MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

MILTON MARKS CONFERENCE CENTER

AUDITORIUM

ADMINISTRATIVE OFFICE OF THE COURTS

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JAMES F. PETERS, CSR, RPR
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APPEARANCES

PANEL MEMBERS

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Jesús A. Araujo, M.D., Ph.D.

Paul D. Blanc, M.D.

Alan R. Buckpitt, Ph.D.

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S. Katharine Hammond, Ph.D.

William W. Nazaroff, Ph.D.

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:

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Dr. Daryn Dodge, Staff Toxicologist

Mr. Brian Malig, Staff Toxicologist

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

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

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PROCEEDINGS

CHAIRPERSON FROINES: Okay. We have a quorum. In fact, everybody on the Panel is here. And so we are going to open the May 3rd Scientific Review Panel meeting. The first person who will be speaking will be Melanie Marty from OEHHA, who will take up caprolactam.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Good morning.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: So at the last meeting we -- staff went through the caprolactam Reference Exposure Level derivation. We received comments from the lead, Dr. Paul Blanc, and also from Stan Glantz met with them regarding one of the studies and potential statistical analysis of some of those data.

I'm going to have Dr. Daryn Dodge, to my left, give the presentation on what we ended up doing, which you all have seen now. And also at the end of that presentation, the Chair asked us to have some slides responding to some of the material that are industry stakeholders sent directly to the Panel. So we have several slides on some of those issues.

So, Daryn.

OEHHA STAFF TOXICOLOGIST DODGE: Thank you,

Melanie.

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OEHHA STAFF TOXICOLOGIST DODGE: For a little review, caprolactam is a monomer used in the manufacture of Nylon-6. Production is, according to US EPA, 1 billion pounds or more in 2006, but it's probably the same in 2010 as well. This is the most recent data that they had.

Seventy-five percent of Nylon-6 is used in fibers, carpets, rugs, clothing, et cetera. The other 25 percent is used in making films, such as films that are used to wrap meat at the supermarket for instance.

Emissions can occur from caprolactam production, and the manufacture, use, and recycling of Nylon-6.

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OEHHA STAFF TOXICOLOGIST DODGE: Now this is a list of the major changes we were asked to consider at the last meeting. The major one here at the top is we changed the procedure for rounding REL values. This caused a bit of a discussion last time, and Dr. Nazaroff sent in some comments which we used, and we'll discuss here in a moment.

Another change is we have no recommendation for the acute REL now, and I'll go into that as well. We also added some details to the document. One of which was detailed to our review of some studies. Specifically, we

included some material for the chronic rat -- or the subchronic rat study, which is used as a basis of the REL for 8-hour and chronic REL. We also added detail from the Ziegler acute study chamber exposure of humans, and the Ferguson and Wheeler occupational study.

We added a section on occupational standards as requested. And this includes what information I could find for the derivation they used from NIOSH and the ACGIH and their occupational standards for caprolactam.

We added summaries of additional studies to provide a more complete picture. Now, this includes oral studies and dermal sensitization studies, many of which weren't published, but they're in there and they provide a more complete picture of the toxicity of caprolactam.

We also added details on caprolactam aerosol particle size information that we could find in the exposure implications.

And lastly, we added pathology findings and conclusions regarding upper respiratory irritant effects.

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OEHHA STAFF TOXICOLOGIST DODGE: For fixing the rounding problem that we discussed at the last meeting, let's first go into what we had discussed at the last meeting.

The 8-hour and chronic REL values were rounded to

one significant figure. And the conversion factor between micrograms per cubic meter and parts per billion is 4.63. But with rounding to one significant figure, we have a seven-fold difference between the micrograms per cubic meter and the parts per billion regarding the -- for the 8-hour REL. For the chronic REL, it's a four-fold difference.

And these rounding errors are mainly due to -- with regard to the 8-hour REL, rounding to a 1 as shown in -- with 1 parts per billion, because this can introduce up to a 50 percent error, because you're not sure whether you're rounding between 0.95 and 1.5 or rounding between 0.5 and 1.5.

So Dr. Nazaroff kindly sent in some suggestions, which we are using for our proposed REL values.

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OEHHA STAFF TOXICOLOGIST DODGE: So we decided we'd use two significant figures when the first digit is a 1 or a 2 to reduce the introduced error from rounding. Using this procedure we now have a five-fold difference between micrograms per cubic meter and parts per billion conversion. And we have a 4.4-fold difference between the micrograms per cubic meter and parts per billion conversion.

PANEL MEMBER GLANTZ: I don't understand why

there's such a big difference, though, because the parts per million to mass conversion, isn't that pretty precisely known? I'm confused. I don't understand.

PANEL MEMBER HAMMOND: Are you confused between 5 and 4.4.?

PANEL MEMBER GLANTZ: Yeah. I don't understand.

PANEL MEMBER HAMMOND: Because of the rounding.

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OEHHA STAFF TOXICOLOGIST DODGE: Well, let's go back and look how we rounded. For the 8-hour REL, we rounded from 6 -- you know, rounded up from 6.7. However, when we converted to parts per billion, we rounded down to from 1.446 --

PANEL MEMBER GLANTZ: Wait. I'm sorry. Are you talking about the ratio between the acute and the chronic?

OEHHA STAFF TOXICOLOGIST DODGE: Yes, the ratio. I'm sorry.

PANEL MEMBER GLANTZ: I'm sorry. I was totally confused. Never mind. No, I think that's fine

OEHHA STAFF TOXICOLOGIST DODGE: We have now no acute REL recommendation following our last meeting. Originally, we had a draft REL based on the occupational study by Ferguson and Wheeler. However, with limitations from this study, which we agree with the Panel, there was a number of them we decided it was just not strong enough

information to base a REL on.

Now, if you recall, this was a study in which 4 of 5 workers experienced transient nasal irritation at 10 parts per million. They were exposed briefly for a few minutes to an uncontrolled emissions source. Now, there was only 5 participants per concentration. This is a limitation, though not a deal killer. However, the uncontrolled emissions source in fact was, because we don't know how much it was varying. They had no standard deviation to explain what the variation was, though they mention in their paper that there was some variation in the concentration the participants were exposed to.

There is only a LOAEL for this study, no NOAEL. And the measurement method used was antiquated. Now, it is a method used in the seventies fairly extensively, but it's -- you know, the accuracy of the measurement methods now are much improved.

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OEHHA STAFF TOXICOLOGIST DODGE: The acute study limitations of the other major acute study by Ziegler, et al., is that when all was said and done all we could establish is that there was a free standing NOAEL in this study. Without a LOAEL, we cannot establish any sorts of REL derivation.

In the human chamber study, the participants were

exposed to 0, 0.15, 0.5, and 5 milligrams per cubic meter of caprolactam for 6 hours.

They looked at both subjective and objective measures. Subjective measures were 29 questions placed in 7 subgroups. One of those subgroups was odor, in which there was 4 of the 29 questions. This was the only questions that showed a statistically significant trend. And the other individual questions and subgroups, there was no trend and no statistical difference between, for example, the high exposure group and the control group.

The other problem was that symptom questions were not independent. A number of them were asking the same questions -- a number of these questions were asking the same thing in a different way, in other words.

There was a total symptom score that was elevated at 5 milligrams per cubic meter, but this appeared to be almost certainly odor driven, because the 4 odor questions were in there. We don't know what -- how significant it would be if you removed the odor questions, because we don't have the individual data here.

Now, the objective measures, there were only non-significant trends. The objective measures were eye blink, nasal resistance, and eye redness.

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OEHHA STAFF TOXICOLOGIST DODGE: We were asked

to apply a Friedman test to the Ziegler data, and specifically the data that showed a trend. And here this is a ranking procedure, in which you give ranks to each of the concentrations.

Now, the main study measures here are the ones that were in the study itself. It's blink frequency, redness -- or eye redness, nasal resistance, and eye and nasal irritation scores. Most of these were median values. And as you can see, there was a pretty good trend for some of these values. Now, when you combine all of this --

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OEHHA STAFF TOXICOLOGIST DODGE: -- you find a significant difference in the ranks by concentration using the Friedman test. There's also the Page trend test we applied, and this also showed a significant difference in the trend.

However, the limitations are that the Friedman test is normally applied only to individual data and we were applying it to summary data, the medians in other words. And it ignores the distribution and variance.

Now, if we could get a hold of the raw data, we would be more than glad to reevaluate it using this test.

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OEHHA STAFF TOXICOLOGIST DODGE: For the 8-hour

and chronic RELs, we used the 13-week rat study by Reinhold, et al. This is a bit of a review. The exposures were 6 hours per day, 7 days per week. Concentrations they were exposed to were 0, 24, 70 and 243 milligrams per cubic meter.

PANEL MEMBER GLANTZ: You mean 5 days a week, right?

OEHHA STAFF TOXICOLOGIST DODGE: Five days. What did I say 7?

PANEL MEMBER GLANTZ: You said 7.

OEHHA STAFF TOXICOLOGIST DODGE: Sorry.

During their second week of exposure and through the rest of the remaining exposure period, there was a treatment-related increase in labored breathing, nasal discharge during exposure. There was also moist rale sounds heard in the animals during exposure.

At sacrifice, after 13 weeks, there was a treatment related increase in nasal and laryngeal or laryngeal tissue lesions. From this information, we found that the LOAEL was 24 milligrams per cubic meter. There was no NOAEL.

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CHAIRPERSON FROINES: May I ask you a question?

OEHHA STAFF TOXICOLOGIST DODGE: Yes.

CHAIRPERSON FROINES: I had considerable

difficulty with this aspect of the discussion -- of what you concluded. Maybe I'll wait till we hear you finish. But I'm looking at table 5, and I have considerable difficulty with your finding of a LOAEL of 24. And so let's come back to that.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. The Panel asked us to include some information from the study that wasn't in the previous draft. And this is one of the tables we included. This is the pathologists grades from that study.

One of the questions was about the age-related effects that we're seeing in the nasal mucosa. And this table shows that in the 0 parts per million or the control group.

In the nasal respiratory and olfactory mucosa, you see that in the control group minimal to slight changes in the respiratory mucosa. And in the olfactory, minimal changes. Nearly all the animals were showing these effects.

However, with exposure to caprolactam, there's an increase in these lesions with regard to both severity -- as its concentration goes up, there's more animals showing severe effects. In other words, if you look at the first row for the respiratory mucosa, we have the moderate grade there, where none of the animals in the control group are

showing a moderate grade for the lesions, but it goes up with exposure concentration.

So this is the information we used from the nasal mucosa. For example, the moderate lesions is what we used for benchmark dose modeling.

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OEHHA STAFF TOXICOLOGIST DODGE: So when you subtract out the age-related nasal effects that you saw on the control animals, you see a nice dose response. And this information is what we use for our benchmark dose modeling.

Now, I should point out the laryngeal tissue did not show age-related effects in the control group, even though it can happen. Apparently, the animals weren't old enough to show this effect yet in the control group or this particular strain of rat doesn't show it.

CHAIRPERSON FROINES: Let me just raise a question for the discussion later. But you have minimal, slight, moderate. And in some cases minimal and slight have controls having effects. So that the question of what do you consider minimal or slight to represent seems to me to be a highly relevant question? And let's come back to it.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

CHAIRPERSON FROINES: I would not agree that 5

should be there is what I'm saying.

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm.

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PANEL MEMBER BLANC: Five?

I'm sorry. I don't understand that comment.

CHAIRPERSON FROINES: Five and 20 -- out of 20 for laryngeal tissue.

PANEL MEMBER BLANC: Oh, because you're discounting -- you're discounting minimal change in the --

CHAIRPERSON FROINES: I'm discounting minimal.

PANEL MEMBER BLANC: So there wouldn't be any effect at all is what you're saying. I don't think I would take the same view, but we can go back to it.

CHAIRPERSON FROINES: Well, but there needs to be some consistency across those 3 criteria. And the question is, is there consistency?

