those exposures were industrial strength, to say the least.

All right. So you're talking about grams internally, not -- right?

CHAIRPERSON FROINES: I'm not getting what you're saying.

PANEL MEMBER HAMMOND: I see what you're saying, and I agree, except that it's hard to believe those exposures were that high. I mean --

PANEL MEMBER BUCKPITT: I tend to agree with you. I only had --

PANEL MEMBER HAMMOND: -- I'm having a lot of problems figuring that out as I was looking at that.

PANEL MEMBER BUCKPITT: Right.

OEHHA STAFF TOXICOLOGIST DODGE: I agree fully with that, because when Dr. Wang made the translation, I go, "Really, that high?"

PANEL MEMBER BUCKPITT: Milligrams or grams.

OEHHA STAFF TOXICOLOGIST DODGE: Caprolactam metabolizes quite quickly down in the body.

PANEL MEMBER BUCKPITT: So, again, to my mind, that makes the data somewhat suspect, right?

PANEL MEMBER BLANC: In terms of extrapolating the --

PANEL MEMBER BUCKPITT: In terms of the urine --

PANEL MEMBER BLANC: In terms of extrapolating an exposure level except to say it was very high.

One --

PANEL MEMBER BUCKPITT: Do you see what I'm saying?

PANEL MEMBER BLANC: One theoretical point, assuming that you -- that it was -- that you were more convinced that it was reliable in terms of the exposure level, a theoretical point is valid that you could make some assumptions and back-extrapolate to what the air levels would have had to have been once you've reached steady state to get there, I suppose. I know we did that once with blood levels in a fatal case of an exposure and found that there were two workers who were exposed to a particular chemical and one died and one didn't. And it was a liver toxin, and they found that the back-extrapolation with rodent data was right at the LD 50. So, you know, it was quite consistent with what we observed. So depending on, you know, on those difficulties.

I made a comment earlier that one of the four areas was language inconsistency. And one of the

suggestions that I had to, even at that time, is that if you're in a situation where you're forced to rely on something that was reported, even if they used the language that you wouldn't have preferred, is sometimes you can put things in quotation marks to make it clear what you're saying.

But just an example -- and it may be good to do some final cleanup. If you go through the table that we're discussing now and you've got these -- these three case reports, all of which have --

CHAIRPERSON FROINES: Paul, what page are you on?

PANEL MEMBER BLANC: It's page 32, the table.

You'll see that the seizures are called grand mal seizures, tonic convulsions, and tonic-clonic seizures. Now, they're actually all tonic-clonic seizures, they're just different euphemisms for the same thing. That's an area in which unless you want people to be confused, I would just say tonic-clonic seizure, which is a more appropriate generic term. And I don't think that's a case where you're forced to use the word "grand mal" even if they used it, although you're translating some of these. But I don't think that's something to belabor here. But just again a very careful edit can help you solve certain --

CHAIRPERSON FROINES: I'm sorry. I'm the one

person who missed the point you made. Could you restate it?

PANEL MEMBER BUCKPITT: I sure could.

So if you look at some of the earlier studies in animals, only two percent of the caprolactam comes out as an unchanged compound in the urine, which means that 98 percent of the compound is metabolized.

CHAIRPERSON FROINES: Sure.

PANEL MEMBER BUCKPITT: So if these measurements are of unchanged caprolactam, it would mean that the exposure levels were huge.

CHAIRPERSON FROINES: Got it. Thank you.

PANEL MEMBER BUCKPITT: True.

PANEL MEMBER ARAUJO: Based on what you're saying, yeah, it makes sense.

In their laboratory resource section, they mention that the amount of policeable caprolactam was 13.6 to 15.4 grams. So that is far from the gray shade that you're saying, but still denotes that is a very high level of exposure.

OEHHA STAFF TOXICOLOGIST DODGE: Thank you.

CHAIRPERSON FROINES: It's still yours.

PANEL MEMBER ARAUJO: Oh, it's still mine. Okay.

So the second comment that I wanted to make is in relation to the Ziegler study.

Given the importance of the study and how much weight you're putting to actually get to a regulatory decision, I wonder whether the raw data should be placed as an appendix in the document, because this is not a study that has been -- the published study doesn't have the data that you have analyzed. And the data that you have analyzed has only been analyzed by the institution, I mean, by you, but it hasn't really been peer reviewed. So if they want really to contest and they really claim that you are like -- you analyzed and that you're cherry picking that you are conducting your own --

PANEL MEMBER BLANC: Can we come back to that?

PANEL MEMBER ARAUJO: Okay. Because I have deliberately not talked about their critique of --

PANEL MEMBER ARAUJO: Okay.

CHAIRPERSON FROINES: I would just say one thing. And, that is, given Ellen Eisen's questions, it seems to me your suggestion for clarity is not a bad one.

PANEL MEMBER HAMMOND: For the data, yeah.

PANEL MEMBER BLANC: I don't think that's what the author agreed to, given his data. I don't think that's appropriate at all.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's what we were just talking about, you know --

PANEL MEMBER BLANC: Well, it's his data.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We didn't ask him. It's his data.

PANEL MEMBER BLANC: So should I now turn to Part 2.

CHAIRPERSON FROINES: No, no, no. We have to do two things: One is to take a break. But before we do that, if it's okay - Bill Nazaroff?

PANEL MEMBER NAZAROFF: I'm here still.

CHAIRPERSON FROINES: You haven't been given an opportunity to speak, so it's your turn.

PANEL MEMBER NAZAROFF: All right. Thank you.

This has been an interesting experience. I can follow 90 percent of what's going on. It helps to have met almost all of you before. And please use the microphone. That's the 10 percent that I can't pick up.

So I have a few comments I want to share with everybody. I did a careful read in the last days of the materials and have forwarded some more detailed comments to Andy Salmon, who had conveyed the document to me originally.

But most of the things that I'm not speaking to now are in the manner of "t" crossing an "i" dotting. These five points that I'm sharing with you are a little bit more substantive.

So, first, an issue of environmental chemistry and proper reporting of levels.

On page 20 and elsewhere in the document there are levels reported in ppm units that are grossly in excess of the saturation vapor pressure. And I think that's a misleading practice, that one generally would not use a ppm unit to refer to any condensed phase material relative to a volume of air.

So in that particular instance, the level reported was 14,000 parts per million. The saturation level is 3 parts per million. So clearly that's almost all particle materials suspended in air. And it just would be much cleaner to use milligram per cubic meter or the equivalent mass concentration whenever it's not a vapor or not predominantly a vapor that one is referring to.

A second point appears in a couple of places in the document, but the first instance is in Table 4. And this just has to do with good practice for clear communication. I found it very hard to make connections between what was presented in Table 4 and what was presented in paragraph form in the narrative. And I couldn't do it easily in either direction, either looking at the table, picking an entry in the table, and then going back and finding it in the text, or vice versa.

So there's several ways that one could solve this problem. And I don't really care what manner is used. The studies could be labeled with a discrete letter. Each paragraph could be given a subhead title that provides the same reference mapping that's used in the particular table. But I think -- I found this same problem in the nickel document, that it's -- there's summary tables that are helpful, but they would be much more helpful if they could be effectively mapped back to the narrative text and vice versa.

My third point is -- it has to do with the general challenge when characterizing workplace exposures of being able to tell us in the summary document what is known, to the extent that anything is known, about the particular particle sizes that were collected in the sampling.

So when in one place there's a reference to light flood of feathery flakes that form. Obviously visible caprolactam condensate somehow suspended in the air. Well, if one collected that material on an open-faced filter sample, you'd get a large mass concentration. But the relevance for inhalation exposure is not apparent at all in that case because those are particles, or even bigger than particles, way too large to be respired. So if one was exposed in that environment, I would guess what

would happen is that you might inhale maybe with mouth breathing and have deposition in the upper part in the head, and then from mucous clearing you might end up swallowing some of that material and it would represent an ingestion rather than an inhalation exposure.

So it's -- I understand that these -- our primary documents are often not clear on sampling techniques. Even when they say they collected material on a filter, we don't know necessarily it was an open-faced filter, which would be total suspended material, or it had some sort of size-selective inlet on it.

But I would encourage you at OEHHA to be attentive to this issue when you're referring -- or reviewing documents and convey as much as is possible into your summary report.

My fourth comment of five has to do with the case that's made within this document for using what is primarily particle phase exposure conditions. And now I'm not referring to the acute REL determination, because that was principally gaseous, but to the Reinhold study, which was principally particulate. There is a case made - it's quite weak - in the REL document that using particle phase exposure is an appropriate means of setting a vapor phase limit, which is, in effect, what you end up doing, because the limit you set is well below the saturation vapor

pressure.

Some effort along these lines was made in responding to one of the criticisms that was submitted on behalf of the Carpet and Rug Institute. I guess that's what they are. That effort helped to make the case, but I even didn't think that was sufficient to make it strongly.

And in any event, I think that case needs to be made in the TSD not in response to a criticism that's off line. Because when you get down to the final analysis, you're setting a reference exposure level for what is primarily going to be a gaseous species at least if it's at these low levels. And you're principally using a particle phase exposure experiment as the basis for doing so. And the translation of one to the other, you know, an argument can be made. But it really needs to be made effectively to substantiate that translation or transition.

And so my final comment - and it's along these same lines a bit - and it has to do with the presentation made today on the very last slide, number 33. And the argument was made in a critique that there would have been a vapor in part of these rat exposures that would have contributed to the total exposure and therefore the exposure levels might have been somewhat higher than the particle level that was reported. I don't find the

response persuasive. In fact, I don't find it persuasive at all.

So, yes, the particles were generated by a 1-to-1 mixture of water and caprolactam that was then dispersed in a spray. And the spray was injected into the exposure chamber, I presume. One thing that might well have happened is that -- and I can't tell from the original paper, but all I have to work with is Reinhold's paper. I don't have the industry report. The water that was in those particles may well have evaporated nearly or completely, leaving behind pure or nearly pure caprolactam particles.

In that event, Henry's Law partition coefficient really has no significance in helping to make an argument that there -- all of this caprolactam would be in the condensed phase rather than establishing a vapor particle equilibrium that could conceivably have risen up to the saturation level.

I couldn't say that the saturation level would be present in the vapor phase in these studies. But I don't find OEHHA's response persuasive otherwise that one should take, for example, the 24 milligram per cubic meter particle level at the lowest exposure and say that was indeed the total exposure for these laboratory animals.

So I'm not sure what the most effective response

is to this particular point. But I don't find the response that OEHHA has made so far persuasive to me in dismissing the concern that there may have been a vapor exposure in addition to the particle exposure.

But those are my comments. Thank you.

OEHHA ENVIRONMENTAL MODELING SECTION SUPERVISOR BLAISDELL: Dr. Nazaroff, would you expect the water vapor to be at saturation so that the evaporation would not occur off the particles to the aerosol?

PANEL MEMBER NAZAROFF: Well, if the water -- you know, when these things are generated, the particles are going to be sent into the exposure chamber. The rats, I presume, are not exposed at 100 percent relative humidity. It may have said in the original paper, but -- and I don't know that. Which means that there's a driving force for evaporation of water to leave the caprolactam/water mix and go into the vapor phase.

Whether -- you know, this is a complicated thermodynamic situation at this point where you've got a material that -- if it's a 1-to-1 mixture of caprolactam and water, even what we know as the Henry's Law constant that's based on a dilute mixture approximation, and so there's activity coefficients and some other complexities. So I don't know whether these particles would completely dry out or they would hold some water behind in

equilibrium and you'd end up with some, you know, liquid water combined with caprolactam mix.

But the argument that the Henry -- because the Henry's Law constant is so small, that therefore there would not have been significant vapor of caprolactam released from the particles, just doesn't hang together.

CHAIRPERSON FROINES: Bill?

PANEL MEMBER NAZAROFF: Yes.

CHAIRPERSON FROINES: This is John Froines.

Do you have a suggestion of how they might improve that issue?

PANEL MEMBER NAZAROFF: Well, you know, it seems to me that the -- one way of doing it is to grant the idea as an upper bound uncertainty estimate - and this doesn't introduce any more uncertainty than the kinds of uncertainties that we're having to deal with anyway in setting regulatory levels - and just allow that the levels might have been as high as an upper bound, as reported here, 37, 83, 256. If you rerun -- if OEHHA were to rerun the analysis that they did assuming that those concentrations applied, and then take it through the exercise of calculating a new 8-hour REL and a new chronic REL on that basis, I don't know what would happen. I expect that the change would be less than a 50 percent increase in the levels that were set. It may be that in

the end, you know, OEHHA would judge that it's -- that the lower standard should be set anyway, given the uncertainty, as a possibility. But I think that that's probably a preferable way to go and just allow for the uncertainty in exposure rather than to dismiss this concern.

CHAIRPERSON FROINES: Do any of the Panel members have a comment?

PANEL MEMBER BLANC: Yeah, I disagree with that if I understood it correctly. And if I understood it incorrectly, then I wouldn't feel as strongly about it.

If the suggestion is that in the text it should say, as a broad experiment, we reran this by increasing the exposure levels by 50 percent and came up with an REL that's 50 percent higher, but we don't believe that there's enough data to support that non-public health protective approach, then that is okay.

But to discount the calculations by 50 percent because you assume 100 percent vapor saturation superimposed on the inhaled dose based on the concentration of the aerosol, I think is not public health protective, and so I wouldn't support that.

PANEL MEMBER NAZAROFF: So let me react to that.

Is that Paul that --

PANEL MEMBER BLANC: Yes.

PANEL MEMBER NAZAROFF: -- that made those comments?

Yeah, thank you.

I'm perfectly fine with the first way that you presented the response. I do want to make clear that the 50 percent number, it's not as simple as that, because it's a constant 13 milligrams per cubic meter. So it's 50 percent at the lowest exposure level and then proportionately lower at higher exposure levels. And so one would really need to rerun the analysis.

PANEL MEMBER BLANC: Yeah, that was the worst case. So I can -- it sounds like we're in agreement. So I don't think that's a problem.

PANEL MEMBER NAZAROFF: Yeah. I mean I don't have any problem in the end if they, as you say, for public health protective purposes say, in the presence of this uncertainty, you know, we're choosing to go with the more conservative value. That's completely legitimate from my point of view.

CHAIRPERSON FROINES: Is that appropriate for you, Melanie.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, that's fine. We can revisit the response to comment as well and then put some text into here about --

PANEL MEMBER BLANC: And then I'll be coming back to other -- he raises another issue in terms of how you deal the responses that I'll come back to you after the break.

CHAIRPERSON FROINES: Okay. I think that we were going to take a break. But it's now 12:35, which means I think we should take lunch.

Forty minutes?

PANEL MEMBER BLANC: That's not realistic.