PANEL MEMBER BLANC: I guess it depends on technically when you did your mathematical derivations from this, how did the 3 separate categories come into play? In other words, did you then say -- did you then add them together? Where you did a benchmark with this -- I'm sorry, you did --

OEHHA STAFF TOXICOLOGIST DODGE: Yes, benchmark dose modeling on each of those endpoints.

PANEL MEMBER BLANC: Separately?

OEHHA STAFF TOXICOLOGIST DODGE: Separately.
PANEL MEMBER BLANC: And did they all yield the same estimated thing --
OEHHA STAFF TOXICOLOGIST DODGE: Yeah.
PANEL MEMBER BLANC: -- or you then took the average of the 3 estimates that you got?
OEHHA STAFF TOXICOLOGIST DODGE: We went with the laryngeal findings, because they didn't have these age-related background effects to worry about, even though that may not be an issue, and because it gave us the lowest benchmark dose --
PANEL MEMBER BLANC: So you felt it was the most conservative.
OEHHA STAFF TOXICOLOGIST DODGE: -- point of departure.
PANEL MEMBER BLANC: Okay.
OEHHA STAFF TOXICOLOGIST DODGE: Though it wasn't much different than --
PANEL MEMBER BLANC: All right. Well, I guess what we should do probably just for the sake of clarity is let you finish your presentation, then come back to the points that seem to be more confusing or more --
CHAIRPERSON FROINES: There's also a fundamental question about benchmark, which is when Crump, for example, wrote his first paper about it, he talked about

the benchmark as being in the range where we have experimental data. And it's not just -- and the question is whether this criteria is actually met in this evaluation.

OEHHA SUPERVISING TOXICOLOGIST MARTY: This is Melanie. I'm going to address that. The benchmark dose modeling is a way to curve-fit your data. And you do do some extrapolation below the range of the data. That's exactly one of the points of doing it.

CHAIRPERSON FROINES: I know, but the benchmark -- Crump's benchmark paper argues that the closer you can get to actual experimental data, the more justified it is. And if you're making large extrapolations, then the benchmark approach is not much different than a NOAEL/LOAEL approach.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, in fact, generally, we're not doing large extrapolations for noncancer effects. So most of the time when you look at a benchmark dose model of the data, your BMD -- the lower bound on your benchmark dose for a 5 percent response rate is relatively close to the no effect level on a study. But the beauty is you don't have to argue over what's a no effect level, what's a low effect level if you model the data using the benchmark dose. You're just choosing a predicted 5 percent response rate as your point of

departure, rather than choosing a NOAEL or a LOAEL, which are subject to the investigator's chose of dose for example. You're also including sample size and all of the data points when you model the data with a benchmark dose, rather than just choosing a LOAEL or a NOAEL as your point of departure.

CHAIRPERSON FROINES: Let's go on. My concern is primarily how do we look at minimal and slight versus moderate, and whether or not that it's justified to include minimal and slight.

PANEL MEMBER BLANC: Well, let's come back to that.

OEHHA STAFF TOXICOLOGIST DODGE: Well, here, in fact, is a benchmark dose figure, which we show at the last meeting. This is for the laryngeal lesions. Point of departure we used was 3 milligram per cubic meter. This is the 95 percent lower competence limit at the 5 percent response rate. And that's shown in the lower left-hand corner there where that is on the curve.

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OEHHA STAFF TOXICOLOGIST DODGE: So a summary of the chronic 8-hour RELs. There is no REL derivation changes from the previous draft. Point of departure is the same, 3 milligrams per cubic meter. After application of dose and time adjustments, and uncertainty factors, the

proposed RELs are 7 micrograms per cubic meter for 8-hour and 2.2 for the chronic.

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OEHHA STAFF TOXICOLOGIST DODGE: We added some additional material, as I mentioned at the beginning. One of these was an interesting oral study in dogs by Hazelton Labs. Dr. Blanc asked us to look at and see what Hazelton had done. In effect, they did do this 90-day study in dogs. It's unpublished, but there is quite a bit of information there. And they essentially found the same effects as the chronic study that NTP undertook in rats and mice. And that the major finding was a reduction in weight at a specific exposure level.

Also, there is an interesting study by Tuma, a case report, in which a worker was exposed to caprolactam at high levels and came into the emergency room experiencing grand mal seizures and dermal irritation covering most of his body. This is the only report that I know of in which seizures were seen in humans.

Now, to get seizures in animals, you have to inject them IP or IV. It seems you can't do it with high level inhalation exposures. You can get severe tremors, but apparently no seizures.

We also added the section on human and animal dermal sensitization studies. Many of these were

unpublished as well.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: So that's all we had to present on the changes to the document. The Chair had asked us to have some comments on the material -- the additional material from industry stakeholders that was sent to the Panel in the last few weeks. So much of this material actually reiterated comments that we received in the open public comment period, which were already addressed by OEHHA. But we do have several slides where we provide commentary on a few additional points or embellished points. So we can go ahead with that, if you'd like.

CHAIRPERSON FROINES: Please.

OEHHA STAFF TOXICOLOGIST DODGE: One of the comments that came in raised questions about why is the NOAEL/LOAEL from the Reinhold study, that's the subchronic rat study?

Many of these comments have been -- also came in in the first go-round, in that the changes seen in the epithelium of the nasal and laryngeal tissues was adaptive or adapting to an irritant and reversible, and that, in fact, they weren't considered adverse.

Some said none of the effects were adverse at any dose, including clinical symptoms in rats, which we find

that hard to believe, because the observations clearly indicated that the rats had a -- the health of the rats were compromised.

Dr. Renne weighed in with some comments. He is a -- he has quite a bit of knowledge in the field of nasal changes and laryngeal changes with exposure to irritants. He's a pathologist. He looked at the paper by Reinhold. Didn't look at the slides, just the paper, the results, and considered that the metaplastic changes occurring in the larynx were mild and reversible and therefore not adverse.

He looked at the nasal lesions and considered the two highest levels, 70 and 243, adverse. Though, he didn't use those words. What he said was at the lowest level was a NOAEL of 24 milligrams per cubic meter. And he also noted that there was a lack of complete recovery at the 4-week post-exposure period that was used in the Reinhold study.

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CHAIRPERSON FROINES: Was he referring to the upper dose?

OEHHA STAFF TOXICOLOGIST DODGE: I'm sorry?

CHAIRPERSON FROINES: Lack of complete 4-week recovery, what was he referring to?

OEHHA STAFF TOXICOLOGIST DODGE: There was a

group of rats that were exposed for 13 weeks along with the main group of rats that were sacrificed at 13 weeks. These rats were continued in clean air for 4 weeks following the exposure. And then they looked at the same tissues to see what kind of recovery there was.

CHAIRPERSON FROINES: I'm really asking what exposures, was it across the Board or was it 243?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It was actually above 70 and 243 is what he commented on.

CHAIRPERSON FROINES: So it was 70 and 243. The 24 milligram wasn't an experimental dose?

OEHHA STAFF TOXICOLOGIST DODGE: You're asking if there was at 24, the low dose there was complete recovery, is that what you're implying?

CHAIRPERSON FROINES: I'm not implying anything. I'm just trying to find out what was the dose -- what was the dose that led to this conclusion, doses?

PANEL MEMBER HAMMOND: There was a dose at 24.

OEHHA STAFF TOXICOLOGIST DODGE: All I -- in his comment, I believe all he said was that 70 and 243 was the increase effective exposure. In other words, he looked at the pathology data in the paper and decided there was enough animals affected at a high enough grade of severity level that --

CHAIRPERSON FROINES: Okay. It's fine. So 24

was not a dose?

PANEL MEMBER HAMMOND: I think 24 was a dose, but it was the dose that the second bullet refers.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER HAMMOND: The second bullet is talking about the second dose interpretation?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

Dr. Renne's interpretation is that 24 is a NOAEL, because, in his opinion, the metaplastic changes seen there were mild and reversible, and therefore not adverse. We happen to not agree with that.

OEHHA STAFF TOXICOLOGIST DODGE: They weren't actually metaplastic changes in the nasal tissue. We're talking about hyperplasia and hypertrophy of goblet cells in the respiratory tissue and the increase in eosinophilic material in the epithelial layer of the olfactory tissue.

CHAIRPERSON FROINES: It may -- I may sound confusing. I just trying to determine if the lack of complete recovery, if they had done a 24 milligram per cubic meter does and there was not -- and there was recovery.

OEHHA STAFF TOXICOLOGIST DODGE: You know, they don't know --

PANEL MEMBER BUCKPITT: The study is right here if you want to read it.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. I don't recall what Dr. Renne's response was in regard to that. I'm not sure he really specific --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I can read you exactly what he said. It's not as clear as perhaps you'd like. But what he says is that, "In my opinion, the data indicate an effect of exposure to 243 or 70 milligrams per cubic meter of caprolactam on the nasal cavity, and a lack of complete regression of nasal lesions at these concentrations following 4 weeks of recovery. However, the incidence severity data in the 24 milligram per cubic meter group at the terminal and recovery sacrifices versus the concurrent controls do not clearly indicate an effect on the nasal cavity at the 24 milligram per cubic meter concentration. I agree with Reinhold, et al., that the low incidence and slight severity of goblet cell hypertrophy hyperplasia in this group should be considered as a localized adaptive response to the inhaled particulate matter."

CHAIRPERSON FROINES: Thank you.

PANEL MEMBER BLANC: That's kind of like arguing that asthma is an adaptive response, isn't it?

(Laughter.)

PANEL MEMBER BLANC: No comment.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. We

hear frequently the argument that mild effects are adaptive, and we just can't agree with that in terms of being a toxicologist or anybody in public health.

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OEHHA SUPERVISING TOXICOLOGIST MARTY: We're never exposed to one thing at a time either, and our statutory responsibility is to consider that.

PANEL MEMBER BLANC: Okay. We can come back to the fuller discussion. But then I guess the other comments that you felt were new among the industry stakeholder interim comments to the revised document would be what? What else? Is this the main thing?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have a few more.

CHAIRPERSON FROINES: Go ahead, Melanie.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. Yeah, we disagree that these so-called adaptive changes are non-adverse. The reversibility is irrelevant. And, in particular, Dr. Renne seems to go against his own published papers, in which he says you have to look at the whole animal, not just the pathology effects and take that in consideration.

I mean, these animals in the Reinhold paper were showing labored breathing, moist rales, red staining facial area, nasal discharge. And apparently this is an

exposure related trend for some of these effects. I don't have individual data for that, though. I just have the information that's in Reinhold.

The problem is that Reinhold talks about it in this results, but seems to ignore it in the discussion. And I kind of feel like the pathologist here, Dr. Renne was also doing that.

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OEHHA STAFF TOXICOLOGIST DODGE: We already discussed this bullet point about the benchmark dose. We don't have to worry about NOAEL/LOAELs for benchmark dose program. This is another comment that actually came up before in our first go round.

Okay. We did a comparative REL based on the nasal tissue lesions, benchmark dose program. We'll go into that right now.

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OEHHA STAFF TOXICOLOGIST DODGE: This table I believe you've seen before. But I ran a benchmark dose program on each of the three major endpoints, the 2 nasal and the laryngeal endpoints. The laryngeal tissue is what we base our point of departure on, 3 milligrams per cubic meter.

But as you notice, for a nasal respiratory mucosa, practically the same point of departure is there.

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OEHHA STAFF TOXICOLOGIST DODGE: In this REL comparison, the dose and time adjustments are the same on certainty factors totaling 60 are applied. These are the same as what we did for laryngeal tissues. And we arrived at 8-hour and chronic RELs, which are just slightly higher, based on the nasal tissue compared to our laryngeal tissue RELs.

And for example, for the 8-hour REL, it's 9 micrograms per cubic meter here. And I believe for the -- based on the laryngeal tissues, the REL is 7.

PANEL MEMBER BLANC: That would be on what page, just to refer us to the main document?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's not in the document.

PANEL MEMBER BLANC: No, not this, but the one you did earlier.

OEHHA STAFF TOXICOLOGIST DODGE: Earlier.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So the derivation is on pages 39, that's the 8-hour, and the chronic is on 43, page 34.