CHAIRPERSON FROINES: Well, do an hour and --

PANEL MEMBER BLANC: Well, still I mean just -- as long as people honor the time you set.

CHAIRPERSON FROINES: Well, 45 minutes then.

Don't you think we can do that?

Somebody else --

PANEL MEMBER EISEN: I do. I think that's good.

PANEL MEMBER BLANC: All right, fine.

Bill, are you going to be on this afternoon?

PANEL MEMBER NAZAROFF: Yeah, I'm -- well, it's well into the afternoon here in Washington. So just tell me when I should be back on. I think I'm -- I lost my support people here. So I'm just going to leave the phone on and put it on mute and do something else for a little while.

PANEL MEMBER BLANC: I think 10 after 1 is when

we should reconvene if that's 45 --

PANEL MEMBER NAZAROFF: Yeah.

PANEL MEMBER BLANC: No, is that right?

No, no, 20 after 1.

PANEL MEMBER NAZAROFF: Okay. Thank you.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: Bill, are you on the phone.

PANEL MEMBER NAZAROFF: I am on the phone?

CHAIRPERSON FROINES: Thank you.

We're waiting for Blaisdell.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Let's just start.

CHAIRPERSON FROINES: Are you sure?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: We're going to start with Paul finishing his commentary.

And so we will officially be restarted.

I don't want you to feel left out.

PANEL MEMBER BLANC: All right. So we're back?

CHAIRPERSON FROINES: We're waiting for you to start.

PANEL MEMBER BLANC: Okay. Just to review, we've concluded the discussion of the existing revised document as you have it. Now, we're moving on to a discussion of OEHHA's responses to the industry comments that they had for this revised document and indirectly to revisions that would therefore appear here but don't appear on the version that you have.

So obviously most of the presentation focused on

comments made on the use of the Ziegler study and OEHHA's response to them. As a generic point, I would say that it's not -- other than changes in the table such that the table -- the tabular only presents the non-parametric ordinal statistical test, it was not clear from the presentation nor is it necessarily clear at all from here except by inference that actually there would be no other textual changes to the document. And this is something that Bill brought up in his comments on the telephone also.

So before I comment on what maybe should be in the texts other than -- because the only other textual change we talked about was in response to Patty's comment, and then Bill brought up a point about the --

CHAIRPERSON FROINES: Patty's comment?

PANEL MEMBER BLANC: Kathy's comment. And then there was a comment from Bill on the phone about more textual justification for one of the analyses.

So I guess what I would like to hear first is a clarification. Were there --

CHAIRPERSON FROINES: Paul, there was the issue of Henry's Law.

PANEL MEMBER BLANC: And Henry's Law as well, which was partly -- yes, there was partly in response to critique -- are there other things that you were planning

to add to the written document that were just implicit in what you were saying or not?

OEHHA ENVIRONMENTAL MODELING SECTION SUPERVISOR BLAISDELL: There was editorial changes here and there, but --

PANEL MEMBER BLANC: Well, what are they that you're planning? Because we don't have a text, so how are we supposed to know?

OEHHA ENVIRONMENTAL MODELING SECTION SUPERVISOR BLAISDELL: There's a few editorial changes, you know, just grammatical things, that sort of thing.

PANEL MEMBER BLANC: No, I meant in response -- are there any -- you know, when you get a journal article back from a journal, you are supposed to send in a response to them -- response to the reviewer's critique. But that's usually insufficient if you just simply respond in the letter but there are no changes in the document consistent with that.

So, again, what I'm asking, not in terms of editorial changes because of other things you've noted, but in terms of the responses that you talked about, are there any textual changes? For example, "Although we considered blah, blah, blah, we determined that we would proceed with blah, blah, blah"?

OEHHA STAFF TOXICOLOGIST DODGE: Okay. We'll

probably need to clarify which eye blink method we specifically used. We could clarify that in the document. In other words, we used the data from the manual traditional lights-off approach. We didn't use the data from the semi-automatic approach, which Dr. Ziegler in his published study felt needed more vetting before he could rely on it.

PANEL MEMBER BLANC: Yes. And I would fully agree that that's one very good example of something that wasn't clear from the revised document and your argument as to why you were -- why you did what you did was cogent and convincing.

I would overall say that your response to the critiques as they related to the use of the Ziegler data were to me convincing and appropriate. I think that the presentation -- it's very difficult to present such a very complex thing in oral format such as this. So some of it didn't come across as convincing -- as convincingly as it might have, but I think in the written comments I think it's straightforward. And I do think that there are key places where one or two sentences introduced into the document, along the same lines as the editorial change that you're suggesting, that I agree with, as to why the standard blink test is appropriate, would be reasonable.

So, for example, when you discuss as a sort of

secondary analysis the eye irritation findings, I believe that it's reasonable to also say that eye irritation correlated with change from baseline in eye blink and that eye irritation -- and that eye blink did not correlate with perceived odor, which could suggest a subjective modifier.

And I also think that there's no reason in the document to go into the length that you were forced to go into in addressing the day-of-test argument, which I think was a stretch to even suggest it. And then I think your rebuttal to it was completely appropriate. I don't think that there is any substantive or substantial evidence in the data that supports such a backwards interpretation that would require you to stand the data on its head. But I do think that simply saying that per the 1-hour time frame at which you -- which was the data time frame that you used, there was no relation -- there was no statistical relationship between day of test and an effect is appropriate. You don't have to say what there was for which the data you didn't use. You already say in the document why you used 1-hour data, I believe, because that's what the standard is based on. So I believe that's why you're there.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, that's correct.

PANEL MEMBER BLANC: And I think what you didn't say in your verbal comments, although it's present in your written text, is were you to proceed with the kind of analysis that was suggested, I would have been sitting here saying that you've overadjusted the data, because I think that that's what it would have done. But in any event.

I also think that the few sentences that have to do with the -- it was just a question John asked about the disassociation between eye irritation and --

CHAIRPERSON FROINES: -- redness.

PANEL MEMBER BLANC: And redness?

-- perceived eye irritation and quantified eye redness. I could go either way because you don't use -- you don't rely on eye redness as an endpoint and you only invoke eye irritation as a secondary, you know, non-definitive thing. But if you wanted to have a sentence saying there, "We do note that there wasn't a dose response for quantified eye redness, this is not inconsistent with what has been reported by other investigators," and that's fine too.

So I think that you should -- without belaboring the point, I think you should systematically go through your written comments, and where you believe it's appropriate to put in additional text that draws on that,

you should do so, without saying, "It has been suggested that such and such but we did such and such." Just the parts that are relevant and demonstrative. And I don't think that I'd feel compelled to review that again, because I've seen, and we all have seen, your written response. And there's not a part of your written response in that regard that I think is -- is not coherent or couldn't be used in that manner.

Does that make sense?

OEHHA STAFF TOXICOLOGIST DODGE: Yes, that makes sense.

PANEL MEMBER BLANC: And, Melanie, can you oversee whatever extraction that is?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

One other little thing we wanted to add in response to Bill's comments about the vapor versus particle. We did talk about that in the last draft on --

CHAIRPERSON FROINES: Melanie, could I ask you to hold that for just one second?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

CHAIRPERSON FROINES: Because Paul's finished his comments, I believe.

PANEL MEMBER BLANC: Almost, I think.

CHAIRPERSON FROINES: Almost. And what I want to do before you respond is to give the Panel -- other members of the Panel a chance to add to or comment on what Paul said.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BLANC: So in summary then, I think that, you know, the responses were cogent and appropriate and convincing overall in terms of that.

And speaking for Dr. Glantz, he is supportive of using the Page test as the sole analytic technique, because he doesn't feel it's more informative to have side-by-side multiple versions of the testing. And I think that's fine. How you handle whether you -- I wouldn't even actually then go into text detail aside from leaving it out of the tables. I wouldn't say -- and we also did, you know, a parametric test, which doesn't have a rank order built into it.

I think that your findings that the trend -- or the exposure response is unlikely to be due to chance is not compromised by having, you know, 20 subjects studied at four different levels. And that's actually a rather large exposure -- human exposure study as those go by.

I also think that there's ample precedent for using raw data when available, generically. We often do

that with unpublished pesticide-related data. And there's other data in this document, in fact, that are not published that are -- the Haskell lab data, for example. I think in this case it's all the more cogent because they -- what they published as opposed to what they didn't publish was the data based on an non-validated metric, which was this novel way of measuring eye blink. So it's a second reason for using the raw data.

I think you could avoid some -- just be cautious when you use the word "trend." It's not your fault. But unfortunately the way people often will use "trend" when they -- inappropriately is to refer to an ordinal level of response, which does not actually meet a threshold for rejecting that all hypothesis, you know, "I saw a trend." So I don't think it's called the Page test for trend, is it? Does it have the word "trend" in the title? Or does it?

OEHHA RESEARCH SCIENTIST MALIG: Yeah, it does have.

PANEL MEMBER BLANC: Okay. So just be cautious. You'd call it that But then as a descriptor, I would try to avoid the word "trend" to not confuse people who are going to -- it's not your fault, but it's just how it's crept into the language.

OEHHA STAFF TOXICOLOGIST DODGE: Right. I'm

aware of that now, thanks to you. But it is called the Page's trend test.

PANEL MEMBER BLANC: Well, you can say that when you refer to it. But then if you just have a sentence where "we saw a trend," I wouldn't say that. I'd say, "We saw a statistically significant effect."

And I think we've -- I've already given you my comment in terms of this exchange about the -- I would not presume that there was 100 percent vapor saturation superimposed on the exposure that's in the aqueous phase for standard-setting purposes.

Another thing that I hadn't prepared to say but it occurred me as Bill was talking about particulate versus vapor phase. I certainly agree with the comment about parts per million, and I saw you all nodding your heads that you would go back and be more attentive to that where appropriate. But I do think that because the end response that you use for the chronic effect is a nasal passages response -- isn't that correct?

OEHHA STAFF TOXICOLOGIST DODGE: Yes.

PANEL MEMBER BLANC: So the issue of particle size as opposed to, you know, vapor issues is somewhat less an issue, it would seem to me in that case. And I don't know whether -- well, larynx too. But I mean it's not -- you're not talking about an alveolar deposition.

So you may want to comment on that or make a sentence that says, you know, just of note this is not an endpoint effect that would be highly sensitive to -- that would misreflect a particle size. Or to the extent it was a particle distribution that would more tend to deposit in this area, that's all the more so relevant, or however you want to word that.

CHAIRPERSON FROINES: Can I interrupt you?

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: Bill?

PANEL MEMBER NAZAROFF: I'm here.

CHAIRPERSON FROINES: Did you just hear Paul's comments about basically issues you raised?

PANEL MEMBER NAZAROFF: Yeah, I heard.

CHAIRPERSON FROINES: I wanted to give you a chance to respond if you wanted to.

PANEL MEMBER NAZAROFF: Maybe we should hear Paul out until the end.

PANEL MEMBER BLANC: I think that's pretty much everything I wanted to say about the responses to the critique.

PANEL MEMBER NAZAROFF: Okay. Well, my, I guess, reaction is that to first -- to first order I think it is, especially in an arena where we don't understand a lot of things at a high level of precision and yet we still have

to make judgments, that coarse particles and water soluble vapor are likely to have comparable places where they deposit in the respiratory tract.

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER NAZAROFF: The concern I guess is just to be a bit cautious and not so sanguine as to say that these processes are exactly the same. A five micron caprolactam particle depositing in the nasal passages is going to have an insult that's somewhat more localized than that same material would if taken up as a vapor. And so -- I mean now I'm getting outside of my depth, but I understand -- in terms of talking about the biological responses. But I understand from the physical science point of view that the degree of localization that would occur could be quite different for particles and for vapor material.

And, again, this isn't a critique about the final determination as to whether a number should be set at what particular level and interpreting the data that we have. The critique is about substantiating or justifying or explaining the rationale. And I do have a residual concern that the document as it stands is just a bit too glib in equating the particle phase exposure studies with what's ultimately a standard to protect us against vapor phase exposure.

CHAIRPERSON FROINES: Do you have a suggestion for how they might address that?

PANEL MEMBER NAZAROFF: Well, I think if there -- I had sent -- I don't remember where I've had a comment on this particular point. I think it's just a matter of expressing with greater -- you know, it may take a paragraph or a couple of paragraphs to express the kind of underlying exposure aspects that would be different in these two cases and to say that, you know, "We've thought about this or reflected on it or considered it," and say, you know, "given the available evidence, this is the best we think we can do." You know, it's a generic problem actually for any semi-volatile species, because we're going to be having -- you can't expose laboratory animals or anybody to extraordinary high vapor phase concentrations because you get above the saturation vapor pressure. So you're going to end up in laboratory studies with particle-based exposures, in all likelihood. And yet with adjustment factors and the goal of public health protection, we're going to want to protect against things that may largely be in the vapor phase.

So, you know, how one reconciles that conflict -- I'm relatively new to this Committee. I don't know how it's been addressed in other settings. But it seems to me to be a fundamental problem in the nature of this work

when we're dealing with a semi-volatile species.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Can I chime in a little bit here? This is Melanie.

Bill, we did talk about that where we're in the section on the derivation of the 8-hour, which is a repeated 8-hour REL. And it's also pertinent to the chronic. But, you know, we recognize that there is -- it creates an uncertainty in calculating the REL. But we also note that, you know, very water soluble gases like caprolactam will scrub out in the upper respiratory tract. So while we recognize there may be, you know, microscopically dosimetric differences if it's a particle versus a reactive gas or water valuable gas, there isn't a whole lot we can do about that quantitatively for this REL derivation.

So perhaps we didn't emphasize that enough. And we can certainly put in more verbiage to that point.

PANEL MEMBER NAZAROFF: And I think that's my main point. The point is not that I'm calling into question the derivations that have ultimately been made. It's just that I found the document a little bit too quick to say, "Well, because it deposits in the nose, and because, you know, they're big particles and because it's a water soluble vapor, therefore we can treat these as" --

lack language, but the sense I have in my memory is "perfectly equivalent." And I'm just cautioning that, you know, if you want to have kind of robust -- we allow uncertainty where uncertainty exists in trying to make a decision, an interpretation, application for public health practice. But when you make another statement that sort of cuts to the underlying science, that goes against what it is that we know, then you'll run into trouble with me as a reviewer.

CHAIRPERSON FROINES: Alan.

PANEL MEMBER BUCKPITT: Not really any further comments. I see what Melanie is trying to say, and I think in a couple of paragraphs that could be taken care of. Because this is a water soluble substance and it's going to deposit in the upper portions of the respiratory tract. It doesn't matter whether it's a vapor or a particle. I think both things would impact.

CHAIRPERSON FROINES: Ellen.

PANEL MEMBER EISEN: So I guess -- I do want to say I think you've done a good job in interpreting and reanalyzing the data and in interpreting the results. But I also feel compelled to say that I think the data are not that strong, that you need -- but it's all there are, so you're going to need -- and you need to make a decision. So I support the decision.

But I do want to go on record as saying I think there is a -- the data are weak, and that if it weren't for everything else we know about this chemical, we'd need stronger data. So I think it's only -- it works okay, suffices I think as a basis for standard setting because of all of the other information that we have in the background. Okay?

I mean I'm okay with your Page statistic. I'm okay with the one hour. I'm okay with going with the old-fashioned blink. I mean all of those things I think are moves that you can justify piece by piece. But you put it all together and you've got one study for 20 subjects and it's thin.

CHAIRPERSON FROINES: Kathy?

Thanks, Ellen. I think that -- I don't know what Paul would say, but I think you're right-on.

PANEL MEMBER HAMMOND: I think I've made all my comments, and overall thank you for an awful lot of work responding to a lot of comments.

CHAIRPERSON FROINES: Jesús.

PANEL MEMBER ARAUJO: I will mention again the same comment or motion that I made initially, about whether it is possible to have the raw data with the permission of the author placed as an appendix. Or I've been thinking, what other way we could think of that can

allow any person who would want to have access to that raw data and wanting to analyze the data themselves and that they could do it.

One of the things that again I'm concerned is about the multiple times throughout their response that they attack or they question or they -- the way or the different ways how you're analyzing the data, how you're picking it and -- or cherry-picking data, how you analyze it in the way you want and that's why you're reaching to different conclusions.

And so I'm looking at -- for instance, I'm looking at their Table 2 in their paper, I'm looking at your Table 1 in your report. And I don't understand why there are some small discrepancies in some of the numbers that -- if the data is basic statistics like average and median, and we should be fair in between the two tables. So unless the data provided included some data points that were not taken into their analysis then and now you're taking it or that there is some little variations in between the data that they use or the data that you use.

But in their Table 2, so they have all the various parameters that they've -- different concentrations and the different time points. I mean at 00.15, 0.5 and 5 and at different time points, 0 minutes, 1 hour, 3 hours and 6 hours.

And in your Table 1, so you refer to the 1-hour exposure, and there are at least two different values in terms of the mean and the standard deviations for different concentrations. Which again if somebody really wanted to question your analysis -- so we'll say what is published is that it -- it says that the mean was 30 -- I'm sorry -- was 29.7 and 5 micrograms per cubic meter, and now you're showing that it's 34.35. So it will introduce a lot of -- I mean it's not just the analysis. It in the data procedures that is different.

Do you have an explanation of why?

OEHHA STAFF TOXICOLOGIST DODGE: Yes. The data in the published report by Ziegler, that Table 2, that's the data from the semi-automatic or neon-light approach, from the new method that was felt to need more vetting, as Dr. Ziegler explained in his discussion.

Now, in the methodology he says you should also rely on, you know -- he indicated you should rely on the standard approach as well and not so much on this other data.

But, yet, in their results section, the only eye blink data they present is from their semi-automated approach. And that's -- and I guess that's -- it's almost like some -- some group in Ziegler wrote the Discussion section and methodology, and somebody else did the Results

section, because their results doesn't match -- their results section just doesn't match what they're trying to say in their methodology and discussion sections.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And, Daryn, did not Ziegler -- you had Ziegler on this --

OEHHA STAFF TOXICOLOGIST DODGE: Well, yeah. It was mostly to confirm some other findings and some of the other objective measures.

But I didn't ask him specifically why they only relied on this data and the Results section based on a method they say they don't really trust yet. My guess is that it's the only set of eye blink data they had full data on for -- you know, for all time points and all subjects. So they wanted to present that.

PANEL MEMBER BLANC: I think that there's a simple solution to this problem, which is just in addition to the added text that you're going to be putting about why you used the old -- the standard eye blink technology. You can have a simple footnote to that table which says, "Note that these numbers differ from the published" -- "the data as published, because they present the automated results." And that will circumvent any misunderstanding.

Don't you think that would solve it?

PANEL MEMBER ARAUJO: Sure, yeah.

PANEL MEMBER BLANC: I actually -- I mean I -- there's two questions here. One is if Dr. Ziegler said, "Yeah, it's okay to publish my raw data as an appendix." Then should you do it? Because obviously if you didn't, you couldn't. And would such an appendix then be helpful?

I think this would be a moot point because I'd be shocked if he said, "You can publish my raw data as an appendix."

CHAIRPERSON FROINES: I think that the --

PANEL MEMBER BLANC: And you have no right to publish --

CHAIRPERSON FROINES: I think that the questions that Ellen raised earlier today might be -- might have -- she might not have had to ask those questions if she had seen the data.

PANEL MEMBER BLANC: Well, again, my -- two part. One is just pragmatic, which I'd be shocked if they said it. My own personal opinion, I don't think you need it as an appendix. But I think it's a moot point, because I just can't believe somebody would agree to that. I certainly don't think if he doesn't allow it, that the document is substantively weakened by not having such data.

CHAIRPERSON FROINES: No, that's clear.

PANEL MEMBER EISEN: I mean I think -- your point is well taken. And I think if someone -- I mean it is interesting. I think that the whole question really comes down to why there's a difference between the two eye blink methods and the 1-hour results. I mean that's -- right? -- because in every other -- in the longer term exposure rows, the new method of eye blink counting does find significant result. It's only in the one hour that it fails to.

So that discrepancy between the old and the new counting method is only relevant really in the place where it counts, which is in the one hour. And it only turns possibly on how many blinks are in the highest category, whether it's 20 -- I mean that's just -- you, know, so it does sort of bring the whole thing down to this very sort of small perturbation in the data, which is -- so I guess I don't think it's going to -- it doesn't really provide any comfort to present those results. It just ought to make people more uncomfortable, because it just clarifies sort of the detail to which the whole result turns, you know, that we're using to justify this PEL. So I don't --

PANEL MEMBER BLANC: Well, I disagree again, because actually it's not just this one thing. In fact, this was the way in which all of the endpoints were going. And they were fairly conservative. For example, they

don't use nasal -- sense of odor because that's not really a necessarily toxic endpoint. They don't use the integrated score of irritant effects, because you're sort of counting things more than once. And they don't use the eye irritation, because that's subjective. But when you look at the data - and this was the response of the Panel the last -- look at the published data even in the paper - and this was the response of the Panel as a whole last time - it's clear that something is happening at five that isn't happening at lower doses, because it's across --

PANEL MEMBER EISEN: Well, I don't if it is so clear. Is it so clear using the other accounting method? No.

PANEL MEMBER BLANC: Yes, it is, if you look at all of the endpoints. It's all there. And there are -- so despite the way that they handled the data, which was weaker than it should have been, I mean that was -- and we actually tried to do -- we looked at another sort of crude non-parametric way of looking at it, which is if you look at what ranks as the highest ordinal response for each of the outcomes, because there are five different outcomes, or four -- is that right, Melanie? Is it four or five?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Total with or without?

PANEL MEMBER BLANC: It's either four or five anyway. I think it's five. And so -- and you have four exposure levels. And so if you -- and you could say for these four exposure levels and these five metrics of effect, who ranked highest ordinally. And for four of them you're highest at 5 milligrams, and four one of them you're tied between 5 and the next lowest dose.

So I mean I suggested, okay, just what is this -- do a statistical test of that as a, you know, non-parametric distribution for endpoints.

PANEL MEMBER EISEN: Right. I mean there well may be trends. I'm not saying that there aren't trends and there isn't an --

PANEL MEMBER BLANC: Trends are unlikely to be due to chance.

PANEL MEMBER EISEN: Possibly. But, you know, exactly where you set a level, I think that's a whole another question.

PANEL MEMBER BLANC: Well --

PANEL MEMBER EISEN: You're having to rely on this to do that. But I think it's week data.

PANEL MEMBER BLANC: But what they're doing is they're saying that that's -- that 5 is not a no effect level. I think that's really basically what they're doing. And because the next lowest one was .5, even if

you said we have no NOAEL, we only have a LOAEL at 5, and then you divided that by 10, you'd -- so it'd be at the same place again.

So from -- and they're not doing a benchmark approach with this endpoint.

So for me the cup is half full, not half empty. That's all that I'm saying.

CHAIRPERSON FROINES: I'm going to take the prerogative of the Chair. And I would like to bring this issue to closure, because some of these issues that are being discussed could go on for a substantial period of time.

And unless somebody has specific suggestions to OEHHA, then I think we should move on.

PANEL MEMBER BLANC: Can I just -- one small thing that I forgot to say?

CHAIRPERSON FROINES: Do what you -- yeah.

PANEL MEMBER BLANC: One very small thing, which is --

CHAIRPERSON FROINES: What if I said no? Would that stop --

PANEL MEMBER BLANC: I could say I'll to it off line.

(Laughter.)

PANEL MEMBER BLANC: You know, there is also in

terms of clarity where you say zero time when they first enter the booth. But isn't that before any exposure? Or their entry in the booth and there already is exposure there?

OEHHA STAFF TOXICOLOGIST DODGE: The measurements were taken about five minutes after --

PANEL MEMBER BLANC: -- they started exposure.

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: So there even is some early exposure. So it's not time zero actually.

OEHHA STAFF TOXICOLOGIST DODGE: That's what they called it in the paper. And then I tried to -- yeah, in parens I was saying, you know, this is what they actually meant.

PANEL MEMBER BLANC: Okay.

OEHHA STAFF TOXICOLOGIST DODGE: Roughly five minutes after exposure they started --

PANEL MEMBER BLANC: After the initiation --

OEHHA STAFF TOXICOLOGIST DODGE: -- looking at all these various endpoints --

PANEL MEMBER BLANC: Gotcha, gotcha, gotcha.

OEHHA STAFF TOXICOLOGIST DODGE: -- which, you know --

PANEL MEMBER BLANC: I missed that in the written thing. That's why I was asking. And I think I was

unclear a couple of times when I read it and when I heard it.

So, if anything, it's all the more biasing towards not seeing an effect because their zero level is not even zero. It's some exposure.

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm

PANEL MEMBER BLANC: So that's fine.

PANEL MEMBER ARAUJO: I have another small point.

CHAIRPERSON FROINES: No, let me just say at this point, what we're talking about is not the generic issue here. We're talking about what do we recommend to OEHHA to improve -- that might improve their document --

PANEL MEMBER ARAUJO: Well --

CHAIRPERSON FROINES: -- at this stage. But I think we have covered most of the ground here.

PANEL MEMBER ARAUJO: Well, we should recommend something that really strengthens the document I think --

CHAIRPERSON FROINES: That's fine.

PANEL MEMBER ARAUJO: -- against. And what I will say a very obvious claim or attempt to pursue this at another level by the people who are responding to this.

And I believe that Ellen's comment is -- it goes right to the point. I mean if you look at just the table, Table 15 that you presented - it's slide 15 - all the P values by the same automated methods from three hours, six

hours, and also four time points are significant by your analysis, right?

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER ARAUJO: So that strengthens your point.

However, all these time points are not significant by their analysis in the same data.

So it all comes to the same data -- exactly the same data analyzed by two different statistical methods. I don't know much and I am not really anybody to really make a thorough opinion on a statistical methodology. But it all comes to the point of what is the technique or the methodology, or depending on what you use. So it is significant or not. And depending on your own -- what you use, you end up regulated or not. I think that that is -- they may still have a strong point.

Then if we go to the left column, which is your manual count method. So they didn't publish that data. And you only have like one time point where it is significant as per your analysis.

So may I ask you, if you did their ANOVA Kruskal-Wallis methodology on this manual count method -- well, the first question is, did you do it? And if you did it, then what did you find?

PANEL MEMBER BLANC: Well, that's the one where

they didn't report the -- they didn't do it.

PANEL MEMBER ARAUJO: I know. I'm asking them.

PANEL MEMBER BLANC: No, no. But they didn't do the test. There is no data. Ziegler did not do the measurement except on 4 --

PANEL MEMBER ARAUJO: No, no, no, no. But they did it on one hour. So they presented the data analyzed by their Page trends test. My question is, this ANOVA test that you are having here is the same ANOVA Kruskal-Wallis and the data that they used to analyze their other data?

OEHHA STAFF TOXICOLOGIST DODGE: I guess the question is, "Did you use their Kruskal-Wallis method in trying to determine the one hour in the dim light approach?"

But we used the repeated measures ANOVA. They used the Kruskal-Wallis ANOVA.

PANEL MEMBER ARAUJO: Because that would be a strong point, if you used even their same methodology as well as your methodology and you come back with the same answer, even for the known very unsophisticated people from the statistics standpoint, as I am, for instance, you know, that tells you that, wow, that sounds like pretty strong, regardless in how you analyze it, you get to the same conclusion.

But it depends on how you analyze unpublished data you come up to one conclusion or another, that still leads to some concern, I would have to say.

CHAIRPERSON FROINES: Let me explain something, I think for the new people on the Panel.

At this stage, what we're doing is we always recognize that we're going to give them more work to do. That's a given, that when we vote on approving their document, we're not approving what is going to be the final version. We're approving the final -- we're approving a version which will be augmented with what's been discussed today. And so when we vote, we are recognizing that Melanie and her staff are going to take everything that you and everybody on this Panel has said and they're going to incorporate that to ultimately come to the final document. And so that's the procedure that we normally would follow.

Now, if there is a fundamental scientific conflict among the Panel, then that's something that has to be resolved before we would take it to -- for a vote. But as I hear it, what I'm hearing are suggestions of what they can do to improve the document for its final form.

PANEL MEMBER ARAUJO: Well, I'm actually having more fundamental concerns than just a suggestion. As I said -- I understand we're in the position of advising,

and they are who ended up -- who will end up taking the decision ultimately. But I read the multiple times like when they question based on the fact that what they will be taking a decision based on unpublished data analyzed the way they want.

PANEL MEMBER BLANC: Well, I want to respond to that, because I really strongly disagree with you.

First of all, as I said before, there is strong precedent for using raw data when available.

Secondly, there are very clear issues with the selective analyses that were published in the publication, which the author himself and the publication provides I think overwhelmingly convincing rationale that the method they chose to present was not the preferred method. And the non-parametric ranked multiple repeated measures analysis technique, in fact, in the critique that was received by the industry stakeholders, they suggested that that was the appropriate method to use.

It's a quite common finding that if you apply a less specific or a less well suited method to data analysis, you may inappropriately accept the null hypothesis. So using a non-ordinal approach to data that are ordinal or using a parametric approach when a non-parametric approach would be more conservative could lead one to conclude that the pattern observed is likely

to be due to chance -- or more likely to be due to chance.