PANEL MEMBER BLANC: All right.

OEHHA STAFF TOXICOLOGIST DODGE: I presented them earlier in the presentation.

PANEL MEMBER BLANC: I just wanted to have it to

refer to as you go through this.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

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OEHHA STAFF TOXICOLOGIST DODGE: Another comment came in. Some said that there is no evidence --

PANEL MEMBER BLANC: Can you just go back. I'm sorry.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah.

PANEL MEMBER BLANC: And then it's 2.98 versus 2.2 basically, is that right?

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm.

Any other questions?

PANEL MEMBER BLANC: Well, and this -- since there were two nasal outcomes, nasal respiratory epithelium and then nasal olfactory epithelium, which one is this?

OEHHA STAFF TOXICOLOGIST DODGE: Respiratory is the point of departure.

PANEL MEMBER BLANC: And would it be even less using the point of departure for the nasal olfactory or that.

OEHHA STAFF TOXICOLOGIST DODGE: It would be slightly higher, yeah.

PANEL MEMBER BLANC: Slightly higher. Okay. But since you used the same approach.

Let me see that again. Sorry.

Right. Okay. Thanks.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

CHAIRPERSON FROINES: Why weren't the models consistent across...?

OEHHA STAFF TOXICOLOGIST DODGE: They are pretty consistent. You mean, the point of departures that --

CHAIRPERSON FROINES: No, the models you used.

OEHHA STAFF TOXICOLOGIST DODGE: Oh.

CHAIRPERSON FROINES: You've got log-logistic for one -- log-probit and log-logistic.

OEHHA STAFF TOXICOLOGIST DODGE: Generally, go with the model that provides the best P value or in the AIC, the Akaike Information Criterion. This is sort of some of the recommendations by U.S. EPA on how to try to determine which model to use among several that you run for each endpoint.

So, for example, respiratory nasal lesions, I ran benchmark dose model probably 8, 9, or 10 of them -- I don't remember -- different models with that data. The log-logistic gave the best fit, though they were all pretty close to the same.

CHAIRPERSON FROINES: Go ahead. I don't -- I find it just slightly disturbing that --

PANEL MEMBER BLANC: It's probably -- You know,

there probably is a trade off in these things. And the trade off, if they were roughly the same, I think, for the exercise that you're doing, the trade off is in favor of using the same model, assuming that the area -- inside the -- what is it?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Akaike Information Criterion.

PANEL MEMBER BLANC: The Akaike Information Criterion are roughly similar, even if there's a numeric advantage to one over the other, assuming that the model doesn't fall apart probably for this comparative exercise that you're doing, it would be preferable to use the same model, or to --

OEHHA SUPERVISING TOXICOLOGIST MARTY: To some degree that's true. I mean, you can use the models and then compare them model to model to model.

PANEL MEMBER BLANC: Because I don't know what your numbers were that made you choose but if you -- from your description, you're saying they were all fairly similar. But on purely technical grounds the log-logistic is scored better for this. But if it didn't score dramatically better, all I'm saying is that for the exercise that you're doing here, which is to get a sense of whether you're coming out with similar numbers, it might have been preferable to use the multi-stage model,

unless it fell apart.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I mean, to some degree, your data drives your choice of model, because the fitting -- if it -- the fitting criteria drivers what you decide -- which model you decide to use. And the data points, to some respect, drive that. So not everything is going to have exactly the same dose response curve is what I'm trying to say, I guess.

PANEL MEMBER BLANC: I know what you're saying. I just want to make sure you understand what I'm saying.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I do.

CHAIRPERSON FROINES: Well, I'll be more blunt. I think that you ought -- you do need to worry about being seen as cherry picking your models.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, you know, the standard operating procedure is to pick the most sensitive endpoint, which has the $BMCL_{05}$ -- that's the lowest $BMCL_{05}$ with the best fit model. That's the standard default when you're using a benchmark dose model, regulatory default.

PANEL MEMBER BLANC: You know, I think we all understand that, and I don't think we're arguing that you shouldn't be using the multi-stage model for laryngeal tissue, if you use the laryngeal tissue. I think all

we're arguing is for an exercise in which you want to see were I not to use, how does it stand against the other things I derive using the other ones. Probably for that exercise, all things being equal, using the same model would be preferable.

Now, if you find that the statistics just are horrific, your test statistics, and that it's inappropriate to do it, that's a different question. But that's not what I heard being said. What I heard being said is they were pretty similar, but these were the best -- if you narrowly guide yourself by the best AIC number, then you choose this one.

PANEL MEMBER HAMMOND: You know, I guess I would just -- I would actually respectfully disagree. I think that generally speaking we do want to find the best model. And the best model that fits the data might actually be different for different outcomes.

PANEL MEMBER EISEN: I mean, I guess I would feel more comfortable seeing the range of results from different models. And I'd feel pretty uncomfortable using AIC as a way to choose the best without knowing how close they fell to each other. And there are also all sorts of model averaging approaches that could be used, because you don't really know.

AIC --

OEHHA STAFF TOXICOLOGIST DODGE: Right. That's one metric US EPA promotes too.

PANEL MEMBER EISEN: -- is measure of model, but it's not a particularly reliable indicator of much, certainly not what's true.

So if you've got very different results using different model forms, I think it would be more appropriate to present the difference -- whether you have -- not matter what they look like to present the range of results using different models.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, if you want, we can put all that stuff in an appendix, if you want.

PANEL MEMBER BLANC: Sure.

OEHHA STAFF TOXICOLOGIST DODGE: I have that information, just not here.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. So it would be more obvious.

PANEL MEMBER BLANC: Sure.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: This comment came in regarding the mention of possibly colony infection I had in a couple of places in the paper. Now, I was operating of a hypothesis that perhaps there is some sort

of infection. And when I reviewed the pathology literature what to look for in the nasal region, if there is an infection, I couldn't find that information in the Reinhold study.

So I rejected the hypothesis. Unfortunately, in my rush to get things ready 30 days ago, I didn't take this information out, so it's already out of the paper.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Comment here. One person thought we used the quantal model in the BMD modeling inappropriately for continuous data. This is not continuous data. The pathology information we had is quantal, so that was just not correct.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: We had some aerosol vapor comments. This comment says that we should not use the Reinhold rat study, because the exposure was in aerosol not a vapor. Regardless of whether it's aerosol or a vapor, at least with the information we have, it's going to be impacting the same area. If we have an aerosol larger than a micron diameter, most of the impact is going to happen in the upper airway for water soluble chemicals. If it's a vapor, it's the same area.

We don't have a lot of information on the size ranges of the caprolactam when it's in an aerosol, but

what we do have indicates it's going to be impacting mainly the upper airway.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: RGDR, that's the Regional Gas Distribution Ratio dosimetry adjustment. The point here from the comment was that it was unnecessary for a point of contact irritant. Our response is that the RGDR is a method employed by US EPA for water soluble gases.

Granted, it's a default, but if we ever have information that's published regarding, for example, pharmacokinetic information for caprolactam and -- in other words, the PBPK modeling approach, you know, for caprolactam specifically, then we could go back and use that information rather than a default.

This type of thing was done for formaldehyde and acetaldehyde because we had chemical specific information, but we don't have that for caprolactam, so we went with the default, which is the RGDR method.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: I think this is the last slide. We had a Dr. Haseman make comments here regarding the Ziegler study statistics. He reviewed that paper. The statistics for the Ziegler study not Reinhold in the first line. That's a mistake. And he had some

comments regarding the ranking of lesions with the Friedman test.

We agreed with most of his comments on the Ziegler paper. We agreed that one needs individual data for a proper evaluation of trends using the Friedman test in the data. We agreed that there -- that the interdependence of the symptom questions in the questionnaire makes it difficult to analyze the data.

Dr. Haseman also pointed out a few potential errors which we will be evaluating in fixing where appropriate.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Okay. We have a few more here we threw in it looks like. A comment here came in that inappropriate to use time extrapolation for an irritant. This goes back to some of the other comments that came in before.

When we have an endpoint that's sensory irritation, that is generally considered concentration dependence. Now, if we're talking about tissue injury with subchronic chronic exposure, it is not only concentration dependent, but time dependent.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Comment here is that some indicated no need for Intraspecies Uncertainty

Factor of 10 to account for sensitive humans, such as children with asthma, because the upper airway irritant would not trigger a lower airway symptom.

And our response is that an irritant may not reach the lower airway to trigger an asthma response. Now, this is a 10-fold uncertainty factor that we have in our methodology that was approved by the SRP. And we apply it, if we don't have information on the effects of a chemical on a sensitive subpopulation of humans.

--o0o--

OEHHA STAFF TOXICOLOGIST DODGE: Another comment. There is no need for interspecies uncertainty factor because the rat laryngeal tissues are more or equally sensitive to irritants than humans. And this goes back to the RGDR modeling. It's the default we use.

If we have information that's published for caprolactam that shows that this is, in fact, true, then we would go back and incorporate that. But we don't have that information, so we use the US EPA default.

That's all of the slides.

CHAIRPERSON FROINES: Well, I'm tempted to raise some of the questions that you didn't address, but I think I'll defer that and turn it over to the Panel. There were lots of comments, Melanie, that your slides did not address. So that's something that we may need to come

back to.

But for the moment, why didn't we turn it over to Paul who was the lead on caprolactam.

PANEL MEMBER BLANC: Well, I think we should start with the major question which is, can you just orient the Panel to precedence where you declined to come to any acute effect level for another substance? What are some other substance where you've done that?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Where we have not had an acute REL. There actually are quite a few. You know, off the top of my, I can't remember what they are.

PANEL MEMBER BLANC: Genre or a few examples would be helpful, just because I don't remember anything recently, so that's what I'm trying to --

OEHHA SUPERVISING TOXICOLOGIST MARTY: There are a number of chemicals where we're had just an 8-hour or a chronic or just a chronic, because the data we felt were not strong enough to support the development of a number, which will then be used in risk assessment. So we have done this before. We probably haven't brought forward an acute REL and then pulled it back. I can't remember doing that.

PANEL MEMBER BLANC: And this you actually brought forward 2 of the acute RELs, right? Because in

your comments you said we've taken away the Ferguson REL, but in fact the Ferguson based one was the second one, because you'd started off using the Ziegler, hadn't you?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right.

ENVIRONMENTAL MODELING SECTION SUPERVISOR BLAISDELL: With a total symptoms score.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We started off with the -- yes, using the Ziegler with the total symptom score, which had issues with it, because it looks like it's driven by odor and not anything else, and all the other issues that we laid out on that.

PANEL MEMBER BLANC: Right.

OEHHA STAFF TOXICOLOGIST DODGE: We do have a -- we can develop a REL based on odor. In fact, we have for hydrogen sulfide. The odor effect did not appear to be adverse enough in the Ziegler study to derive an acute REL.

PANEL MEMBER BLANC: And what would be the process by which, let's say, 6 months from now Ziegler sent you his raw data, what would the process by which you would amend this document? Is there a process in place?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER BLANC: Have you ever gone back on any of the other ones that you couldn't set an acute REL and then later recommended an acute REL?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I don't know remember if we've done that. But we've certainly updated existing reference exposures levels, chronic and acute, so --

OEHHA STAFF TOXICOLOGIST DODGE: Based on new information.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, based on new information or the new methodology.

PANEL MEMBER BLANC: So I --

OEHHA SUPERVISING TOXICOLOGIST MARTY: To answer your question, if we did get the data and we could apply that ranking to the raw data, we could come back with an acute REL. No doubt.

PANEL MEMBER BLANC: I should have started off by saying, well, one thing is I think that you've been very responsive to the feedback that you received at the last pleating, and have strengthened the document by including a lot of data that was available, even if it wasn't classic peer reviewed published data.