So on those three grounds, I don't have any trouble with the application of the Page test for trend to these data. I think that if I were reviewing the original paper and they said in their own discussion that this is an analytic method which is unproven and not as reliable, I would have raised questions of their paper. So I don't have any problem with that and I don't have any problem with using a reanalysis of data. In fact, that's what the Panel told OEHHA to do at our last meeting.

And also I think that even the data as published, certainly on face evidence, indicated that something was going on at the 5 milligram dose which represented a response that wasn't seen at lower doses. But I absolutely agree with you that it's important to put the best and clearest and most transparent presentation on that as possible. And I think that there are ways in which the text could make that point a little bit clearer. And perhaps even this last point about the published -- even the article as published is not inconsistent with -- or as highly suggestive as the 5 milligram being a low-effect level and not a no-elect level.

And that was basically the thrust of the critique of this Panel at our last meeting about this, which was, you know, "Come on, guys. Don't throw out these data; you

know, try to use them effectively." And the best way to do that would be to get the raw data since the analysis as published is not very transparent. And then they did all that.

So I don't have a fundamental question about the acute reference value using the human exposure data. Rather than saying we cannot come to an acute reference level, I think this is a chemical with enough exposure out there that it's appropriate. I think it's actually in the big scheme of things a luxury to have controlled human experimental data. And 20 subjects is not trivial. EPA has regulated criteria air pollutants on not much more than that in terms of human subjects depending on what the outcome is.

So on all those reasons, I don't agree that it brings in too fundamental question, the fulcrum, which is 5 milligrams per cubic meter low effect level or not. That's really what all this boils down to, which is -- which is -- maybe that's fortuitous because, yes, if we were going into more subtleties of a multiple dose response with a benchmark calculation, it would be I think a shakier ground.

But that's my view as the lead reviewer. And I think that -- I can't speak for detail for Stan Glantz, except to say that he was very satisfied. And he's the

one who suggested, yes, just present the Page test for trend data. We don't need to see side by side, for example, the multiple test -- multiple comparisons, I know, with these data.

PANEL MEMBER EISEN: Can I make one suggestion?

CHAIRPERSON FROINES: Of course.

PANEL MEMBER EISEN: Maybe it would be help -- when you originally suggested that they published their raw data, I was imagining this whole study design with the five levels and the five weeks and the five days a week -- four days a week. Anyway, it seemed like too much to me. But I do think I guess it would be helpful to see if you can get permission to publish just the means and the standard deviations in each of the -- basically every place that you report a P value and for each of those cells, the row that that's based on, you know, the means that that comes from, whether it's the old method of blink counting or the new method to present the data that went into the P -- if you're going to present the table of the P value --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: You know, actually --

PANEL MEMBER EISEN: Is it in there?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, we actually have it in the draft

document.

CHAIRPERSON FROINES: But you don't have permission.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So it's a -- well, no. This is -- no, this is the summarized data from our analysis of their raw data.

PANEL MEMBER EISEN: Can you see what page it's on?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Page 11, Table 1. And then Table 2 also.

PANEL MEMBER EISEN: So is that both methods of counting or just the one method of counting?

OEHHA STAFF TOXICOLOGIST DODGE: Just the one method.

PANEL MEMBER EISEN: So I guess I think it should have the other method.

PANEL MEMBER ARAUJO: Do you have the -- sorry.

PANEL MEMBER EISEN: Go ahead.

PANEL MEMBER HAMMOND: Actually I would say I think that to have the discussion that there is a conventional method of counting that has been used and that's the one you're going to use seems to me sufficient. And to say that there's a new method used but it's not been vetted, which is what the author says --

PANEL MEMBER EISEN: But it's been published. They published it.

PANEL MEMBER HAMMOND: But the author himself apparently said in the Discussion section - I didn't reed that part - that that hadn't -- was still not validated.

CHAIRPERSON FROINES: Right. That's stated many times in their rebuttal.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think we could put in we showed our responses to the industry comments that went to the Panel; we showed them up here with the tables; and we showed the analysis of the newer method, which was statistically significant, not at 1 hour but at 3 and 6. We can put that in here. I don't see any problem with that. It's summaries, not the raw data. I mean Ziegler knew we were going to take his data and analyze it and make tables like this. So we could --

PANEL MEMBER BLANC: Yeah, I don't see that -- if that's the question, I agree with you, there's no limitation to you putting means and standard deviations. I just think, you know, a listing of each subject and each data point is not -- he's not likely to agree to it. And I don't --

CHAIRPERSON FROINES: I agree with Ellen.

PANEL MEMBER EISEN: Somebody else to say. It

says in his abstracts he reports on the new method of counting. That's what he describes in the abstract. He doesn't say anything about the old method. And as a result, he only has the results for up to 1 hour. He doesn't have them for the other time periods for the old method. I'm not saying we shouldn't report the old method. I think you should. But I'm just saying it seems --

CHAIRPERSON FROINES: But what he says is consistent with what they did.

PANEL MEMBER EISEN: Yeah, yeah, right, exactly. But it looks a little, you know, shifty I think to only report the one method when --

CHAIRPERSON FROINES: So -- I'm the one who wants to move ahead so that -- Melanie, are you comfortable with what Jesús and Ellen have said and Paul's responded to?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: Are the people I just named happy with what I said?

PANEL MEMBER EISEN: Yes.

CHAIRPERSON FROINES: Ellen is and Paul is and Jesús is -- are you okay?

PANEL MEMBER ARAUJO: I'm okay.

CHAIRPERSON FROINES: Well, you people have heard

your argument so that -- and Paul's responded to it and there's been subsequent discussion.

So the point is that my job is to move this forward so we can vote on it.

PANEL MEMBER ARAUJO: So just following up on Ellen's suggestion. So we don't need to have authorization or we wouldn't need authorization of the author to republish the mean standard deviations. How about the statistical analysis and the P values according to the Page trend test? Because --

PANEL MEMBER BLANC: I think what Melanie just said is if they did that, they would present that as well.

Just to -- you know, just to say that it was Stan who said, you know, cut out all -- you don't need to present all the rest of this in the revisions. But I don't think they're opposed to reproviding that.

PANEL MEMBER ARAUJO: Okay. Or an appendix then.

Like the table that you have in slide 15, is that table being part of the -- or would be part of the -- I cannot find it in the --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: This is the one I was thinking of.

PANEL MEMBER ARAUJO: That one, exactly.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We could put this one into the document.

CHAIRPERSON FROINES: We should -- this table is absolutely necessary for this document.

PANEL MEMBER ARAUJO: And maybe with a legend saying or mentioning who is doing this statistical analysis. I mean the statistical analysis done by --

PANEL MEMBER BLANC: Well, that's all their statistical analysis.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, this is all our analysis here, using the Page's trend test.

CHAIRPERSON FROINES: That's what I'm saying it's absolutely essential, because it is their analysis.

PANEL MEMBER ARAUJO: Yeah, that would be certainly helpful.

CHAIRPERSON FROINES: I just wanted to make one -- since I haven't said anything. I've been not saying anything because everybody else has been saying things.

I do want to say that I thought that the revised section -- the comments that you put in tended to be repetitive at times. And so that as you go forward, I think that there's some stylistic issues that one might pay attention to.

PANEL MEMBER BLANC: It's funny you say that, because, just as an aside, when I have to respond to a particularly complex or irksome critique of a journal

article submission, sometimes I'll take their approach and just figure I'm just going to wear the editor down. And I'll say, "As was noted in comment 2 by reviewer 1, here in comment 3 by reviewer 2," you know, blah, blah, blah, blah. But that's irrelevant.

CHAIRPERSON FROINES: So can -- so I think we're ready to move ahead, unless somebody disagrees strongly, in which case I need a --

PANEL MEMBER BLANC: I guess it falls to me because Stan is not here. So I would move that we accept the revised document on the presumption that the further revisions that have been discussed and agreed to here are reflected in the final final version. And I think the -- they're not part of the motion, but I think the transcript will adequately reflect that.

CHAIRPERSON FROINES: Is there a second?

PANEL MEMBER BUCKPITT: I'll second that.

CHAIRPERSON FROINES: Is there a discussion?

All those in favor?

(Hands raised.)

PANEL MEMBER NAZAROFF: Aye here.

CHAIRPERSON FROINES: That's unanimous.

So we have finished caprolactam.

Of course the Panel can take a look at the changes and always come back and reconsider. But in 350

chemicals we've never done that, but it's certainly an option.

So having said, Melanie, do we have some nickel people?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, we do. Andy and Joe Brown.

CHAIRPERSON FROINES: Nickel and dime people.

We had two leads on this chemical, Bill Nazaroff and Ellen Eisen. And so at this point, we'll start out with Melanie and her staff making a presentation.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Joe Brown's going to make the presentation.

CHAIRPERSON FROINES: Just for everybody's knowledge base, we do have written comments from Bill Nazaroff that came in actually yesterday. So that people probably haven't had a chance to read them. But he can go through them as he comments on the process.

Go ahead, Melanie.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Dr. Joe Brown will give the presentation. Joe's going to go over the revisions made to the draft based on Panel comments from the previous meeting.

Joe.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA STAFF TOXICOLOGIST BROWN: Okay. These were the revisions made to the draft after the last meeting. It was I think sent out toward the end of July for the August meeting. So some of the slides here are those that were prepared for that August meeting.

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OEHHA STAFF TOXICOLOGIST BROWN: The first two slides are basically a summary of the revisions that we made. There actually were two substantive revisions; namely, New Acute REL. You remember the old REL based on the Cirla study. It was thought to be inadequate. So actually replaced that with the study of Graham, et al., and in this case supported by a newly analyzed study by Adkins. Both of these are immunotoxicity studies.

CHAIRPERSON FROINES: Can I make one comment?

OEHHA STAFF TOXICOLOGIST BROWN: Sure.

CHAIRPERSON FROINES: Melanie's not in the room but you can convey it. George is here.

I would actually like to see -- before you have this slide, I would have preferred a slide that listed the issues that the Panel raised and then go into what you did. So that you remind everybody who's forgotten -- and I suspect there's more than me. And so think about the

future -- and I'm not talking about it right now. I'm just talking about as a future procedure --

OEHHA STAFF TOXICOLOGIST BROWN: Okay.

CHAIRPERSON FROINES: -- process issue.

OEHHA STAFF TOXICOLOGIST BROWN: Well, I didn't do that here. So I'm sorry about that.

CHAIRPERSON FROINES: That's okay. So make sure that we understand where this came from. That's all I'm saying.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Well, just to recap, there was a lot of discussion about the Cirla study, which is a human study. And it was based on a decrease in lung function, FEV-1. And there was a lot of criticism of it. And it was a study we'd used before. But I think the criticism was just. Then we went back and we just removed it.

And so the backup study to that was the Graham, et al., study, which we now moved up in line to be the primary study upon which we're basing the acute REL. And there'll be another couple of slides about this down the line.

But I'd just like to summarize the various revisions that we did make. We also replaced the 8-hour REL. This was based on suggestions from NiPERA that the NTP study on lung lesions would probably be a better basis

for that. And we sort of agreed, and so we actually adopted their suggestion for that.

We put in a new section on physical and chemical properties affecting toxicity. This was suggest by Dr. Glantz I think. This sort of ties together issues like particle size, density, and solubility and how they might affect the toxicity in the nickel particles.

We had a new table on solubility and solubility products of nickel compounds. We expanded a section on the uses and sources, including a new table on environmental airborne nickel.

We put in a new section on various air pollution studies of nickel as a species of particulate matter.

We revised the sections on epigenetics, both animal and human data and also on nickel-induced cardiovascular effects, both human and animal data.

And we added a new section on lung injury. This was sort of speculative. But I think we took some of the suggestions from Dr. Froines. I think he had some interesting ideas there and we tried to tie those together with what we could find in the literature supporting some of these ideas.

There's a new toxicity summary table. It doesn't include all of the toxicity studies, but it concludes the major studies. It's in the appendix. It's in sort of

chronological order as you go through the text. The sort of key toxicity studies are in this appendix table, which is quite large.

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OEHHA STAFF TOXICOLOGIST BROWN: We revised and extended the rationale for deposition based on -- the deposition-based DAF, or the dosimetric adjustment factor, for the chronic RELs. And generally we tried to add where possible particle size information on studies throughout the text. There was a criticism that we weren't putting this in. And Dr. Nazaroff felt this was very important and we should have it on all studies. So we went back, looked at all the studies, tried to dig out that information and stick it in parenthetically in the text.

We added new articles to the table on genetox. And an additional rationale for inclusion in noncancer assessments of this information basically on ties between DNA damage and cardiovascular effects and other noncancer effects. And there's an article by Cooke, et al., which brings some of these things together.

Overall we added 48 new references to the document supporting these various revisions. And we tried to reorganize the document by moving and combining text for improved intelligibility. For example, in the revision the immunotoxicity's all now in a separate

section. I'm not sure how successful this was, but at least we gave it a shot.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. The acute toxicity. Now, here we are now using the Graham study. You've seen this study before. It was originally used as the key study for the 8-hour. Now we're using it for the acute. Six-week old mice exposed to various levels of nickel chloride, less than three micrometers diameter, for two hours.

The exposed animals gave a significant decrease in antibody-forming cells after antigen challenge. I think they used sheep red blood cells as the challenge. And there were some levels quoted in here. We actually did a benchmark analysis on this using the benchmark of a loss of a hundred plaques per million cells. And we got a benchmark of approximately 165 micrograms of nickel per cubic meter.

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OEHHA STAFF TOXICOLOGIST BROWN: And I think there's a slide here which shows that benchmark analysis showing the benchmark and the lower bound on it for these data.

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OEHHA STAFF TOXICOLOGIST BROWN: The derivation

of the acute REL is a little bit different than for the 8 hour. We are essentially using an overall cumulative uncertainty factor, because this is now an animal study and not a human study, of approximately a -- of about a thousand for this study. So we have a benchmark of 233 micrograms of nickel per meter - this is a 1-hour adjustment - divided by a thousand is .2 grounded micrograms of nickel per cubic meter.

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OEHHA STAFF TOXICOLOGIST BROWN: The supporting study for this is new. It was mentioned in the document before, but it wasn't analyzed as such. So this is now a study by Adkins, et al., ('79) for increased mortality in nickel-treated mice after experimental infection with Streptococcus pyogenes. So we're looking at mortality as an endpoint here.

Exposure is 289 to 499 micrograms of nickel per cubic meter. It's a nickel chloride aerosol. Less than 1.4 micrometers diameter for two hours.

We analyzed this with benchmark dose, using a 1-hour adjustment, at a value of 733. Using the same overall uncertainty factor of a thousand gives us a final value of .7 micrograms of nickel per cubic meter for this.

And the dose response is shown on the next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: This is the benchmark dose response where in this case the benchmark is a doubling of mortality. You can see it there, the background is about 3 1/2 and the benchmark is at 7. And the lower bound on that is shown there in the lower vertical line.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. The 8-hour value now is also new. This is now based on NTP (1994), which -- well, we're supporting it with the Graham study, which we've previously used as the main study.

The study population here is male and female rats.

Exposure: Inhalation of nickel sulfate aerosol six hours a day, five days a week. In this case, 16 days to 2 years. We actually used a 13-week data for this derivation.

The effect is lung lesions, primarily alveolar proteinosis.

And here we used a NOAEL of 30 micrograms of nickel per cubic meter; and using a human equivalent, a continuous value of 5.7.

An overall uncertainty factor of 100 gives a value of .06 micrograms of nickel per cubic meter.

Now, the previous value was .08 for this. So

it's not much of a change, although the study is a more robust study.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay.

CHAIRPERSON FROINES: What's the rationale for the square root of 10 for the interspecies?

OEHHA STAFF TOXICOLOGIST BROWN: Yes, I think that's -- the reason we used this instead of 10 was the MPPD model we used for the deposition modeling. We figured that that took part of this kinetic component away. So I think that's the rationale for that. Although it's not really stated there, is it?

CHAIRPERSON FROINES: Say that again. I'm sorry. I missed it.

OEHHA STAFF TOXICOLOGIST BROWN: We use a computer deposition modeling, the MPPD2 model for deposition of the particles in the respiratory tract. And we reasoned that that in part took care of a kinetic component of the difference between humans and animals.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It's a standard provision in the guidelines that where we have what we consider an appropriate kinetic model, we can replace the kinetic subfactor for -- one of these uncertainty factors with that model. So it's several of the derivations you will see that in the

absence of the model we have an interspecies extrapolation uncertainty factor of 10. But if we have what we consider an adequate model, then we take away the kinetic component. So the interspecies uncertainty factor is the remaining square root of 10, which represents the toxicodynamic uncertainty.

OEHHA STAFF TOXICOLOGIST BROWN: That's how we view it. But, you know, it's open to argument certainly.

CHAIRPERSON FROINES: I must admit I'm a skeptic that it wipes out the toxicokinetic side of the coin.

But let's let it go. I don't want to hold you up.

OEHHA STAFF TOXICOLOGIST BROWN: I think -- well --

CHAIRPERSON FROINES: It's a stretch, I think.

OEHHA STAFF TOXICOLOGIST BROWN: It's somewhat of a stretch, but -- I think we discuss in the document, you know, our thinking on this a little bit more about, you know, where this toxicity takes place, you know.

Anyway, we think deposition is a key component in what's going on here, as opposed to uptake and capitalism and so on. The effect is in the lung. I think deposition is a key process going on here. So the modeling of the deposition is a key kinetic component. That's the way I view it anyway.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So in other words if this were a systemic toxicant and we only had dosimetric adjustment, we would not completely abolish the kinetic side of the equation. But in this case, it's essentially site of contact toxicity that we're talking about. So there's not metabolism distribution excretion to worry about.

CHAIRPERSON FROINES: Well, it also -- the issue of size distribution is not irrelevant to this in the discussion.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We consider the size information in the analysis, you know, in the analysis of the NTP study. The problem of course is that, you know, prospectively we don't have size distribution information at the other end. But, you know, what we don't know about, we can't deal with.

OEHHA STAFF TOXICOLOGIST BROWN: No.

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OEHHA STAFF TOXICOLOGIST BROWN: The chronic values have not been changed. So these slides you've seen before. You know, they're basically the same studies, same values.

For nickel compounds except nickel oxide we're also using basically the same study, discontinuous

inhalation of nickel sulfate.

CHAIRPERSON FROINES: Can I say one more thing about this?

OEHHA STAFF TOXICOLOGIST BROWN: Sure.

CHAIRPERSON FROINES: And then I'll stop --

OEHHA STAFF TOXICOLOGIST BROWN: Do you want me to go back to the other slide?

CHAIRPERSON FROINES: The problem is we have used from the time life on the planet occurred the interspecies factor of 10. There is by no means any guaranty that 10 is an adequate number. It could be much larger, in fact. And so when we start to take its square root of 10, when you actually could have a factor that -- there is literature suggesting that that's not sufficient -- 10 is not sufficient. So that that's where I get a little bit nervous, because there's a contradiction between the literature that says the uncertainty factors are underestimated versus the literature that says, like your guidelines, where you can take a square root of 10 for the reasons that you said.

But go ahead. That's just --

OEHHA STAFF TOXICOLOGIST BROWN: Well, you know, in fact we've taken the alternative view on intraspecies, as you can see from the slide.

But, yeah, you've got a good point. You know, we

frequently are criticized for overestimating these uncertainty factors. And I think where we have a model and an effect that we believe is the key effect, I think we're justified in reducing that. On the Other hand, I see your point.

But, anyway, this is still a draft. We'll consider it again.

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OEHHA STAFF TOXICOLOGIST BROWN: As I said, the chronic values have not changed. So the value for nickel except nickel oxide is the same as before. We used a benchmark dose here. We have an average experimental concentration of 5.4 micrograms of nickel per meter and an equivalent human concentration of 1.4 based on the deposition model.

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OEHHA STAFF TOXICOLOGIST BROWN: And with a cumulative uncertainty factor of a hundred, again using the square root of 10, but also 30 for intraspecies, we come up with the value of .014 micrograms per cubic meter. We think this is a pretty conservative number, health protective sense.

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OEHHA STAFF TOXICOLOGIST BROWN: For the chronic REL for nickel oxide, we're using here a mouse study from

the same NTP group of studies.

Critical effect here was also changed in the lung. Have a benchmark dose of 117 micrograms per cubic meter based on 5 percent alveolar proteinosis; average experimental concentration of 20.9; human equivalent concentration of 2. This is based on Hsieh, not on the MPPD model; so there's actually a published study on this. And the same overall cumulative uncertainty factor, 2 divided by 100, .02 micrograms of nickel per cubic meter for this value.

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OEHHA STAFF TOXICOLOGIST BROWN: Now, the oral value is the same as before, based on NiPERA study. And the endpoint is perinatal mortality in a two-generation study. LOAEL of 2.23 milligrams of nickel per kilogram dye. NOAEL of 1.12. Human equivalent, 1.1.

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OEHHA STAFF TOXICOLOGIST BROWN: And basically the overall values:

.2 for the acute. Originally this was 1.1 based on a human model. Now it's .2 based on the animal data.

The 8-hour REL, .06. Originally it was .08. Not much of a change, but the study's changed.

The chronic values are the same - .014, .02. And 11 micrograms per kilogram dye, based on the same -- it

had the same basis as our drinking water PHG, so it's basically the same study.

And that's about it that I was going to present.

You know, I didn't go through the comments -- I mean I tried to address as many of the comments I could in the time I had before the document was due to be sent out again in July.

But certainly we have a pile of additional comments from Dr. Nazaroff that we can address in our continuing revisions.

CHAIRPERSON FROINES: Well, because I think -- I'm not sure, but I think the Panel hadn't seen this before today. So I think that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Nobody's seen it before today. It was written yesterday.

CHAIRPERSON FROINES: I understand that. That's my whole point.

PANEL MEMBER BLANC: Not blaming us.

CHAIRPERSON FROINES: I'm just saying that -- Paul understands.

So what I would propose is that Bill comment at this point so that we have the benefit of his insights.

PANEL MEMBER NAZAROFF: Okay.

CHAIRPERSON FROINES: Well, wait, wait, wait.

Andy is raising his fingers.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Just one very small point. I wanted to point out, before it may cause any confusion, on page 107 of the documents, the derivation of acute reference exposure, we actually spotted a typographic error for the BMR uncertainty factor. We accidentally wrote square root of 3 when we meant square root of 10. That was a case that we -- yeah, we use either 3 or the square root of 10. Unfortunately we kind of -- we kind of got our wires crossed there. So it should be --

CHAIRPERSON FROINES: Yeah, I didn't catch that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, neither did we until about a week ago.

Burt I just intrude that point in case it causes somebody to wonder what's going on.

CHAIRPERSON FROINES: So, Bill --

PANEL MEMBER NAZAROFF: Yeah, I'm here, John.

CHAIRPERSON FROINES: -- go ahead.

PANEL MEMBER NAZAROFF: So first I guess mea culpa in my capacity as lead -- one of the leads with Ellen that I did get an updated version of this document several months ago and it just sat on my to-do list, near the top but not reaching the top until this meeting was

imminent. And so the -- it would have been more orderly, I'm sure, had I sent the comments that I've provided in months ago. But I did the best I could and that's what I could do.

So what I'd like to do with your indulgence is just take the time to read through orally the first couple of pages of my written remarks, not the detailed ones, because I think they do speak to broader issues about the current state of this draft REL, and I think it's appropriate for the collective to hear them. And it will take ten minutes at most.

So what I write is:

"I appreciate the effort that went into making revisions in response to the comments on the earlier SRP review draft. The document is clearly improved.

"Among the five concerns that I had raised in the earlier round of comments, strong improvement is evident for four: The environmental chemistry of nickel, the importance of particle size for respiratory tract deposition, environmental exposure to nickel, and environmental epidemiology. The residual concerns on these points are relatively minor."

Although I'll inject an editorial here that I

didn't write, which is that the sort of laboratory-based studies that involve environmental chemistry of nickel I think need some more clarification. And I'll get to that point in this summary.

I go on to write:

"On the other hand, I do not see significant improvement with regard to one of the concerns originally expressed, which was 'flow, balance, and connectivity in the narrative.' And here's the original critique on that point.

"An Old saw applies: "Tell 'em what you're going to tell them, tell 'em, and then tell 'em what you told them.' This report could be improved in the 'tell 'em what you were going to tell them' aspect. The sections describing health effects often dove into paragraph-length recapitulations of individual studies with little connecting tissue between the paragraphs and no preamble to guide the reader through the material.

"I was struck by the contrast: 70 pages of dense pros presenting extraordinary detail about individual studies of acute and chronic effects of nickel followed by only a few paragraphs each

supporting the REL derivations. The connection of the latter (the part that matters most in this document) to the former could be improved. Especially the decisions to base RELs on the particular studies selected could be much better substantiated.

"In reading the revised draft (which I did prior to reviewing my earlier comments), the original concern resurfaced without significant attenuation. Between page 30 and page 106, especially starting at page 36, the dominant style is paragraph-length summaries of numerous separate studies with little to connect them either to a larger conceptual framework or, more importantly, to the ultimate goal of substantiating the derivations of REL values. On the positive side, the paragraphs are mostly clearly written. They're also logically clustered into sections and subsections. There are also very brief narrative summaries that attempt to synthesize the material in each section. But overall, I found that these sections did not efficiently advance my understanding of the foundation for setting RELs.

"The most important sections of the document,

those that present the derivations of the acute and chronic RELs, are compressed into 14 pages. Here the text is terse, even telegraphic in places. Out of the hundreds of studies reviewed in pages 30 through 106, fewer than 10 are selected as points of departure or in support of specific REL development. The rationales for these selections are not transparent. Why were these particular studies chosen and why were all the others not chosen?

"To summarize this point, while I'm impressed with the scope of the literature that has been reviewed, I find that the evidence presented is not effectively marshaled for the purpose of scientifically substantiating the derivation of REL values. The development of the RELs is the primary purpose for this document. The present draft overemphasizes the goal of summarizing all of the scientific literature on nickel health effects at the expense of clearly explaining and substantiating the bases on which the RELs were developed.

"A second important technical concern emerged from this review. This concern relates to the environmental chemistry of nickel. When

exposures are established in laboratory systems to insoluble nickel through means other than particle inhalation, it seems that the size of the particles would remain a key factor to report. Yet that information is largely, maybe entirely, missing from the present draft. I'm referring here to cases in which laboratory animals were exposed to insoluble nickel species through ingestion or installation, or in which cell cultures were exposed to insoluble nickel species.

"In a few cases, the exposure levels are expressed in molar units, seemingly inappropriate for a hydrosol. In other cases, the dosing is expressed in mass or a mass density such as micrograms per square centimeter, or mass concentration units, but the particle size is not reported.

"As an example, given the conceptual representation for genotoxicity shown in Figure 2, it seems that particle size could be key for insoluble species effects. The number of cells that could be influenced by nickel would be related to the number concentration of particles in suspension, which would depend on particle

size for any given mass concentration. Engulfment of particles into cells seems like a process that should be particle-size dependent. Dissolution of nickel from the particle surface could be kinetically limited for low-solubility species. And if so, then the surface area of the particle could influences the biological effect. There are numerous instances in the text where this specific concern would apply. Examples" -- and they occur on page 69, page 75, page 89, page 90. I haven't listed nearly all of them. But they concern species such as Ni_3S_2, which I guess is nickel subsulfate -- subsulfide, Ni_2O_3 and NiO.

"A related concern is the use of the oxidative state, NI(II), to designate the species of interest in any particular study. Since Ni(II) can refer to nickel in several different forms, including the ion, NI2+ and the solid nickel oxide, for which distinct RELs are proposed, the document should be chemically specific wherever possible."

So I go on and offer some specific comments. But these specific comments are really relatively minor by comparison to these two major overall points.

And let me just say, in summary, that I think the document could with reasonable effort be improved to a point where it would allay my concerns on the second point, the technical point that I've raised. It would just require going back and making revisions that are parallel to the kinds of revisions that took place between the earlier draft and the one that we're currently looking at.

I'm less clear about what to recommend with respect to my first concern. And I raise it in part because I think it's a generic -- potentially a generic issue for how OEHHA thinks about preparing the REL documents. I really -- you know, if this was a student's dissertation chapter, I'd send them back to do a rewrite, because it doesn't do an effective job in meeting the primary goal, which is to explain to the reader the scientific justification for why the particular studies that were used to support the development to the RELs were used -- were selected, why other ones were not, what analysis that led to the REL derivations was. I know there's text to those points, but that text is very concise to the point of not really being clear. And there's a lot that's in this document that really probably ought to be in an appendices rather than in the core document itself, because it's not there to support REL

development directly.

So that's the end of my comments. Thanks, John.

CHAIRPERSON FROINES: Well, I'm tempted to ask Melanie to comment. But before that, maybe we should continue with the Panel.

Bill has obviously raised substantial issues.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Would you mind if I just said a few things?

CHAIRPERSON FROINES: Well, let me just make -- let me say, given what Bill has said, are there members of the Panel who want to comment at this stage?

PANEL MEMBER BLANC: I was just going to ask, if Ellen was prepared with her comments, then it would help me put -- if Ellen would make her comments, it would help me put them both into context together and then it might clarify questions.

CHAIRPERSON FROINES: I thought Ellen didn't have comments.