So I think that overall that makes the document stronger, and I think that you've also provided additional detail of the key studies that you did use. And I think that that's helpful too in making the document more transparent. I think there may be appendix material that you want to prepare in light of some of these things. And

I think that the appendix material probably should include what the acute effect level would have looked like had you used 5 milligrams per meter as the LOAEL, which would have been the net effect of interpreting Table 3 as showing that there was a clear effect once you were at 5 milligrams per meter.

I think that your discussion that is just below Table 5 -- 3, I'm sorry, on the test for trend and why you felt you couldn't rely upon it was not wholly convincing for me, because what we're really asking ourselves is the common sense question, is something going on at Table 5 that would allow 4 of the 5 endpoints to have the highest -- have the most effect there, and one of them to be tied with the next lowest level?

So that's not exactly the same question as a test for trend -- that a test for trend is asking really. So I also -- since you say which ones are medians, if you look at the first column, then is the default assumption that nasal resistance and redness as a mean value, and all the others are median. You don't say that.

I mean, I think you should clarify it. But then when you start saying many of these measures when using means as supplied in the paper, since many of these measures, but we are not using the means for this, except for maybe two of those measures where you don't say.

So three of them you're using medians, right?

So I'm not really clear -- I'm not really clear why this issue about the means and the skewed distributions is so important to you? I think it's overstated.

CHAIRPERSON FROINES: Paul, where are you reading from?

PANEL MEMBER BLANC: Well, I'm looking on page 11, the paragraph just below table.

OEHHA STAFF TOXICOLOGIST DODGE: It wasn't entirely clear from the study in all cases, but it appears that all three of the objective measures were medians.

PANEL MEMBER BLANC: Well, blink frequency you're saying is objective. You say it's median.

OEHHA STAFF TOXICOLOGIST MALIG: Yeah, blink should be. Your interpretation is right. Where we explicitly say median -- oh, sorry. Brian Malig.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Here, Brian, you've got speak into here.

OEHHA STAFF TOXICOLOGIST MALIG: So where it's explicitly written down that medians are the study measure are is where we use the medians

OEHHA. SUPERVISING TOXICOLOGIST MARTY: So blink frequency, eye symptom score and nasal symptom score are medians. Redness and nasal resistance are means.

PANEL MEMBER BLANC: Well, then that's not many of the measures, is it? It's 2 of 5. That's not how I would use the term "many". So I think you're overstating it. I think you're --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I think our -- the major issue that we had is that in order to do this properly, we need the individual data not the -- just the means or the medians, because you're then ignoring the distribution of the data.

PANEL MEMBER BLANC: And I'm not convinced that's true either. But if that's your main point, then drop the other part, because it makes it -- you talk about skewed data when you're using the median. That ignores any skewness.

OEHHA STAFF TOXICOLOGIST MALIG: Yeah. So it's valid for the measures where we use the means.

PANEL MEMBER BLANC: Do you believe that for nasal resistance the skewness was such a problem for that. I believe that they presented the medians for the ones they thought were the moist skewed. Do you actually believe that the ones for which they used the mean, they shouldn't have, the nasal resistance and the redness -- degree of redness?

OEHHA SUPERVISING TOXICOLOGIST MARTY: If you look at the paper, you can see that there is quite a bit

of variation in those data. And it's hard for me -- I mean, yes, you can think that there's probably a trend, but to nail it statistically, we still need the individual data. And that's where we're all hung up.

PANEL MEMBER BLANC: No. You would prefer to have the individual data.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we need to have the individual data.

PANEL MEMBER BLANC: And I don't agree with you, but -- and I'm not trying to make you go back and redo this, if you don't want to present an acute REL that's better than presenting the wrong one, which I think would have been the case using the Ferguson data. But I do think that those two paragraphs could be rewritten. And I think they're overblown, frankly, or at least they don't -- you know, one could make an argument in the other correction. And I think there's a heterogeneity of views probably on your advisory committee on that regard.

I think it's great that Table 3 is in the document. I'd like to see it stay there, because I think it makes the point just on a sort of a common sense level that something is going on at 5. Whether there's a statistical approach that would satisfy -- be more satisfying, I think, we're probably too late in the game to figure that out.

But I think it -- and I think you're on solid ground when you say you wouldn't have a lot of precedent for using an analytic approach like this for arriving at a low effect level. But on the other hand, I think you throw the baby out --

OEHHA SUPERVISING TOXICOLOGIST MARTY: With the bath water.

PANEL MEMBER BLANC: -- with the bath water a little bit on this.

So I don't think you need to -- I think you should rewrite those two paragraphs, let's just say, and be more conservative than the other way. Even though I'm not asking you to suddenly reintroduce this as the basis of your -- is that acceptable?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. No. Yes. You know, I would also like to hear if other people on the Panel think we should go back and try to come up with an acute REL? I mean, we're still trying to get the raw data. We're not having much luck.

PANEL MEMBER BLANC: And he just doesn't answer Emails?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We've contacted all three authors and the Person who's listed as the statistician and not an author.

PANEL MEMBER BLANC: And none of them have

replied.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, they replied, but not with the data.

PANEL MEMBER BLANC: What are they saying?

OEHHA SUPERVISING TOXICOLOGIST MARTY: You know, well everybody said, "Oh, Ziegler has it", and Ziegler has not replied.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: Ziegler won't reply.

PANEL MEMBER BLANC: And have you reached him by telephone?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: We haven't tried that yet.

PANEL MEMBER BLANC: I think that would be one thing to do is to call him on the telephone. I don't know what the budgetary limitations are currently?

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have to permission to make an out-of-country phone call.

PANEL MEMBER GLANTZ: You're kidding me?

PANEL MEMBER NAZAROFF: How about on Skype?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I wish I were.

OEHHA STAFF TOXICOLOGIST DODGE: Dr. Blanc, you may have looked at the comments there and noticed that Dr.

Haseman had access to a little more information, and that's provided in the published paper. And he seemed to feel that the -- in regards to the nasal resistance information, it wasn't as strong as it appears in the published paper.

PANEL MEMBER BLANC: Well, I don't think that that's anything that we can base any action on, one way or the other. But I'd be happy to yield my time on other points if it would be a more coherent discussion to first focus on this, rather than me say other things and then come back to the issue of the acute REL and how the Ziegler data should be utilized.

Again, just to reiterate, I'm not telling you now to go back and use the Ziegler data for an acute REL derivation, but I believe your argument for why you can't interpret the data in Table 3 is showing a no effect level of 5 is overstated, if that makes sense.

So I'm happy, Dr. Froines, if would you like to --

CHAIRPERSON FROINES: Let's ask the question. Are there others who would like to address the acute issue?

PANEL MEMBER GLANTZ: Yeah, I agree with your decision to take it out for the reasons you did, but I also think you could back off on the language. I mean, I

think if you look at this table there's certainly a very strong suggestion of a trend. Even though I think you're right that to try to use the Friedman statistic is pressing it a little beyond what it should be.

But I agree with Paul, I think you are a little bit throwing the baby out with the bath water. So I just think toning the language down here a little bit. And frankly, I think you should -- I bet, if you needed us to vote, that you should be allowed to make an international phone call, we would do that. Or if you wanted to come over to UCSF, you could use my phone. I mean, I do think it's a lot harder to ignore a phone call than an Email.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We will try.

CHAIRPERSON FROINES: I think that you're a reviewer of their document and coming over to your office and using your phone is not appropriate.

PANEL MEMBER GLANTZ: Okay.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: We'll do the phone call.

PANEL MEMBER GLANTZ: We would endorse you using your phone. I mean that's kind of crazy.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I'll use my home phone.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: We'll

figure out how to do the phone thing.

PANEL MEMBER GLANTZ: Yeah. It's really easy to ignore --

PANEL MEMBER BLANC: Dr. Ziegler is at what university in Germany?

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: He's in Heidelberg.

PANEL MEMBER BLANC: And I think the other thing to consider is contacting his chair as it's a hierarchical system, his department chair or his rector. In fact, I would actually exactly recommend that. If the phone call is not successful, I would go to the rector of the university.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. And just in response to Dr. Blanc, I do agree, and we were all looking at that, saying well, it looks like there is a trend, but we just can't get our hands on it statistically, so we were not as comfortable just --

PANEL MEMBER GLANTZ: Well, I think all you have to say is just what you said, that if when you look at these rankings there appears to be a pattern, but there's really not a worked out, well accepted statistical technique for putting a P value to that conclusion.

I mean, it is possible to make observations without calculating P values. But you I also would second

what Paul is saying. I mean, I think this guy completely ignoring you is pretty irresponsible. And if he won't respond, going to his department head would be appropriate, because that's -- you know, he's published this stuff. He's put it out there. He should make that information available.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: Yeah.

CHAIRPERSON FROINES: Are there others who want to weigh in on this issue?

PANEL MEMBER ARAUJO: Yes. I have an issue really to the acute toxicity. And it has to do with the case report --

PANEL MEMBER BLANC: Let me come back to that first step. That's a separate issue in my mind, I think. If I don't addresses your point, then come back to it.

PANEL MEMBER ARAUJO: Okay.

PANEL MEMBER BLANC: And nobody else commented on --

CHAIRPERSON FROINES: Paul, before you -- Paul, excuse me.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: Are you about ready to take a break?

THE COURT REPORTER: If you want to take one, that would be great.

CHAIRPERSON FROINES: Maybe this would be a good time to take a short break before we start.

PANEL MEMBER BLANC: Sure.

CHAIRPERSON FROINES: I'm just trying to make sure he's comfortable.

PANEL MEMBER BLANC: I'm into his carpal tunnel.

(Laughter.)

CHAIRPERSON FROINES: So let's take a -- how about a 5 minute break, is that okay?

(Thereupon a recess was taken.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I add in one more issue that didn't come up about the statistics that should be in here, and I see is not.

So I'm going to hand it to Brian Malig.

STAFF TOXICOLOGIST MALIG: Well, I just had a question or concern about when you use -- I'm Brian Malig.

CHAIRPERSON FROINES: Put it closer to you, please.

PANEL MEMBER NAZAROFF: Yeah. Also be sure to speak up, because older people start to lose hearing acuity.

STAFF TOXICOLOGIST MALIG: But I guess when you're using the medians in this sort of way, aren't you sort of -- aren't you basically ignoring the fact that there's sort of a repeated subjects design inherent in

this study, and that we should really be looking at the dose responses over each person and say applying a Friedman that way, so that you have rankings over each individual and then sort of taking all of those individuals into consideration in total?

PANEL MEMBER GLANTZ: He's looking at me.

(Laughter.)

PANEL MEMBER GLANTZ: I think that would be better, but I think that it kind of comes down to how you want to think about the problem. You know, if you want to take -- it's like if you say, okay, well, if I want to weigh myself this morning, you know, and I get on the scale five times, I'll get five slightly different numbers, you know.

And so if I just average them and I'm plotting my weight, you know, I should really -- I'm leaving out the variance within each day, and you are. So, I mean, if you did -- you know, looked at the dose responses within each individual, and took all that variance into account, that's going to be better, because you have more information. But lots -- there's nothing wrong with comparing averages, if you just realize that's what you're doing, because the thing that you gain when you -- by doing what you want, you get a better estimate of the variance, but that also can fuzz things up too, but you

get more degrees of freedom. So how it's all going to come out in the wash isn't totally obvious.

Generally, when you -- if you're just comparing averages, throwing out the variances, you know, you're actually throwing away information, so you're going to lose sensitivity. You're throwing away degrees of freedom, so you're going to lose sensitivity.

So the kind of very crude thing that you have in this table -- you know, and the fact that there is a pretty strong pattern when you just look at it, to me is reasonable evidence that there's a trend. The problem is that, you know, all of the statistical theory to prove that you can use the free -- specifically, the Friedman test on this, you're right, that isn't there.

So, you know, I think that you've got pretty strong evidence that there's a trend here. It's just that there isn't a really good statistical method that's well worked out to use it. But there's nothing wrong with, you know, summarizing the data with a mean or a median and then looking at patterns in the means or medians. People do that all the time. Is that an appropriately --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: Thank you.