PANEL MEMBER EISEN: Well, I do now.

CHAIRPERSON FROINES: You do now. Okay.

PANEL MEMBER EISEN: I mean I didn't actually look at it in advance. There wasn't much epidemiology in the document last time, and I -- so what I had to prepare last time was rather thin. But I see you have added more epidemiology this time and reviewed some of the

environmental literature. And looking over it now, I mean, I just think it does help to underscore Bill's point, because although you now have a paragraph-by-paragraph discussion of some of these large epidemiologic studies, there's no attempt really to put them into the context of the RELs that you've proposed. And it may be that you can't do it; maybe that the way that they've analyzed their data and described their results make it impossible for you to do that. But then that ought to be said.

And I don't know that that's really -- you know, they used interquartile ranges a lot as the unit of analysis and they look at change in outcome per interquartile range in nickel, for example, exposure. So it may be not so straightforward.

But I do find that it doesn't really help. It doesn't help build the case for what you're proposing. And it just seems a little too, I guess, glibly summarized to say that you can't use it because there are multiple air pollutants.

That's all.

CHAIRPERSON FROINES: I think nobody else wants to speak at this point.

So, Melanie, we're going to need you to --

CHIEF MARTY: Yeah, I think -- well, a couple points.

If you'll recall, those that have been on the Panel a long time, the REL documents used to be pretty short. And we kept getting asked to add more and more and more into them because it was hard for you guys to review it if you didn't happen to already know literature on that chemical.

So, you know -- for a lot of chemicals there isn't very much literature. Caprolactam was one example. For nickel there is a ton of literature. So we started out not putting everything in there and we just keep adding. So I think that's part of -- you know, sort of a mechanical problem of then not summarizing enough to make the reader understand why that material is even there to begin with.

So, you know, that's one issue which we can deal with by having more expansive summaries.

One of the other issues is, you know, we're -- we look at the studies; we look at whether the dose response information is usable; we look for the most sensitive gender site in the body, so toxicological endpoint species, et cetera, when we're doing the study.

If we have human data, we tend to -- and this is all in the Technical Support Document, which, you know, you guys probably haven't read in a long time. But it,

you know --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Which is appendix.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

So I think, you know, part of the issue is reviewing something so huge. You have the TSD, which is a different document. And, you know, unless you keep going back and forth and reviewing that, it's hard to know why we're doing what we're doing. So a couple of things.

So that's -- for the overall flow, balance, and connectivity I think, you know, that's fixable.

For the particle size distribution used in the study --

CHAIRPERSON FROINES: Can I ask you a question about what you just said.

Are you suggesting that one of the things that you can do is to provide a context based on -- not just on your -- see, what bothers me is is you say, "Well, we have these guidelines." Well, that's all well and good, and we -- and this Panel approved them. But it seems to me that rather than saying they're in our guidelines, what would be useful would be to give the contextual framework for the RELs so that what then follows makes sense to the reader who's looking at publications.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, that's right. And, you know, one approach you could take for a document that ends up getting so big, like nickel - and there's a few other coming down the pike which are going to be big - is to use the appendix approach and put all the technical summaries in the appendix and have something more integrated up front than the REL derivation, then all the rest of this stuff in the appendix. So that's another approach that would help with the readability or, as Bill puts it, the connectivity.

CHAIRPERSON FROINES: Ellen wants to --

PANEL MEMBER EISEN: Can I make another suggestion? I'm just now looking through the epidemiology section again as you were talking.

So you have in here studies of wheeze, with studies on birth weight, with mortality studies, and they're all sort of mixed together. So I mean it makes sense what you just said, that you'd want to pay most attention to studies of the most sensitive endpoints. So then you just dismiss all the mortality. We don't need to look at mortality studies, right? It's like irrelevant really. So then, you know, say that and get rid of them instead of mixing them all up.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH

CHIEF MARTY: Yeah. Here's an example.

And, you know, if you remember from this last time --

CHAIRPERSON FROINES: Can I make --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I'm sorry.

CHAIRPERSON FROINES: Let me make a comment.

I just want to -- as far as I'm concerned, you can have a huge number of studies. At one point I wrote a standard for lead for OSHA. And what we did was we had hundreds of studies to deal with. And we had to select the ones that could form the basis for the standard. So that might not be a lot of studies. But what has to happen is that the ones you select as the basis for your decision making, it needs to be explained so everybody can understand that.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right. So that's, I think -- you know, we have a little bit of that in here, but apparently not enough, because people couldn't follow it.

And in terms of nickel as a component of ambient PM, you know, I think we discussed last time whether or not to even put that in here, because, you know, it's clear that the speciation -- the epidemiology on particulate species is not all that well developed and

there's still a huge issue with confounding by all of the other substances present in PM.

CHAIRPERSON FROINES: Well, if we --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So we did not want to use those studies as the basis of reference exposure levels.

CHAIRPERSON FROINES: Well, we have an issue, right? If you have nickel as a component of ambient PM, then you have to deal with reactive oxygen species and oxidative stress. If you have a particle of nickel, you may have a different mechanistic issue that you have to address. So that it's actually complicated, it seems to me.

And Paul knows more about nickel as nickel than I do. But I know something about nickel as part of ambient air.

Do you have a comment on that?

PANEL MEMBER BLANC: Well, I think what all of you are saying is true and consistent with other attempts to deal with some of these things that, for example, have a literature that can't be applied to the question at hand. And, thus, everybody's really discussing what's the most efficient way to handle a summary of the literature. And I think you've been in this situation before where you have to give enough of a nod to the issue so that the

reviewer and the reader knows that it's not like you don't know there's nickel in ambient particulate pollution. But beyond that, there's -- you know, we've chosen -- here are five studies that document that, but we haven't chosen to utilize that literature because obviously there's no study of ambient pollution which can tease out nickel's effect alone.

And sometimes you face that with these documents where you have to say at least enough so that the absence of the information doesn't raise the question, "Are these people even aware that there's" -- you know, "that they consider that there's nickel in ambient dust?" And I think -- you know, so some of that could be shortened, not need to be moved to an appendix nor not moved to appendix. It can be just, you know, greatly shortened, enough so that it's like: There's a lengthy literature on ambient pollution -- ambient particulate pollution and it's been shown in other studies. You know, give the citations. We won't be analyzing it beyond that because it can't be teased out from co-pollutant effects and cannot be used to derive any standard in terms of end-organ toxicity. It's interesting to note that there have been associations with particulate pollution and blah, blah, blah, you know, or not.

So I suppose in your cardiovascular disease

section, which you added since one of the big issues with ambient, you know, particulate pollution is its relationship to adverse cardiovascular outcomes, that would be an example of something you could say. You know, "Please see our experimental section which talks about cardiovascular effects." And I think that that's a logical way.

And I think another thing that would help even if you didn't move summaries to an appendix is -- even the order in which these summaries of studies are presented is not necessarily straightforward. It doesn't seem to be temporal. You're not going in chronological order necessarily, I don't think. Although I'm not sure. Maybe you are. But, for example, with the -- and this may be addressing Bill's point as an example. In the chronic REL derivation, in the animal studies, you know, halfway into the animal studies you get to the animal study that you use for the REL. Is there a reason why that's midway in the animal studies? Or it's just how this thing grew and then you decided that that's --

OEHHA STAFF TOXICOLOGIST BROWN: Chronological.

PANEL MEMBER BLANC: I don't think there's a logic to doing it chronologically. Well, I don't think it's necessary. In fact, what it means is that since people tend to be more skeptical the older the study is in

terms of the methods, there's no reason not to start with a study which you think is the key study and then do the studies that you think are --

OEHHA STAFF TOXICOLOGIST BROWN: There's a certain historical mechanics to this. We generally treat the animal, then human, and acute, subchronic --

PANEL MEMBER BLANC: No, that's not the part I'm -- I'm talking within section. I understand that part. But let's say you're within chronic and --

OEHHA STAFF TOXICOLOGIST BROWN: Within the section, okay.

PANEL MEMBER BLANC: Within the section and then you're within animal studies of chronic. And then somewhere in the middle of that is this key study that you end up using now.

OEHHA STAFF TOXICOLOGIST BROWN: Generally we try to arrange them chronologically within the section. But that's not absolutely the case. So sometimes something gets inserted somewhere where it probably doesn't belong.

PANEL MEMBER BLANC: Right. So I'd suggest reordering it. I'm assuming this is an end note. So if you change where things are, you don't make your life completely miserable.

OEHHA STAFF TOXICOLOGIST BROWN: Well, as I said in the presentation, there's been some reorganization of

text, which tends to jumble things up a little bit too, even though we try to compact --

PANEL MEMBER BLANC: Right, right. So, anyway, that would help and would address this issue of synthesis. Because then the reader sees all the rest of the studies relevant to chronic toxicity in light of the study which is ultimately the study you use.

OEHHA STAFF TOXICOLOGIST BROWN: We try to put enough studies in there that indicate that we have done a --

PANEL MEMBER BLANC: Oh, no, I agree with that, absolutely.

OEHHA STAFF TOXICOLOGIST BROWN: -- review. So connecting these things together sometimes is a little bit difficult.

PANEL MEMBER BLANC: No. No, no, I see that, and that part doesn't bother me and I understand the motivation for that. As I said, you need to show enough that somebody knows that --

OEHHA STAFF TOXICOLOGIST BROWN: Did the due diligence --

PANEL MEMBER BLANC: Right, right. And some of that you can do with tabular forms.

And so I think that that's one partial solution that doesn't address all of Bill's critique, but it would

help.

CHAIRPERSON FROINES: Well, I was talking to somebody in the rear of the room, so I missed the beginning of what you said. But Bill should comment, because one thing that I felt in looking through -- in going through the document was just the list of one study after another. And it's sort of like it's a series of almost abstracts, and therefore it doesn't provide the underlying basis -- it provides a lot of information, but it doesn't really provide the underlying basis for how you reach REL conclusions.

OEHHA STAFF TOXICOLOGIST BROWN: Well, in some of the studies you'll see an analysis attached. For example, you see a study described and actually analyzed the data, did a dose response analysis on it. Maybe that's a red flag if that study's going to be used later on or could be used in a derivation. If there's no analysis, it's basically a supporting study of the type that we're using to show you should look to the main issue --

CHAIRPERSON FROINES: Well, I think that -- let me just -- I really think we don't need all the studies. I think they -- a lot of them could be in an appendix. I don't know what Paul said, so I'm maybe repeating him.

OEHHA STAFF TOXICOLOGIST BROWN: Well, it was about the organization.

CHAIRPERSON FROINES: But I think that what you need is the studies that form the basis for the decision and the underlying reasons for that basis.

PANEL MEMBER BLANC: Well, you know, there's a hierarchy. So there's the study that you use for the REL. And then there are studies which are looking at similar endpoints and for which you've done some analyses and you get a REL which is within half an order of magnitude of what you came to with the study that you picked. And then there are studies which can't really be used for any kind of REL because of their nature, for one reason or the other, but in fact it's the same endpoint, and so it's supportive. And then there are a bunch of studies of other endpoints that are clearly not as powerful studies or not as sensitive an endpoints, and those studies certainly can either be just presented in a table with the kind of tables that you do for some of the stuff already appears that way or it can be an appendix or whatever.

I think the stuff that shouldn't be in an appendix would be the studies with similar endpoints or supportive exposure effects.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I'm feeling guilty --

CHAIRPERSON FROINES: Wait, wait. No, wait. Let me just stop you, because I interrupted Ellen, who was

trying to get in.

PANEL MEMBER EISEN: No, no. We're all -- I feel like we're all sort of saying the same thing.

CHAIRPERSON FROINES: So Ellen's next and then Kathy's next and then you're next.

PANEL MEMBER EISEN: Okay. I'll just say my next same thing -- my way of saying the same thing is that I think what you just said about how if you exceed the response table, that's a red flag. I think we shouldn't have to rely on red flags. I think you should be explicit, like this is a study we're going to pay a lot of attention to, you know, and here's a dose response table, right? And let us know what -- and then let us know what are the supporting studies. That's all.

CHAIRPERSON FROINES: Kathy.

PANEL MEMBER HAMMOND: I would say, first of all, I actually have shared this concern for a long time, that it makes it very difficult to read these documents. It's one of those things I've dealt with. But I actually think that this meeting isn't the place where we should be discussing this. I really feel this is not the appropriate way for us to design and editorialize how to do this. But if -- and I know that there are a lot of things that go into how things are done. They have to do with history, they have to do with what you've been asked

to do by prior SRPs, they have to do with what's probably legally required. A lot of things that are kind of -- that we could have a whole meeting on this and we could -- if we want to do that, fine. But I would really like to -- I suggest that, yes, it might be great to have this improved, but could we not take this meeting time to do that and work on science.

CHAIRPERSON FROINES: Well, let me just make a proposal in that respect.

Obviously these folks have to go back and work on nickel. So they need to hear from us what we think about that issue. So that's what you're saying let's focus on. I agree with that.

I would argue that in the next meeting that we have an agenda item on the process of how we should recommend that they approach these issues, recognizing that we all -- that we suffer from our own negligence insofar as we approve their guidelines, but their guidelines don't go to the questions really that are being raised here today, I think. I think we're -- the process issues that were being raised today are a little bit different than the guideline issues.

So I would propose that we defer this, as Kathy said, till the next meeting, but the next meeting we actually have a discussion about it.

PANEL MEMBER BLANC: You don't mean defer nickel; you mean defer the issues that have come out of --

CHAIRPERSON FROINES: It's the process issues.

PANEL MEMBER BLANC: Yeah. And I don't -- by the way, I agree with Kathy in that. That's why I think my comments were, you know, things that could be done with a word processor in ten minutes and I wouldn't -- not ten minutes -- probably ten hours, but I wouldn't -- it wouldn't keep me from, you know, science-based content approval that -- and actually I think that Bill's critique, as I interpret it largely, was not also an indication that ultimate conclusions weren't appropriate scientifically. It wouldn't be like we'd say you have to bring this revised document back to us again the way we said last time, that it would also be a sort of contingent approval, but please clean this up in the following, you know, generic ways.

But --

CHAIRPERSON FROINES: Isn't that a question for Bill?

PANEL MEMBER BLANC: That's my interpretation. I'd like to hear whether Bill thinks I've misinterpreted what he said.

PANEL MEMBER NAZAROFF: No, you haven't. But let me just make a couple of observations from what I've been

listening to.

I think if we go back to your previous comments, Paul, you expressed really quite well one way to organize this document at the subsection level that would allay my concerns.

And just to hit what I remember as the high points, instead of having a chronological sort of paragraph-by-paragraph, every-study-treated-roughly equally approach, as is currently done, the subsection could begin with a paragraph or two -- actually what I think it needs to begin with is sort of a preamble paragraph that says, "This is sort of the nature of why nickel is a concern for this particular health endpoint and," you know, "here are some specific examples of things that we're going to be telling you about now that have been studied and some things that maybe haven't been studied."