PANEL MEMBER BLANC: And to follow up --

PANEL MEMBER GLANTZ: I think the bottom line is I think we all agree what you should do. I think what you should do is, you know, be a little less harsh about the conclusion you're drawing from this, because I think there is a pretty strong pattern here. And then I think you should aggressively pursue the raw data, so that we don't have to have this discussion.

PANEL MEMBER BLANC: So two follow-ups from that. One, is to return to -- let's assume there's a scenario when you don't get the raw data in a timely fashion. And we should probably give you guidance as to what that time cutoff would be, if that will make your lives better, rather than saying we're going to decide on the document today, and that's it. So you'd have to come back with a formal revision.

But if you don't get the raw data in a way that let's you satisfactorily analyze it, then I do think an appendix should include what the acute REL would have looked like had you taken 5 milligrams per meter as the LOAEL. And I hope that's acceptable to you.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER BLANC: So let me then -- and I --

PANEL MEMBER GLANTZ: I think that that's a good compromise.

PANEL MEMBER BLANC: So let me make some comments

now, and I hope this subsumes one of the things that you were going to say.

First of all, I think that the language that describes, or the language that speculates in terms of the impressive single human case report is -- the speculative part of that language should be deleted. And I don't think it's appropriate, like maybe he ingested it.

OEHHA STAFF TOXICOLOGIST DODGE: Well, I was asked to speculate more at the last meeting, so I was -- that's what I was doing.

PANEL MEMBER BLANC: Well, but that's not the direction I'd take. Speculation -- I think the speculative thing to say would be rather that the inference is that this chemical does have neurotoxic potential, even though we're limited to a single human case report.

And similarly, I think the discounting of the animal data in which there is neurotoxicologic data is also downplaying and over back pedaling on the potential meaning. You're a public health agency. It's not your job to speculate explanations for why observed neurotoxic effects in animals should be ignored or discounted or, you know, well these were high doses. They were near death. You can't give it a this has to be done.

There are many reasons why a neurotoxin might be

more evident given parenterally rather than orally. You don't know anything about the first pass metabolism. I mean, there's just a lot of stuff.

So I think that that language, which I think is both -- follows the case report and then follows the animal data should be revised, toned down certainly -- at a minimum toned down, so that it's less apologetic for the observation.

And then finally, I think that in the same realm, in addition to the argument for the child protective factor that stems from your consistent approach to irritant potential chemicals being presumed to have potentially differential effects in children. I think also the neurotoxicants you have generally presumed. And I think that that should be stated there, not as your driving force, but as yet another consistent --

CHAIRPERSON FROINES: What are you referring to?

PANEL MEMBER BLANC: Well, there's a factor of 10 used as the child protective. And that's based on the irritant effect and its potential relationship to asthma.

CHAIRPERSON FROINES: Right.

PANEL MEMBER BLANC: And I believe that a neurotoxicant similarly, in general, the approach of OEHHA has been to also presume that children might be at higher risk from --

CHAIRPERSON FROINES: Neurologic --

PANEL MEMBER BLANC: -- neurologic toxins or seizurogenic things.

Also, in terms of that human case report, you have a discussion, unless I misread it there, about how well animal studies don't show that -- no. There's no other data that show that it's a sensitizer. But later on in the skin section, you talk about the human case reports of contact dermatitis.

Now, maybe you are thinking of those as being entirely different types of sensitization. And it's true that contact dermatitis is generally a Type 4. And, you know, we don't classify asthma sensitizers maybe in the same way. But it was weird, that statement was inconsistent within the later data.

So unless I misread what you were trying to say or misinterpreted. You know, there are two places where you talk about sensitization --

OEHHA STAFF TOXICOLOGIST DODGE: In the animal section and the human section.

PANEL MEMBER BLANC: Right, but then you're talking about the human cases later on. I could find where it is, but it's not at the place where you say there's no data to show that it -- there's no other human data to show it's a sensitizer. And then, you know, later

on you talk about the human cases of contact dermatitis.

CHAIRPERSON FROINES: What page are you on?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah. I think I can clear that up. But part of the problem is that in order to get this possible so-called mild sensitization, the concentration of caprolactam placed on the skin was rather high and caused --

PANEL MEMBER BLANC: It's an irritant.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, caused damage to the skin, which caused --

PANEL MEMBER BLANC: That's always a problem.

OEHHA STAFF TOXICOLOGIST DODGE: There apparently was a --

CHAIRPERSON FROINES: If you are at page 22. It's not till page 22, second full paragraph, a few reports of dermal hypersensitivity resulting from long-term exposure to caprolactam had been published. Aguirre 1995, Hausen 2003.

OEHHA STAFF TOXICOLOGIST DODGE: Right. Right.

PANEL MEMBER BLANC: Considering the widespread occupational and consumer use of Nylon-6 materials that few reports of individuals becoming hypersensitive to caprolactam exposure appear to indicate that hypersensitivity is an unusual outcome of caprolactam exposure. No evidence for respiratory hypersensitivity

was found in the literature. Now, first of all, I think that's misplaced there, because you don't talk about those case reports when you talk about the human data. That's one thing. So, first, you need to talk about them when you're talking about human health effects.

OEHHA STAFF TOXICOLOGIST DODGE: Would you like me to put a summary of those papers in there?

PANEL MEMBER BLANC: Yes. Well, I don't think you have to detail them. But where you talk about the human evidence, like this one case report, you make that sound like that's the only case report of any adverse effect in the medical literature related to this chemical. But I would say that if there are case reports of contact dermatitis, it would be appropriate to put them there as well. I'm not saying you have to give some detailed, you know, business about them.

And also since you say in that other place there's no evidence of sensitization, because that guy had skin effects as well as seizures, this argues against that, right? It certainly contradicts the statement that there's no other evidence.

Does that make sense?

OEHHA STAFF TOXICOLOGIST DODGE: I believe so, yeah.

CHAIRPERSON FROINES: Paul, are you going to go

on with that paragraph, because I had a problem with it.

PANEL MEMBER BLANC: Well, let me say a couple other things about that paragraph. What does long term mean in that paragraph to you?

OEHHA STAFF TOXICOLOGIST DODGE: Well, for example, one of the case studies that is not in here, the patient was -- had skin tumors, and he went in for a period of 10 years to have them removed and then they used a suture that was actually made of -- had Nylon-6. So after roughly, I don't know, 10 years of exposure, he became sensitized to caprolactam in the Nylon-6.

PANEL MEMBER BLANC: So he had sutures in constantly for 10 years?

OEHHA STAFF TOXICOLOGIST DODGE: He was going back -- yeah, he had roughly 20 operations, I think over a period of time.

PANEL MEMBER BLANC: Yeah, but each time he would have had the sutures in for a week or something, right?

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: So that's not long term.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's more repeated.

OEHHA STAFF TOXICOLOGIST DODGE: Well, he continually repeated, I guess is more --

PANEL MEMBER BLANC: So repeated. But all

contact dermatitis inducing agents by and large, if it's allergic contact dermatitis, have repeated exposures. And then one becomes sensitized at some point. So I'm not sure what that is mean -- is that one of these case reports that you cite here?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, yeah.

PANEL MEMBER BLANC: So which one is it? Aguirre or --

OEHHA STAFF TOXICOLOGIST DODGE: I don't recall which one. It's either Aguirre or Hausen.

PANEL MEMBER BLANC: Okay. And those were the only two that you found of contact dermatitis.

CHAIRPERSON FROINES: No, but I thought you said that there was one missing that you didn't put in.

PANEL MEMBER BLANC: You meant you didn't put the details in there is I think what you mean.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, right.

PANEL MEMBER BLANC: Were there other case reports of contact dermatitis you didn't cite or these were the only two you were --

OEHHA STAFF TOXICOLOGIST DODGE: These were the two published ones I could find, yeah, that deal specifically with Nylon-6 or caprolactam.

PANEL MEMBER BLANC: Right, right, right. So in any event, I wouldn't use that and I don't think I

would -- actually, the whole discussion of well it's widely used and these are the only two case reports, so it must be exceedingly rare. I mean, I'm not sure that that's the point. I mean, often there are things that we only have a few case reports. One of the biases in the literature is if somebody has already published a case report, it's hard to get another case report published, because it's not novel, unless you do a whole case series.

There may be data out there lurking where they've used caprolactam in, you know, a group study, where they're looking at cross sensitivity. I don't know. I haven't -- you know, I haven't done that literature review.

One thing that you might do just to satisfy yourself, is to send an Email to Dr. Howard Maibach at UCSF, who really is sort of the repository of all contact and irritant contact dermatitis data. And just, you know, ask him personally, if he's ever seen a case. I mean, I wouldn't -- just in terms of am I missing something, you know, asking yourself, not in terms of including text.

But I think this language here is another example of where I was struck by a kind of back-pedaling in a way that was unnecessary.

CHAIRPERSON FROINES: Paul, can I just comment?

PANEL MEMBER BLANC: Sure.

CHAIRPERSON FROINES: They say appear -- based on the few reports indicate that hypersensitivity is an unusual outcome of caprolactam exposure. I don't -- I think the word "unusual" is inappropriate, because I think that the evidence indicates that there are effects. There is hypersensitivity. And we know that the data we've been working with are a very limited number of studies. So to draw a conclusion that it's unusual seems to me to be believing that because we don't have more data, it's not highly prevalent, but that's not necessarily a conclusion I think you should draw.

OEHHA STAFF TOXICOLOGIST DODGE: We can go ahead and take that out.

PANEL MEMBER BLANC: Anyway. So those are -- in terms of the acute effects, I think that also where you -- first of all, this applies to other areas, but it was particularly relevant because of the challenging database you were dealing with. When you say unpublished, when you use the term "unpublished", don't you really mean unpublished in the peer-reviewed literature?

OEHHA STAFF TOXICOLOGIST DODGE: I tried to do distinguish that.

PANEL MEMBER BLANC: Because sometimes you say not peer-reviewed and sometimes you say not published. It probably would be safer for you to go back and edit that,

so that if what you mean to say is it hasn't been published in the peer-reviewed literature, that that's what you say, because some of these things, I'm not trying to nitpick, but things which are available on the Internet or published on the Internet, they're just not published in a peer-reviewed -- so some of these things you access because they're in databases. They're publicly available.

And then there's non-published proprietary data, which you somehow got ahold of maybe in some other way. I don't know. But you see the point I'm making.

OEHHA STAFF TOXICOLOGIST DODGE: Yes, I do now.

PANEL MEMBER BLANC: I think you're on safer ground just to say -- if that's what you mean, and I think that's really your implication, just say it every time consistently.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

PANEL MEMBER BLANC: Non-published in the peer-reviewed literature.

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: So the data that, you know, that I had pointed out to you, which was on a database, which was these -- the study -- the acute studies in several species. And that -- well that's, can you just orient me which page again that's on? It's in the animal data, so it's got to be starting somewhere on 14 or 15.

OEHHA STAFF TOXICOLOGIST DODGE: It's probably in more than one place, because...

PANEL MEMBER BLANC: Well, there's a place where you said that the cats were more sensitive or something was more sensitive, but they didn't really say how.

OEHHA STAFF TOXICOLOGIST DODGE: Well, it was a statement --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Page 15.

OEHHA STAFF TOXICOLOGIST DODGE: -- made in the paper I had. And, yeah, there was nothing to back it up.

PANEL MEMBER BLANC: Was that 15, page 15 or 16?

OEHHA STAFF TOXICOLOGIST DODGE: Right. It's on page 15 at the top, first paragraph, "Rabbits and cats are said to be more sensitive to caprolactam, but no data was provided". Okay, that's -- I couldn't find -- they didn't have any information there to back it up.

PANEL MEMBER BLANC: And this is in the BASF data reported by Ritz in 2002. Is that what that is? Because somebody is reporting somebody's data, but you were never able to access the original data, is that what all that means?

I mean --

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, I believe that's probably what it means.

PANEL MEMBER BLANC: So it's not exactly

transparent. And then the other study, the one that was -- is that the 1950's study or -- it was not clear who -- the one that was submitted anonymously, so it wasn't actually clear, I think -- it's the EPA one. The one in the EPA database, which one is that?

OEHHA STAFF TOXICOLOGIST DODGE: You mean the one that was submitted to the US EPA just a few years ago --

PANEL MEMBER BLANC: Yeah, but from old data.

OEHHA STAFF TOXICOLOGIST DODGE: -- based on data from the early fifties.

PANEL MEMBER BLANC: Yeah, which one is that?

OEHHA STAFF TOXICOLOGIST DODGE: I labeled that one, US EPA 2009, because that's when they received it.

PANEL MEMBER BLANC: And where is that in this section here, just to orient me again? Is this under chronic toxicity to animals?

OEHHA STAFF TOXICOLOGIST DODGE: That's where we're looking.

PANEL MEMBER BLANC: US EPA 2009, "A skin sensitization test was conducted on guinea pigs and dogs at the end of their inhalation exposure regimen".

OEHHA STAFF TOXICOLOGIST DODGE: Where do you find that?

PANEL MEMBER BLANC: On page 29. And it's before that in dogs. Okay, so when one goes to your reference

list and gets US EPA 2009, and you see it's epsilon-caprolactam, right?

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm.

PANEL MEMBER BLANC: First of all, I think at some -- in the text you should say that this was -- what these data were, right? This is data from the fifties, not data from 2009, right? It's like a --

OEHHA STAFF TOXICOLOGIST DODGE: Right. Right. I'm sure I did that in spots, but not everywhere.

PANEL MEMBER BLANC: But isn't this the only place you talked about it or is it at the beginning, an unpublished study, with 4 dogs, 6 rats, and 2 rabbits, right?

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: And this study was conducted, but only -- okay. There it is. Okay, never mind my comment. But I think you should say it was reported -- it was done in 1952, but who did it is not publicly known or something.

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: Okay. But it was industry study presumably.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah. That's what it looks like.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we

can -- probably the easiest thing is to point out under what statute was this submitted?

PANEL MEMBER BLANC: Yeah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And why?

PANEL MEMBER BLANC: And then I think when you have the thing at the back, you know, the reference, you -- US EPA 2009, you could actually --

OEHHA SUPERVISING TOXICOLOGIST MARTY: We should change that.

PANEL MEMBER BLANC: Well, no. You could just put reporting data from or something and the references.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Submission by

PANEL MEMBER BLANC: Right exactly.

In any event, one thing that I think didn't quite come through with the toxicology section, because you've got the acute, then you've got the chronic, which is a -- which strengthens, what is otherwise, you know, very herterogenous and spotty data, is that you do have multiple species with data.

It may be acute. It may be chronic. I wonder whether a very simple table which would have species on one axis, and the effects which would be acute irritant, chronic irritant, acute ever chronic whatever if you would be a nice summary table or some -- don't you think that

would sort of strengthen things?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It would make it easier to look at stuff.

PANEL MEMBER BLANC: Right. And where to put that is a bit of a question, because if you've got acute and then chronic, but it could somewhere sort of just towards the end of your complete review of the data.

And that way you could deal with the irritant and sensitization neurologic, because you really do have multiple species in the end. And that was one of the reasons why I brought this, you know, even though it's crude study to your attention was because it hadn't dog data and it, you, know some other thick even though its -- you know, it's not the strongest data in the world.

But when you start to see -- it's kind of like the corollary of your table, your semi-qualitative table of the Ziegler data. When you start to see the same effects across multiple species, it makes your index a suspicion or stronger that you're seeing a pattern. Is that fair enough?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah. We could create a section that sort of summarizes the animal data in a table.

PANEL MEMBER BLANC: And I'd put in the human effects where you have them there.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

PANEL MEMBER GLANTZ: I would actually put that near the beginning, because it would make it easier to kind of work your way through the report.

PANEL MEMBER BLANC: Wherever you decide from my point of view. It's hard to put a table like that before you've actually presented the data, that's why sometimes doing it as a summary is sometimes good.

But in any event, I know that Dr. Froines has his feelings about the interpretation of the data, the animal data, in terms of the nasal and laryngeal effects. From my point of view, because I view the effects on the larynx as being deeper down, and therefore a bit more indicative of a concerning end organ, I do not find a problem with using your cutoff for a yes-no for that effect as being minimal or above. Whereas, for the nasal respiratory and nasal olfactory, you use a cutoff of above that, because there appears to be in the controls such a baseline effect.

So, to me, I think that's acceptable, and I made my comments before about the -- in your -- I think you countered that what you would do is in the appendix provide additional detail on what the derived benchmarks would look like were you to use the others with presenting all three types of models, so you'd have nine rows

essentially. I think that would be good for transparency.

CHAIRPERSON FROINES: Well, since you raised my name --

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: -- my question has to do with consistency as you look at that Table 5, and whether or not we're -- how -- what kind of criteria we should use and should we have what does slight mean, what does minimum mean, because it gets used differently in different places. And that concerns me insofar as should there be consistency of approach, and what are the implications of that. You understand?

PANEL MEMBER BLANC: Yeah. And so I would say that perhaps a way of addressing that, aside from presenting the appendix data that we talked about, would be to make sure that your text explicitly states 2 rationales for that.

One is I think the one that you stated, which is that there's such an effect in the referent group, if you use a cutoff, including slight, that the data would not be interpretable. And you argue that it's an age effect. I'm not sure if you have outside data to show that that's what it is that has -- at time zero, they wouldn't have had that. But I think the second rationale is more convincing or as convincing to me is that any change in

the larynx may have more health implications.

CHAIRPERSON FROINES: Well, part of the problem is we're stuck with these -- these minimal, slight, moderate, moderately severe. And here, we find with the laryngeal, and I agree with you about the physiology, that we see minimal changes at 24 and nothing with slight changes at 24, and nothing at 70, in fact, under slight.

And so I'm just concerned about the consistency of what -- how do we deal with what does minimal and slight mean, because slight theoretically is a greater level of severity. Whereas, minimal is a lower level. And so it's the inconsistency that's concerning me.

PANEL MEMBER BLANC: And maybe a way of addressing that is just in your text to -- if it's not record there and I might have just missed it, what it is that the author -- this is Reinhold, right?

CHAIRPERSON FROINES: Yeah.

PANEL MEMBER BLANC: -- what the author -- how the author defined those terms in each organ, and the ways in which -- sort of how high his threshold was. Was he calling minimum something that we would take seriously, even though he used the word minimal? So you're talking about, you know, squamous metaplastic changes. I'm assuming that that's not just in the 8 slightly exposed animals.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think -- let me turn it around for a second.

PANEL MEMBER BLANC: Slightly -- not slightly exposed, slight --

OEHHA SUPERVISING TOXICOLOGIST MARTY: What we're looking at is treatment-related changes.

PANEL MEMBER GLANTZ: Is what?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Treatment related changes.

PANEL MEMBER BLANC: Exposure related?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, exposure related changes. And I think even though -- if you have no change, for example, in the larynx and the controls, and you have minimal/slight change in the low dose group, or whatever treatment group, then that is a treatment related change. That's what we're looking at.

I think arguing over what's minimal versus what's slight versus -- is just red herring.

PANEL MEMBER BLANC: Well, it's not necessarily a red herring if the author was overly conservative in how he used the terminology. So I'm only making an argument that supports your interpretation of the data and the way you do. So if he's saying metaplastic changes are slight because he has some explanation that it's -- he views metaplasia as adaptive, we don't care what his -- I'm

trying to separate out his results from his discussion.

CHAIRPERSON FROINES: I want to -- Melanie, you need to do more, because I don't think it's a red herring. I think the consistency, or lack thereof, is an issue throughout this Table 5. So I've said my peace.

And what I want to do now is stop you if -- on this topic, are there other people who have comments?

PANEL MEMBER BLANC: Just like we did before.

PANEL MEMBER GILL: Just as a clarification, the analysis of the data that's done in Table 5 ADCR analysis or it is what is reported by the author as such.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, it's a modification of a table that's in the paper.

PANEL MEMBER GILL: So when use the terms, therefore it is your interpretation of what is in the data?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's what's in the table

OEHHA STAFF TOXICOLOGIST DODGE: Well, this is what's in the table in the public data.

PANEL MEMBER GILL: The exact terms that I used in the Table 5 are the exact terms in the paper?

OEHHA STAFF TOXICOLOGIST DODGE: Oh, yes, in terms of the gradings minimal, slight, moderate.

PANEL MEMBER GILL: Because the terms tend to be

used differently in different publications. So at the bottom of the table, it may be nice to annotate exactly what is implied by the author, so it's not your interpretation, so it becomes more precise information in the document, as to where the terminology comes, because it may be different in different tables. And so that interpretation becomes very consistent throughout as a consequence.

PANEL MEMBER BLANC: Just to add to that. I think there are places in the document, but this is one of the clearest ones where the targeted use of quotation marks would make it clear when it is you're just saying what the author said or what term the author used, versus a more generally accepted terminology. That's just emphasis -- I'm just amplifying what you just said.

PANEL MEMBER GILL: So it becomes clearer exactly as to the origins of the terms.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

PANEL MEMBER BLANC: Who's here a pathologist?

CHAIRPERSON FROINES: Nobody.

PANEL MEMBER BLANC: Alan, you don't do pathology at all?

PANEL MEMBER BUCKPITT: (Shakes head.)

CHAIRPERSON FROINES: Alan?

PANEL MEMBER BUCKPITT: You're looking at the

wrong guy.

PANEL MEMBER BLANC: Well, also, I mean -- I know you've attempted -- actually, you've attempted to do what Dr. Gill said in a way, because you have these footnotes that say goblet cell hyperplasia. But that's only saying the generic endpoint, but it doesn't tell us what then, you know, minimal is a touch of goblet cell hyperplasia or it means that less than 25 percent of the cells show goblet cell hyperplasia?

OEHHA STAFF TOXICOLOGIST DODGE: Yes. I wondered the same thing. It's the pathologist's interpretation. You know, it could be different from one pathologist to another. But the paper doesn't really specify what is exactly meant by each grade level there.

PANEL MEMBER BLANC: It's just the endpoints. So therefore for laryngeal tissue, the endpoint is metaplasia, but for nasal mucosa, it's intracytoplasmic eosinophilic material. Whereas, for the nasal respiratory mucosa, it's goblet cell hypertrophy or hyperplasia, right, that's correct?

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm.

PANEL MEMBER BLANC: So I think I would then try to -- maybe I'll be a bit more definitive in my statement. I would say that minimal metaplasia trumps slight eosinophilic conclusions, if I'm thinking about it from a

adverse health endpoint perspective.

So I think that, although you're not -- it may be inconsistent with the terminology that the author has used, in terms of what he calls slight versus minimal. In fact, it's hard to make an argument that -- I would -- let me put it in the positive way, I think it's perfectly reasonable to say that you're going to use any kind of metaplasia minimal or more as a reasonable threshold for saying positive, but you're going to be taking slight or more eosinophilic conclusions as being something that you can hang your hat on. Even though that's inconsistent with the terminology of the author across the endpoints, it's more consistent with a reasonable pathologic public health endpoint.

CHAIRPERSON FROINES: Paul, can I just say one more thing about my concern about this?

On Table 6 you have nasal respiratory mucosa, and you only include moderate. Then you go to nasal olfactory, and you include slight. And then you go to laryngeal and you include minimal and slight. And that concerns me, because there's not a consistent approach to the pathology, and so I don't know what to make of -- obviously, you're making a pathologic judgment. And I don't see how we can do that.

OEHHA STAFF TOXICOLOGIST DODGE: Well, I'm trying

to show you the effects caused by caprolactam exposure, over and above the minimal or slight effects that occur in the controls.

PANEL MEMBER BLANC: Well, I think --

OEHHA SUPERVISING TOXICOLOGIST MARTY: In other words, those were the treatment related effects seen in those regions of the nasal laryngeal --

CHAIRPERSON FROINES: But what I'm saying is you choose different treatment related effects in here. You're not consistent.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's because that's what was observed to be treatment related. It doesn't matter whether it's consistent from one region to the other. You have different background histology in those regions with the age of the rodent in the control.