And then it would have a paragraph or two that would highlight what the main study that supports the REL development teaches us, it would have follow-up with the studies that provide good support, and then very brief synopses -- they don't have to give us, you know, blow-by-blow account of every exposure condition and every other detail, just a sentence or so or maybe even just a listing of the other references that were considered or

the other types of studies that were considered, and some comment about why those were not selected, why those were judged not suitable.

While I agree with the point Kathy made that, you know, we're not using meeting time to do editorial decision making, is inefficient and ill-advised, I think this issue goes to a more fundamental concern though, which is the scientific justification for REL setting. And if that point is substantially obscured, which I find it to be in the current -- in this current document, then it's harder for me to be in a position where I'm ready to support the answers.

And so I think I am ready to support, but I ended up having to spend an awful lot of time reading this document a second time for things that seem to me not important that I understand in order to know why OEHHA is proposing REL values at the particular levels that they are.

And I think that attention to everybody's efficiency, yours, OEHHA's staff, in writing these documents; ours, as an SRP, in reading, reviewing carefully and ultimately approving them; and then the people who are ultimately going to do something with them on the other end, you know, that behooves us to be attentive to making the communication as efficient as we

can make it, even at the expense of spending some committee time to talk about it.

CHAIRPERSON FROINES: Well, you are raising substantial issues. But in your most recent comments, your issues were reflective of what Paul commented on. And so, what I need as a chair is to hear whether or not you feel that you can go forward with an approval with changes or whether you think that there's still major issues that need to be addressed.

PANEL MEMBER NAZAROFF: And I would be comfortable going forward with a recommendation that, you know, OEHHA do what they can as best they can to address the comments that I've expressed; and with a little bit stronger comment that in the future, you know, we really need to have them take - at least this is my opinion - need to have them take quite seriously this issue of using the document as a place, not first and foremost to review every detail of -- or summarize every key detail of every scientific study relating to the toxic concerns of a particular chemical, but to focus the text on what reviewers and the general public need to know to understand the basis on which they're proposing to set RELs, the rationale for that, where the scientific support comes from, where the uncertainties lie, and so fourth.

CHAIRPERSON FROINES: Thank you.

Melanie.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I think that's eminently doable. And as you guys were talking, I'm thinking of the other group that I also supervise, which produces the recommendations for the ambient air quality standards. And there again is another huge literature for the -- the particulate matter for California's ambient air quality standards, that my group sends ARB the recommendations. And we take a massive literature and condense it. So, you know, that's another good model I think of a way to do this.

So I would hope that we could come back to you in a few months with a document that's formatted more like those, so that you don't have to wait through all -- excruciating detail of all these studies.

CHAIRPERSON FROINES: Well, I actually think there's an interesting issue here. And, that is, on the one hand you are developing regulations or recommended regulations, whereas here we're basically approving risk assessments. And those are different. Those have different criteria that we end up using in making decisions. And so on the assumption that a REL isn't just a number that somebody has to think about, but that the REL has implications for control of a substance, that it's probably very worthwhile to think about the linking of the

two programs you deal with in terms of the underlying context.

PANEL MEMBER BLANC: You know, another -- just moving around sections, word processing thing that might help too. You know, bearing in mind that this thing grew, are you sure that subsections of subsections are always where it makes the logical sense for them to be? For example, you know, these cardiovascular studies of, you know, I expose a rat for four hours and look at its, you know, R to R interval, you know, it's not clear to me why some of those are in chronic and then some were in acute. I can see why it might have happened. But can you just go back and take a look, especially if this is in a program that's not going to entirely mess up all of your referencing numbers.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, sure.

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, sure.

PANEL MEMBER BLANC: And then a science-based question. And I might have lost track of this somewhere along the way. These RELs are supposed to be noncancer endpoints, right? So that's why there's no cancer here even though nickel was a carcinogen?

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: And is that said explicitly at the very beginning, that there is a separate --

OEHHA STAFF TOXICOLOGIST BROWN: There's a statement there upfront.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I believe --

PANEL MEMBER BLANC: All right. You might want to say it more than once or something. It just -- because I think people are going to expect -- you know, are going to remember that.

Then I know you very kindly put in the physical stuff about nickel carbonyl, even though it's not included here. Again, for the same rationale, as I say, well, what about nickel carbonyl, isn't that nickel? And then you said it won't -- you said that the nickel carbonyl data won't enter into this REL, and also nickel oxide --

OEHHA STAFF TOXICOLOGIST BROWN: I could put it in that table somewhere.

PANEL MEMBER BLANC: -- has its own REL or something. Is that what you said?

But you mean that nickel carbonyl also has an REL -- or will have an REL or something -- or should have an REL.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It doesn't --

OEHHA STAFF TOXICOLOGIST BROWN: An REL --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We haven't dealt with it.

PANEL MEMBER BLANC: So it's not clear -- so the reason that nickel carbonyl will not be discussed further in this document is that it operates in an entirely different kind of way and it's in separate literature, right?

OEHHA STAFF TOXICOLOGIST BROWN: Exactly.

PANEL MEMBER BLANC: But how am I supposed to know that? It just says, "With the exception of nickel carbonyl." Again, it has to do with who reads this as -- are they going to understand what you understand why it is? It's like five words, but just -- you know. Because I wasn't sure when I read that. It's a "period, In addition, nickel oxide has a separate chronic REL." Does that mean that nickel oxide in addition to nickel carbonyl has a separate -- no, that's not what you mean.

OEHHA STAFF TOXICOLOGIST BROWN: No, that's not what --

PANEL MEMBER BLANC: All right. So just --

OEHHA STAFF TOXICOLOGIST BROWN: Maybe we should clarify that.

PANEL MEMBER BLANC: -- clarify that.

Now, A more fundamental science question. Your

chronic REL's based on alveolar proteinosis?

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

PANEL MEMBER BLANC: In the rats, right?

OEHHA STAFF TOXICOLOGIST BROWN: Rat and mice.

PANEL MEMBER BLANC: Or rodents or whatever --

OEHHA STAFF TOXICOLOGIST BROWN: Rodents.

PANEL MEMBER BLANC: So what is your view of alveolar proteinosis as a medical or toxic endpoint?

OEHHA STAFF TOXICOLOGIST BROWN: Well, I think it's a valid endpoint.

PANEL MEMBER BLANC: Well, yeah. I mean that's not --

OEHHA STAFF TOXICOLOGIST BROWN: It's serious.

PANEL MEMBER BLANC: What do you think it is as a genre of condition?

OEHHA STAFF TOXICOLOGIST BROWN: It's related to inflammation, isn't it?

PANEL MEMBER BLANC: Well, I mean people don't really know. It's not exactly pulmonary fibrosis, right?

OEHHA STAFF TOXICOLOGIST BROWN: Well, I mean it's a histological reading, you know, from a pathologist --

PANEL MEMBER BLANC: Well, it's also a fatal disease in humans. So I think it's worth saying that it's --

OEHHA STAFF TOXICOLOGIST BROWN: It's a serious effect.

PANEL MEMBER BLANC: Well, it's a fatal disease, I'm just saying. It's a life-threatening, often, mostly fatal.

But the second thing is that in humans it's identical to acute silicosis.

OEHHA STAFF TOXICOLOGIST BROWN: Really.

PANEL MEMBER BLANC: But that's a minor piece of what the disease is. Most of the disease in humans is immunological. It's related to a very odd antibody. It stays -- it's kind of -- it's considered idiopathic nobody knows why people get it.

So the three points I would make is, one -- and I think you alluded to the fact that you're viewing this as an immunological as well as a --

OEHHA STAFF TOXICOLOGIST BROWN: Yes, I mean they're related in a way. I mean --

PANEL MEMBER BLANC: Right. So I think that's good and important. But then when you get to your section on immunological endpoints, you never say, "We've already dealt with alveolar proteinosis, which we consider an immunological endpoint." Then you talk about all this other immunological stuff.

Two, I think you have to say that there is a

condition -- it is a condition that occurs in humans, is life threatening, and in a subset of humans is related to a occupational environmental exposure, right?

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Yeah, that's good. We'll do that.

PANEL MEMBER BLANC: And do you feel comfortable though with the -- again, this is a benchmark derivation, right? So you feel comfortable with a .05 traditional thing?

OEHHA STAFF TOXICOLOGIST BROWN: That's what we've been -- that's what we've been using for animal data. For epidemiological data we'll generally go lower, maybe a percent.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The convention is in choosing the benchmark response rate to choose a response rate which is within the range of observable data. And then if we feel that the -- for instance, if we have some concerns about, you know, variation in sensitivity or severity at the endpoint, then we would -- we would use uncertainty factors to reflect those extra considerations. But the key thing --

PANEL MEMBER BLANC: Rather then the benchmark?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The key thing is that the benchmark needs

to be chosen on the --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Use the BMDL of 1, Andy, from this data.

OEHHA STAFF TOXICOLOGIST BROWN: So we did use 1 percent --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, I'm sorry. That's the supporting.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's the supporting study.

Yeah, for the NTP study, the .05 was the one which was --

PANEL MEMBER BLANC: And why did you use a .1 on --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, the supporting study is an epidemiological study.

OEHHA STAFF TOXICOLOGIST BROWN: Larger number of animals.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And in that context, the .01 is within what we consider the observable range of the data. So we in that case chose the one so that the driving consideration for choice of benchmark response rate is the range of observable data. But then we --

PANEL MEMBER BLANC: And then you used the

traditional tenfold animal to human and tenfold --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We actually use -- for the nickel chronic REL based on the NTP study, we used an interspecies of -- where we used a dosimetric adjustment factor based on the deposition model. We used an interspecies of the square root of 10 to account for interspecies toxicokinetic extrapolation -- sorry -- toxicodynamic - excuse me, I'm crossing my words here - the toxicodynamic uncertainty, which is not addressed by the deposition model. And then we in fact used intraspecies uncertainty factor of 30, which reflected -- which has a large -- has tenfold uncertainty factor for toxicodynamic because of our concern for severity of endpoint, potential diversity including adverse impacts on children and so on.

And then we used a square root of 10 toxicokinetic for intraspecies. Because although there is uncertainty there, again we have some information and it's basically a point of contact effect.

So the opportunity for diversity is not so great that we would necessarily go for a larger uncertainty --

PANEL MEMBER BLANC: So the total comes out to be --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- 100.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- a 100.

PANEL MEMBER BLANC: So it's as if you did 10 and 10 in the end?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. It becomes -- it's 10 and 10, but in --

PANEL MEMBER BLANC: For different reasons?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- it's actually for -- in different places it's root 10 and 30.

PANEL MEMBER BLANC: So, Bill?

PANEL MEMBER NAZAROFF: Yeah, I'm here. I have the mute button on.

PANEL MEMBER BLANC: Was all of that okay with you?

PANEL MEMBER NAZAROFF: Actually I wasn't following super closely the uncertainty factors because that's not an area that I understand very well. But the rest of it was fine.

CHAIRPERSON FROINES: I just had one comment.

I read your mechanism section, the new section. And I have some trouble with it. I don't -- I don't think it's quite right. And so -- but I'll put it in writing for you.

OEHHA STAFF TOXICOLOGIST BROWN: Make some suggestions --

CHAIRPERSON FROINES: Yes.

OEHHA STAFF TOXICOLOGIST BROWN: Make some suggestions for us and we'll try to improve it.

CHAIRPERSON FROINES: I'll put it in writing. So I'll give you a layout of what --

OEHHA STAFF TOXICOLOGIST BROWN: We got your memo originally and we tried to write something based on your suggestions.

CHAIRPERSON FROINES: Well, I didn't know if you'd gotten stuff about signaling trans-pathways and transcription factors and inflammation as a result.

OEHHA STAFF TOXICOLOGIST BROWN: There were a couple of articles we found. But if you have some other articles that --

CHAIRPERSON FROINES: Well, we have a whole bunch of articles.

OEHHA STAFF TOXICOLOGIST BROWN: I think we could flesh that out and it would be very useful. Thanks.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We could always make the document longer.

PANEL MEMBER BUCKPITT: Right.

OEHHA STAFF TOXICOLOGIST BROWN: Yes, it would make it longer.

CHAIRPERSON FROINES: Not really.

PANEL MEMBER BLANC: So is the genotoxicity stuff that's in here, since you're not considering cancer endpoints, that's a residual of something that we decided on in the appendix and you have to cover that, that's by fiat?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, we don't consider the relevance of genotoxicity findings to be just as a predictor of cancer. We are concerned about if it was an indicator of other kinds of damage and precursor of other source of damage as well.

PANEL MEMBER BLANC: Like?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, one --

PANEL MEMBER BLANC: Other than reproductive toxicity in --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, that was one of the first examples I was going to point to.

PANEL MEMBER BLANC: Well, other -- they have a section on reproductive toxicity. So they --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Developmental and reproductive.

PANEL MEMBER BLANC: Yeah. So why isn't it with

that?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, because it's a different class of experimental data, I suppose. And it has relevance for other things besides. So we conventionally have listed it --

PANEL MEMBER BLANC: Okay. So it's just convention.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- as a separate category, because it has implications for several -- potential implications for several --

PANEL MEMBER BLANC: So, you know, it may be something that you just use as a canned language every single time you do one of these then. But apropos of this sentence at the beginning which says, "We're not going to be considering. This is the noncancer endpoint document." Then at the very beginning of genotoxicity a sentence --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It wouldn't hurt us to have some boilerplate to that effect.

PANEL MEMBER BLANC: Yeah, you know --

CHAIRPERSON FROINES: A sentence that says, "Well" --

PANEL MEMBER BLANC: -- "even though we're not

considering cancer endpoints, we believe genotoxicity is relevant for other endpoints which are relevant. And even though reproductive toxicity, which has already been discussed separately, is a prime example, there may be others such as premature death," --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- immunotoxicity.

PANEL MEMBER BLANC: -- or whatever you want to say.

CHAIRPERSON FROINES: Well, do you really think that's true. I think --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: -- it operates by a binding with proteins and not with DNA, so that --

OEHHA STAFF TOXICOLOGIST BROWN: Gene expression.

CHAIRPERSON FROINES: I mean are we --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I wouldn't want to bet that it wasn't that -- or might not be.

CHAIRPERSON FROINES: No, I understand that argument. But --

PANEL MEMBER BLANC: I was making a generic -- if that's their generic reason to have genotoxic sections in noncancer endpoint documents, so it would be nice to have

a little introduction every time they do it that's pretty much the same. That's all.