So what we did was say okay, if, for example, nasal respiratory mucosa, you did see minimal and slight changes in the control group, but you didn't see any moderate changes in that region. You did see that in the treated group. So we're focusing on the treatment related changes by doing that.

CHAIRPERSON FROINES: Okay. Paul.

PANEL MEMBER BLANC: So I think maybe -- maybe Table 6 is more complicated than it needs to be, because doesn't Table 6 actually for the -- not for the

recovery -- at 4 week recovery, doesn't it just reiterate what's in the previous table in summary form?

CHAIRPERSON FROINES: Not really.

OEHHA STAFF TOXICOLOGIST DODGE: We didn't use the 4 week recovery information in Table 5.

PANEL MEMBER BLANC: No. No. I'm saying the lines -- the rows that -- not of the recovery but of just the effect. It's just summarizing what's in the previous table, right?

OEHHA STAFF TOXICOLOGIST DODGE: I'm sorry, could you repeat that?

PANEL MEMBER BLANC: The rows which don't talk about status at 4 week recovery, but just the baseline status, are reiterating the data, which is in the previous table.

OEHHA STAFF TOXICOLOGIST DODGE: Yes.

PANEL MEMBER BLANC: So why not just get rid of those lines, the four week --

OEHHA STAFF TOXICOLOGIST DODGE: The 4 week recovery line rows?

PANEL MEMBER BLANC: No. Those you haven't presented before, no.

OEHHA STAFF TOXICOLOGIST DODGE: No, I haven't.

PANEL MEMBER BLANC: No. the other data. The data that you have presented already.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

PANEL MEMBER BLANC: And then you would have much -- because it is, at first glimpse, a little confusing, because you're repeating, right? Am I not -- Melanie, do you understand what I'm saying?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, I know what you're saying. So I think what we need to do is read his State clearly what incidents data were used in the benchmark concentration analysis? Which is in here, but it's not the 4 week recovery data.

PANEL MEMBER BLANC: Right.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And then how we arrived at those incidence data from the data in Table 5, which is the data reported by the State Auditor's --

PANEL MEMBER BLANC: And you could probably delete the rows that are --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER BLANC: And if you wanted, you could probably move that whole table and its discussion into the appendix, for all I care. It doesn't --

OEHHA SUPERVISING TOXICOLOGIST MARTY: I can't remember who asked us to put this in the last time.

PANEL MEMBER BLANC: Well, but it could be in the appendix. It wasn't me.

CHAIRPERSON FROINES: I don't think it belongs in an appendix.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think it's important to have what incidence data we used.

CHAIRPERSON FROINES: I think it's important that people understand -- I mean if you take a person off the street and you look at the inconsistencies, you're saying -- the average person would say, this data is all over the map, and you need to make sure people understand what you've actually done. So I don't think it's an appendix. For me anyway, it's a crucial piece of information. And I'd like to see that actually defined relative to the pathology.

OEHHA STAFF TOXICOLOGIST DODGE: Yes, I agree. And I attempted to try and clear it up, but apparently I haven't quite got there yet.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's easy to know what you did when you did it.

CHAIRPERSON FROINES: That's a Yogi Berra-ism.

PANEL MEMBER BLANC: So I think that -- I think that those are my substantive comments. Again, I think that the inclusion of a lot more data where it's available is a strength and conclusion of some of the details of the studies that you have done is a strength. I think that you've heard the consensus view of the Panel, in terms of

the comments on Table 3. I'm not asking you to go back and redo -- reinsert an acute reference value, unless you get the raw data, but to include in the appendix a calculation of what a 5 milligram per cubic meter low effect level would look like.

And similarly to include in the appendix material the nine calculations of benchmark with the other data using the three models for each and showing what those look like.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's actually more like six or seven models.

OEHHA STAFF TOXICOLOGIST DODGE: At least, yeah.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Each.

That's okay. We'll put it in.

PANEL MEMBER BLANC: Well, whatever it is, you figure out a way to present it that is -- can be looked at.

CHAIRPERSON FROINES: Paul, are you --

PANEL MEMBER BLANC: I just would resummarize the basic points just to make the record clear.

To take out the language which appears in various places in document, which is speculative and could be misinterpreted as back-pedaling to move the human data on sensitization earlier in the document when you're talking about human data. And be cautious there in your wording.

To provide a table that looks across species for endpoint organ sensitivity or target organ data essentially is what I'm asking for.

And that, I think, summarizes my comments. And I don't know whether I actually got to -- oh, and also the point about neurological target toxicity, which I think will come forward in that table we've discussed, but as a rationale also for children's sensitivity.

CHAIRPERSON FROINES: We'll come to Jesús.

PANEL MEMBER ARAUJO: Yeah. I agree with pretty much all the points that you made. But I would like to add some --

CHAIRPERSON FROINES: Before you start, can I make -- do one final finishing comment for Paul.

Jay Murray who's here is, I'll quote part of his comments, which is, "The minimal clinical effects observed in the Reinhold, et al., 1998 study represent adaptive changes not adverse effects. Based on what you've said thus far this morning, I would assume that you basically have concluded that they do represent adverse effects. And so I'd like that to be on the record.

PANEL MEMBER BLANC: Yes, I mean. I agree with the statement that was made by OEHHA in general and is not so specific even to this particular chemical that we do not presume that adverse effects that are seen in human or

animal studies are, in some way, adaptive and that labeling such a response as adaptive means that it's not an adverse endpoint. And that would be inconsistent with the approach that OEHHA has used throughout. It's history, which this Committee has always been found to have a good scientific basis.

In fact, I think that the -- overall the input from the industry stakeholders can be divided into two types of comments. Many of them are generic comments about processes, procedures, approaches, and assumptions that are used by OEHHA and risk assessment, for which there's precedent and for which there's no basis to go away from established practices, procedures, and precedent.

And then the second group of comments pertain to much more specific questions about the data at hand. And my interpretation of the comments made by OEHHA, both in their original set of responses to the first round of comments and then to these is that they've acceptably addressed those more specific ones as well.

CHAIRPERSON FROINES: Are there any comments about what Paul just said?

Okay Jesús.

PANEL MEMBER ARAUJO: Yeah. So I would like to add some points in relation to the acute toxicology or

acute neurological effects, given that these are likely the most severe adverse effects that are being reported.

So number one, and so you mentioned that there is only one case report and this case report is from Tuma, and published in the Archives of Internal Medicine in 1981. I haven't read the article. I'm only having access to the abstract.

And unfortunately, there doesn't seem to be biochemical data, in terms of the levels of caprolactam that were in the blood. I don't know if you had access to the full article and whether that information wasn't there. And from what you are describing in the text, that it appears as this could be related to a large dose that this patient was exposed to.

But we don't have that information for certain. And we don't know if this is due to a large exposure or if it is due to idiosyncratic reaction and hypersensitivity reaction.

But more importantly, I found another case report that is in another journal -- in a journal that I couldn't find in PubMed, so it's in the Korean Journal of Occupational Environmental Medicine. And the description of the case is very similar to the description given by Tuma.

And I will give you the full reference. It's

published in 1998. And the full reference is 10 -- Issue number 10, and page 116 --

PANEL MEMBER BLANC: Volume number 10.

PANEL MEMBER ARAUJO: Or volume number 10 and page 116 to 120. One of the problems is that it appears to be in Korean. Again, I don't have access to the full article, only to the abstract, but the abstract is in English. And I will read it because the description is so similar to the other one.

> "Two young men were seen with nausea, vomiting, dermatitis, seizure after two to four days of occupational exposure to caprolactam, a nylon fiber precursor. There were no significant results in laboratory test, brain CT, EEG except leukocytosis, hyperglycemia. Caprolactam has been shown to induce convulsive disorder in experimental animal studios and Tuma et al (1981) described that one worker acutely exposed to caprolactam developed generalized tonic-clonic seizure with leukocytosis. The coincidence of typical skin lesion with otherwise unexplained generalized tonic-clonic seizure in those young man strongly suggests that caprolactam was a causal agent."

So I believe that even though it is in a non --

or in a journal that is not found in PubMed, given the importance of the effect, I think that probably we should try to locate the article and have it translated and see exactly -- see whether more useful information can be derived from here.

But given the coincidence in between these two case reports and that are 17 years apart, I think that it is an effect and that maybe important to take into consideration, certainly to document in this document.

The second point in relation to the same issue is about the animal toxicological data. So you mentioned about the -- that this convulsive -- or seizures also occur in dogs after large doses by gavage. And we do a percentage -- you also mentioned that in other animals when the dose was given intravenously or intraperitoneal.

But I don't know if I missed it in the document, but I didn't see references of these intravenous and intraperitoneal administrations. Maybe I missed it, but if I didn't miss it and it's not in there, and indeed that is the case, I think that it should be also included in the document.

Because this raises an important question that goes back to my initial consideration. Are these effects due to very large doses and very high levels of caprolactam in the blood or are these affects due to

idiosyncratic and hyper -- and reactions and due to hypersensitivity?

If it is the first case, the coincidence that you have with dermatitis and seizures makes you wonder whether it is that either the dermatitis is due to the caprolactam, the dermatitis could be increasing the bioviability and the absorption of the compound. So maybe those could be a propensity to have very high levels of caprolactam and develop the neurological symptoms and problem.

So it would be important, because people with dermatitis could be advised not to work or to be -- or, yeah, to be dismissed or not to work during -- or until the dermatitis is resolved.

So that's one point I wanted to make.

And the other has to do with the conversations and considerations that you were having about the Table number 5.

PANEL MEMBER HAMMOND: May I ask a question?

PANEL MEMBER ARAUJO: Sure.

PANEL MEMBER HAMMOND: Perhaps a naive question. But if the question -- if what you were saying was that the dermatitis could increase the dermal absorption, could that also mean that for a child that has a skin rash, you know, or a cut crawling on a carpet that that would be an

issue?

PANEL MEMBER ARAUJO: Absolutely.

PANEL MEMBER HAMMOND: So that there's a non-occupational way to translate that too to children.

PANEL MEMBER ARAUJO: Yes.

PANEL MEMBER HAMMOND: And children often have cuts and bruises.

PANEL MEMBER ARAUJO: Yes or any condition that increases the dermal absorption. So it could be -- but the problem is that we don't really have data to distinguish in between different possibilities. But until we have the date and given the importance of the effect, I think that it would be relevant to mention it and to raise it as a possibility.

So the other has to do with Table number 5. And I understand the point that John is making about that it doesn't really make much sense and the lack of correlation or continuity in the different categories. On the other hand, I think that what you're trying to do is just combine the data from the different tables that are presented in the publication.

So I did look at the publication and look at the date that you're compiling. And I don't know if I am making my numbers right or wrong, but some of the numbers don't really quite fit the numbers that you have in the

data, in the Table. I don't want to go in excruciating detail. Maybe we can go after and I can show you some of the places where I'm finding inconsistencies.

But what I'm saying -- what I -- I understand what I think that you did is that you combined the data for the males and females in each one of the exposure groups.

OEHHA STAFF TOXICOLOGIST DODGE: Yes.

PANEL MEMBER ARAUJO: And I'm adding up some of the numbers and they don't really coincide with the numbers in here. So I think that -- I don't know if that's going to resolve some of the inconsistencies, but rather than just present that it's inconsistent or not, this is -- data is data, and this is as much as you have from the paper. And I think that as well as you present in your legend and the true descriptions and what it's presented in the paper, I think that that's -- that should be okay.

Another note, and I don't know if this would be important, but in the table, in the description of the incidence of nasal mucosa olfactory, which is your Part C of the middle table, it says you're mentioning intracytoplasmic eosinophilic material, they're actually describing in the table as epithelium intracytoplasmic.

I'm not a pathologist. Although, I have been

appointed in the pathology section.

PANEL MEMBER BLANC: Ah-ha, so you admit it.

(Laughter.)