CHAIRPERSON FROINES: Yeah, but I would argue a little differently. I would argue that what we need in these documents are justification for the science that we use to set the RELs. And if you've got a genotox that you sort of throw in and says it may have some relevance, I'm not convinced that's not a wasted effort.

And so that unless I understand the relationship between the decision making that goes on and the genotoxicity, then it seems to me the genotoxicity isn't appropriate, unless you think it has a function that you could describe as a basis for how you make your decisions.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Can I just briefly --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I'm not sure we could describe any of the mechanisms as the reason we choose a study for the REL derivation. I think we have it in there because of the interesting information to understand the toxicity of the chemical in general. But it's not something that's driving our choice of, you know, the NTP study, for example, or, you know, the chronic animal study.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We do have a little paragraph on page 80,

which is our initial attempt at providing some sort of background justification for what we have in this sense.

PANEL MEMBER BLANC: Oh, I see, I see, I see, yeah. Yeah, yeah.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So if you have any recommendations as to how we should beef up or either generalize or particularize that, they would be very welcome.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I mean nickel is a chemical that produces all different kinds of toxicity. It's a really fascinating chemical. So, you know, it's hard to know where to stop when you're --

PANEL MEMBER BLANC: No, I think that's -- that's the kind of thing I was thinking of. That's okay. And I got it now. I'm sorry I missed that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And I think -- we certainly take the point that something like that is a generic requirement.

PANEL MEMBER BLANC: Yeah, yeah.

PANEL MEMBER NAZAROFF: John, let me make a comment here too, just to be sure that my comment overall isn't misunderstood.

I don't even need for the document to be shorter. I just need for the information that's presented to be

structured in a way so that there is this kind of connectedness that explains why the studies that are being reviewed -- we have to go back to the transcript - it's getting late in the day here for me here in Washington - to what Paul described as kind of the essence of going from a series of abstracts, which is in essence what major sections of the core of the document are now, to something that's a more reflective, synthetic, coherent explanation of what individual studies collectively tell us about and don't tell us about nickel as an environmental toxicant, as a basis for setting the RELs.

So I don't mind if, you know, the genotoxicity stuff is in there. I found the mechanistic discussion of the way that cytotoxicity may behave really interesting and informative, even though it didn't connect directly to an REL. That was fine to read that. The part I have trouble with is when I have sort of paragraph after paragraph of, you know, for several pages, of a material that's under one subheading without enough synthesis to kind of help me put the thing into a broader context.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think that if we follow the suggestion of how we order the material and preface it with an explanation of why -- what we're looking at and why we chose the key studies as what they in fact are, I hope

that will address that consideration.

PANEL MEMBER NAZAROFF: I think that will go a long ways. And I think the other kind of key point that I heard in the discussion today was to not treat every study that's in the literature with equal weight.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So the back-end we can leave it in tabular format.

PANEL MEMBER NAZAROFF: Yeah, a very terse summary or concise summary of what the -- without reporting to us all of the exposure detail, for example. If you didn't use the work for the REL, we probably don't need to know every single kind of exposure condition that was investigated in any particular study. So even if the studies were -- I mean they could be summarized in a table, they could be summarized in a sentence each, or they could just be a list of references that are under the general heading of "Additional Work has been done in this Area."

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. We can pull that together based -- using the table we have as our appendix as the starting point.

PANEL MEMBER NAZAROFF: Right.

CHAIRPERSON FROINES: I still have significant

problems with the genotoxicity and the mechanistic section, and I will communicate with you. Because if you're talking about hydroxyl radicals under Genotoxicity, that should be in your Mechanism section because that's where you talk about oxidative stress. So you've got supporting information. The genotoxicity isn't -- the relevance of it isn't genotoxicity, it's hydroxyl radicals reacting with macro molecules.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We can certainly include a cross-reference, as it were, to that effect.

PANEL MEMBER BLANC: Can I ask something about also - this is a science question - about alveolar hyperplasia, and -- I'm sorry, not alveolar hyperplasia -- alveolar macrophage hyperplasia, and what that is generally viewed as being in the pathological literature. I don't remember that as an endpoint that came up recently in -- a toxicologic key endpoint in one of your studies. You know, we do a lot of things where it's epithelial hyperplasia.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I would assume that hyperplasia -- the macrophage hyperplasia would reflect some kind of inflammatory response. And I would imagine it's a marker of that.

PANEL MEMBER BLANC: What do they -- is the NTP study such that they don't actually have a discussion of the implications of the --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: They're not always very good about implications. You know, they tend to name things very systematically and carefully and just leave it at that. But we can --

PANEL MEMBER BLANC: The reason I why I bring it up as a science-related point is -- and it comes again back to Bill's overarching comments -- is that it makes you wonder about alveolar proteinosis. Although that supposedly is a dysfunction of the alveolar -- actually I don't if people know. It might be also macrophage driven as opposed to alveolar-lining-cell driven.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: There's a number of things that might be dysfunctional that could contribute to that, both in the macrophages and also of course potentially I guess damage to the capillaries as well.

PANEL MEMBER BLANC: It doesn't -- well, I don't know, because it's a disease where there's this accumulation of fluid in the alveolar. And the source of that, it's proteinaceous. That's why it gets its name.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: So It's essentially -- it's interstitial fluid, is it?

PANEL MEMBER BLANC: It's worse than that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Worse than that.

PANEL MEMBER BLANC: So I think it's worth some kind of cursory review of the pathological issue, because if you were convinced that -- it's an odd term too -- if you were convinced that pulmonary macrophage hyperplasia is an early lesion that in some systems is seen before you see alveolar proteinosis or something --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: We could research whether we could -- you know, if we find --

PANEL MEMBER BLANC: It was just seeing the word "hyperplasia," you know, makes you think, well, are they talking about some kind of pre-cancerous lesion, because that's how hyperplasia's often looked.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes. In the case of the macrophages, one's immediate thoughts go to some sort of inflammatory context rather than that. But that I think is specific to the macrophages, and there are many other hyperplasias.

PANEL MEMBER BLANC: Yeah, and especially because you're using -- it wouldn't matter if you weren't using it

as the endpoint in the 8 hour. But since you are and since chronic is this other condition for which alveolar macrophages may play a role, I just don't know if anybody --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, we explore whether there's a --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Connect the dots.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Connect the dots there. Yes, we should do that.

CHAIRPERSON FROINES: Can I -- are you done?

PANEL MEMBER BLANC: Yes, I am.

CHAIRPERSON FROINES: Thank you.

My concern at this point is that Jesús and I have a 5:30 plane to Los Angeles, so time is getting a little tight. Although it's not very far to this airport obviously.

So that doesn't -- that's not intended to cut off conversation. But it's just intended to hopefully have people sensitive to it.

So let me go around the room and see where we are at this point.

So, Alan.

PANEL MEMBER BUCKPITT: I didn't have a lot to

say on this. It is an extensive document obviously, and I think it could be trimmed down. But I thought the basis for the standards was clear.

PANEL MEMBER EISEN: I have nothing else.

CHAIRPERSON FROINES: I didn't mean to cut people off. I'm sorry if I did.

PANEL MEMBER HAMMOND: I think there's some very interesting scientific questions that have been raised today. I don't know how far -- nickel is an area, as you said, that has huge amounts of data. And I think there's some very interesting challenges. And I like Paul's and John's comments about ways we could look at these in more detail. I don't know if that's what we want to do as a committee. I mean there's a lot to be said for that scientifically. But that would be another meeting and a lot more work.

And then if we are going to go forward and do this again, I do think it's a good idea to have some organization structure, as Bill has recommended, where we would at least have a page that summarizes what the key things are or which studies you should really pay attention to as the rest are being reviewed.

CHAIRPERSON FROINES: Yeah, I think there's agreement on -- generalized agreement on that.

PANEL MEMBER HAMMOND: But I do -- I think

there's plenty of good science in here to go forward as it is. But if we want to extend that science, that's a question that -- as Paul and John have suggested, that's a question we have to as a committee decide.

CHAIRPERSON FROINES: Yeah. Well, I mean for me as a person who does mechanism, I of course want as much mechanism in the document as possible. But that doesn't necessarily mean that it should -- it should be there.

I knew you were hinting at that.

So I think we can work this out without too much of a problem.

PANEL MEMBER ARAUJO: I don't really don't have much to add.

I think there is a lot of very good interesting data. And you have already said that it is more descriptive than a synthesizing document. And Bill properly mentioned it very well in his first sentence of the "Tell 'em what you're going to tell them, tell 'em, and then tell 'em what you told them."

(Laughter.)

PANEL MEMBER ARAUJO: A couple of suggestions, one for the document and maybe the other for the future.

This could be a good opportunity of really, as you're going to be going through the exercise of reviewing the whole data, determining what are the studies that

support the REL, what are the studies that made you -- do you need to say less and reorganize and reordering, that maybe there could be some sort of like a -- I don't know how to say -- like a manual or allegory of things that for future documents that it says, you know, what are the things that need to be covered and in what order? And they're in future documents, and so we pay attention that we're covering all those.

Like in your case that you're calling product to be checking on each one of the studies where you're spending a lot of time describing it. Does it really need to be described to this extent? Is it really supporting this REL or not, you know? And sort of like have this close in mind whenever we are to approach another topic.

CHAIRPERSON FROINES: May I make a suggestion?

A lot of the issues we've been talking about today are not necessarily -- or they're not related to the guidelines that we approved. But there are people here who are new to the committee, and it would be useful if they had copies of the guidelines so at least they know what's being discussed when the board guideline comes up.

So it would be good if you guys could send --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We actually sent them out.

PANEL MEMBER ARAUJO: It is possible, yeah --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We can resend them out. We had -- I can't remember if it was for the January meeting or the May meeting. But we did realize, wow, these guys have never seen this.

CHAIRPERSON FROINES: Oh, well, then forget it. Forget it. Forget it. That mean we'll put the burden on the people who have received them.

PANEL MEMBER ARAUJO: No, we receive a lot of material. We probably didn't have the chance of going through everything.

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll send the link again.

PANEL MEMBER ARAUJO: Those are the binders and manuals and --

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll send the link again. They're on our website.

PANEL MEMBER ARAUJO: I'm not talking about a binder, John. I'm just talking about a piece of -- a sheet.

CHAIRPERSON FROINES: No, no, I knew what you were talking about. I specifically started out by saying I wasn't referring to what we've been talking about, so there was no confusion. Because we've been talking about

process as opposed to guidelines. And so I stand corrected, that -- because I must have gotten them too.

(Laughter.)

OEHHA AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, in response to what Jesús just said, I think this is -- nickel is a -- it's one of the -- absolutely one of the longest ones we've done for a -- not -- this is not toxic identification -- toxic air contaminant identification document. Those are gigantic. But this is the longest REL document I think we've ever done, and so it's a little bit out of the box that way.

But we can use this one as a prototype for the next chemical that comes along that's got a big literature like nickel. So I think, you know, we can use it that way.

CHAIRPERSON FROINES: It's interesting, George and I spent an afternoon together talking about how do we improve the SRP's activities vis-a-vis OEHHA. And one of the things that I recommended is dealing with classes of compounds rather than individual compounds. And so that will come up at some point in the future. So that the -- and Lynn Terry from ARB wants to talk about how to improve the activities of the SRP. So there are some issues that George and Lynn Terry are going to raise about what goes on. And so that should be pretty interesting for us to

communicate to the Panel and potentially discuss.

PANEL MEMBER ARAUJO: One additional comment. And I don't know if it is something that needs to be necessarily in the document somehow or if it is more like a forward discussion. But it would be helpful when you present in the elite study or the main recent what you are taking or proposing one decision or another, that you very briefly summarize the context of the other pertinent studies and why you chose that study. Because what I -- what I've seen is that just -- I imagine that is the most representative, maybe the best. For one reason or the other, it will be good to have -- to know the reason. Because in addition to the study that you have chosen, I imagine there are priority in other studies that show different results or maybe negative results on those.

CHAIRPERSON FROINES: Thank you.

You know, everybody's talking about the future as though this meeting's over.

And it's not. We actually have to vote.

PANEL MEMBER BLANC: So let me just say that nothing that I said should be interpreted as deferring a decision on the document, in essence, today. I think it's all stuff that I can -- I would feel comfortable tentatively, you know, approving -- contingently approving the document on the presumption that good effort will be

made to do those changes, almost all of which will really relate to reordering existing parts with, you know, altogether I think what's been described as probably not more than two or three pages of text --

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER BLANC: -- new text for you.

So I'm happy to move that we approve it.

CHAIRPERSON FROINES: Second?

PANEL MEMBER HAMMOND: Can our leads make the motion?

PANEL MEMBER BLANC: Please.

Bill, are you there?

PANEL MEMBER HAMMOND: I would feel happier if the leads made the motion, because they know the document best.

PANEL MEMBER NAZAROFF: How about if I just second the motion that Paul made, because he expressed it very well.

CHAIRPERSON FROINES: So we now have to go back and take Buckpitt out of the picture and --

PANEL MEMBER NAZAROFF: You can leave Alan -- I didn't Alan. So I'm seconding thinking that there was no second.

CHAIRPERSON FROINES: There wasn't. He did caprolactam. So --

PANEL MEMBER NAZAROFF: Oh, I see what you're saying.

CHAIRPERSON FROINES: So following Kathy's model --

PANEL MEMBER NAZAROFF: Yeah, yeah, yeah.

CHAIRPERSON FROINES: Anyway --

PANEL MEMBER BLANC: Stan wasn't here.

CHAIRPERSON FROINES: Because Stan wasn't here. That was why.

PANEL MEMBER HAMMOND: Well, at least --

CHAIRPERSON FROINES: Anyway, I'm joking. I shouldn't.

So all in favor?

(Ayes.)

(Hands raised.)

CHAIRPERSON FROINES: Unanimous.

Thank you very much.

And I think we can have a motion to close, unless there's further discussion.

PANEL MEMBER HAMMOND: I so move.

CHAIRPERSON FROINES: This is your turn. You always make these motions to close.

PANEL MEMBER HAMMOND: No, I want to hear Alan chime in.

Why don't you second the motion to adjourn.

PANEL MEMBER EISEN: I'll second the motion.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: I didn't give you a chance for discussion. But I think nobody really wants it.

PANEL MEMBER BLANC: Are we adjourned? Mr. Chair, are we adjourned?

CHAIRPERSON FROINES: We're adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 3:54 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, 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, James F. Peters, a Certified Shorthand Reporter of the State of California;

That the said proceedings was taken before me, in shorthand writing, and was thereafter transcribed, under my direction, by computer-assisted transcription.

I further certify that I am not of counsel or attorney for any of the parties to said hearing nor in any way interested in the outcome of said hearing.

IN WITNESS WHEREOF, I have hereunto set my hand this 9th day of November, 2011.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063