PANEL MEMBER ARAUJO: I'm not really a pathologist, so I cannot really weigh in on these issues. Bus what I would invite is just to present it as it was presented in the original publication --

OEHHA STAFF TOXICOLOGIST DODGE: Okay, right.

PANEL MEMBER ARAUJO: -- so it gets in with the description. Epithelium intracytoplasmic --

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, right.

PANEL MEMBER ARAUJO: Because otherwise it is a little bit bad, and intracytoplasmic where in what else?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay.

PANEL MEMBER ARAUJO: And that's pretty much it.

PANEL MEMBER BLANC: You know, I would come back to one other thing just to amplify this issue of the neurologic endpoint. Elsewhere where you describe the animal data, you talk about tremors, but not seizures. But these were not studies where they did EEGs at the time that they saw these tremors. So I think you have to at least more explicitly say that it is certainly possible that what was described as tremors was seizure activity.

OEHHA STAFF TOXICOLOGIST DODGE: Okay.

PANEL MEMBER BLANC: I mean a tremulous mouse

could be a seizing mouse until proven otherwise, right? I mean, just -- again, it's just -- it's really amplifying your comment.

And one other thing about the similarities between the two case reports. Looking at the abstracts, these were both -- their reports were also after two to four days of working. So that's not a trivial corollary. So that means that really the dermatitis, if it's related, was simultaneous to the neurologic, not that they had dermatitis for weeks, you know, and then -- the issue of dose related versus idiosyncratic is important, because to the extent that it's an idiosyncratic response that will occur in a certain percentage of the population, these are at-risk individuals, who will respond at levels which are fairly low.

So it means that the argument that this is only an effect that you see with massive exposure, and therefore one could invoke a threshold explanation that would imply that extrapolation to lower dose effects is not relevant biologically, is not the case, if the scenario of toxicity is an Idiosyncratic response, in which an X percentage of the population is going to respond at a fairly low level or could respond at a low level of exposure. That's really the same issue with contact dermatitis, and why the comment this must be a

very rare event.

Well, that's not really the issue. The issue is if it's -- it may not be dose related in that sense, and yet there may be a sensitive subset of the population. Again, coming back to why you're using a safety factor that's relevant for children.

CHAIRPERSON FROINES: I think that the comments that you just made and Jesús made should go into the document.

Jesús.

PANEL MEMBER ARAUJO: Yeah. Your comment of extending and implicating that the tremors could actually be a manifestation -- a neurological manifestation is very well taken.

The case reports are about drastic effects. The case reports were about grand mal generalized tonic-clonic seizures. I mean, a major effect with loss of consciousness and perhaps and -- so this could be an effect that has been underestimated. And seizures can be and can come in various different ways and in a whole spectrum, from very mild, minimal, from things that can be undistinguishable from a tremor as you mentioned, and to the largest expression of it, which is the tonic-clonic seizures.

And in animals, it may be quite difficult to

distinguish what is a partial seizure or what is an -- or to distinguish what is a tremor versus an actual seizure. So these could be more important than what we're seeing just through the case reports.

PANEL MEMBER BLANC: John, there was something that I forgot to ask about.

CHAIRPERSON FROINES: Go ahead.

PANEL MEMBER BLANC: You know, I thought this part was rather interesting where you alluded to early in the document about oligomers that can be present, so that it's not just large polymeric Nylon-6 versus caprolactam monomer.

Do you know whether the analytic methods that are typically used to quantify caprolactam in samples, either of air or dust, would fail to identify -- would only identify monomeric caprolactam?

OEHHA STAFF TOXICOLOGIST DODGE: The methods that they used, I think, it's a high pressure liquid chromatography, yeah, can get separate peaks for various oligomers or in caprolactam.

PANEL MEMBER BLANC: So the approved NIOSH method for caprolactam is --

OEHHA STAFF TOXICOLOGIST DODGE: Would not pick up these other --

PANEL MEMBER BLANC: Because that's not a high

pressure liquid chromatographic --

OEHHA STAFF TOXICOLOGIST DODGE: I'm not sure what method they used there.

PANEL MEMBER BLANC: So I think it would be useful to have a sentence or two that would say all of the things we're talking about are unlikely to have included, the health -- or we do not know anything about the health effects of the oligomers. And many of the studies would -- we have no way to know whether they're extrapolable or not.

Just some caveat like that, because it's sort of a black box. And it may have public health significance that we don't know about. I think you indicate that it's not an insubstantial proportion relative to the caprolactam monomer, right, that's present.

OEHHA STAFF TOXICOLOGIST DODGE: Right. The monomer seems to be the most prevalent that's there. But yeah, when you add up all the other products of caprolactam that could be there, yeah, it does add up.

PANEL MEMBER BLANC: So think that that's sort of alluded to you, but then there's never any follow through on it. And I think it's important to get it out there a little bit more explicitly.

And finally one other point I meant to ask and I forgot to. In your list of uses, the bullets on page 3,

is followed by a paragraph of discussion. And generally speaking, the paragraph is consistent with the bullets, except for one thing and that's tire cord. I always thought that it was Nylon-6,6 that was the predominant nylon that was used in tire cord, but I could be completely wrong about that. Are you sure about that bullet?

OEHHA STAFF TOXICOLOGIST DODGE: That's -- I got that from the Nylon-6 website, the Nylon-6 group. I forget what it is. I reference it in there, yeah. But they claim tire cord is one of the uses. I don't know if -- it's quite possible that both Nylon-6,6 and Nylon-6 are used for tire cord.

PANEL MEMBER BLANC: Because then it's not in the narrative that follows, so that's why I was asking. You know, you have nice examples of all the rest mainly. I mean, if 75 percent is used in fibers, textile, industrial carpet and 25 percent for plastics, I don't know, I guess the fibers could include the fibers used in tire cord, but I -- just double check that, so that you feel comfortable with it. Because if tire cord is like a trivial and very uncommon usage, you might not want to -- you know, if 99 percent of the nylon that's used in tire cord is Nylon-6,6, don't -- you know then delete it, because it only makes it sound like we don't know what we're saying.

And I do think, by the way, that the clarifications that you made on particulate versus -- solid particulate versus aerosol versus vapor was useful.

OEHHA STAFF TOXICOLOGIST DODGE: Thank you.

CHAIRPERSON FROINES: Are you finished, Jesús?

PANEL MEMBER ARAUJO: Coincidentally, I had one paper where they approached the point that you just mentioned about the monomers versus the polymers. It is an article in Biomaterials and that was not cited in this document, in 2005. And they look at the cytotoxicity of -- in various polymers by LDH assay and MTT assay. And they found that the monomers are much -- have much greater toxicity than the corresponding polymers.

But rather than just summarizing, I can also give you the reference. I know you feel --

OEHHA STAFF TOXICOLOGIST DODGE: Yes, thank you.

PANEL MEMBER BLANC: How long were the chains of the...

PANEL MEMBER ARAUJO: We can look at the paper quickly. Well, actually quite significant changes.

PANEL MEMBER BLANC: I mean, how long were the -- I mean how long were they? Were these oligomers or really big chain polymers?

PANEL MEMBER ARAUJO: Oh, I see. I thought that you were asking how significant were they?

PANEL MEMBER BLANC: See, there's these oligomers of you know two or three molecules, and that's going to be pretty different than, you know -- not that they shouldn't cite this paper, but I'm just saying.

PANEL MEMBER ARAUJO: I'm sure that within this paper I will be able to find out.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We'll look at it.

PANEL MEMBER GILL: When you look at it, the free amine should actually have the greatest toxicity, if you look at the structure. Did you look at the free amine itself? It should be a precursor to the caprolactam?

OEHHA STAFF TOXICOLOGIST DODGE: I'm sorry.

PANEL MEMBER GILL: The free amine. Do you have any information on the toxicity of that compound, because that's what a precursor should be.

OEHHA STAFF TOXICOLOGIST DODGE: No, I don't.

CHAIRPERSON FROINES: Jesús, are you finished?

PANEL MEMBER ARAUJO: Yes, I'm finished. Sorry.

CHAIRPERSON FROINES: Okay. Kathy is leaving at 1 o'clock, so why don't we move to Kathy and see if she has any comments, because -- but we should probably break about 12:30 for lunch.

PANEL MEMBER HAMMOND: I don't have any comments.

CHAIRPERSON FROINES: What?

PANEL MEMBER HAMMOND: I don't have any comments at this point.

CHAIRPERSON FROINES: So jumping -- since we're talking about exposure, Bill, do you have comments.

PANEL MEMBER NAZAROFF: Just a few.

So, first, I conveyed a few comments to Melanie in response to receiving the document. And I just want to reiterate the key points from that. I thought overall the exposure -- the response to the exposure critique or the critiques about the exposure aspect was handled quite well. And I'm satisfied, at this point, with how the issue of gas versus aerosol, and how that relates to exposure is described in the revised document. Thank you for those changes and that responsiveness.

There are some -- this is a minor point, but some places in the document where references to tables are inaccurate, so that needs to be checked to be sure that everything is internally consistent.

I had raised the point that was addressed in the presentation, appropriately I think, about rounding. And just to get this on the record, it doesn't make any sense to me to, if one is rounding to one significant figure to apply that rule when one and most commonly usefully as well too, is the first significant figure, because there's considerable ambiguity and much larger error when that

first digit is one inherently.

So what I had recommended, and I think you've responded to in a way that is consistent with that, is if the first digit is a 1 or 2, you use two significant figures and then use 1 significant figure for the rest, and that keeps the error scale roughly commensurate across the different numbers. It's the 1.5 significant figure rule.

PANEL MEMBER HAMMOND: I never heard that rule and I --

PANEL MEMBER NAZAROFF: There's no rule. I made it up.

(Laughter.)

PANEL MEMBER NAZAROFF: It's completely logical.

(Laughter.)

PANEL MEMBER GLANTZ: It's the Nazaroff rule.

PANEL MEMBER HAMMOND: It makes really good sense. I mean -- but I've just never seen that before. No, I think it's a great idea.

PANEL MEMBER NAZAROFF: So then the last thing, and this is also pretty picky, but as long as we're here, on the poster where they have sort of America's most hated units, there's a special entry there for millimeters of mercury for pressure.

It just is -- you know, if you want to be clear

in communication, you don't use a height of a particular fluid as a way to express a pressure. I mean, I know what it means, but it's like -- it's not good scientific communication. We should express pressure units in their fundamental basis, which is force per unit area. Pascal is appropriate. Atmosphere is fine. A bar, if you want to use a bar is okay.

PANEL MEMBER HAMMOND: Torr?

PANEL MEMBER NAZAROFF: A Torr is okay. My preference Pascal. Millimeters of mercury no. Really, it --

PANEL MEMBER BLANC: How about as a compromise that they put one or the other in parentheses, because I have to tell you that most of the available tables that health professionals and safety have, have these kind of units. And so it will be obscure and inaccessible if they do only what you say.

PANEL MEMBER NAZAROFF: I will accept the compromise. A transitional period is acceptable, but we're on our way to having units mean what they mean and measuring in the right sets of dimensions inherently.

That's all. Thank you.

CHAIRPERSON FROINES: Ellen.

PANEL MEMBER EISEN: No, I don't have any comments.

CHAIRPERSON FROINES: Okay.

Stan.

PANEL MEMBER GLANTZ: I don't have anything more.

CHAIRPERSON FROINES: Sarjeet?

PANEL MEMBER GILL: Nothing more.

PANEL MEMBER BUCKPITT: Nothing more.

CHAIRPERSON FROINES: My goodness. You really did a number.

PANEL MEMBER GLANTZ: You wore us all down.

(Laughter.)

CHAIRPERSON FROINES: So we've had --

PANEL MEMBER GLANTZ: That was a joke.

It was very thorough.

PANEL MEMBER BUCKPITT: Thorough.

PANEL MEMBER BLANC: You know where you talk at the beginning, by the way, about sources of exposure in the manufacturing of the Nylon-6, and then in the places where it's been put down and all that kind of stuff and recycling, which is all great. Obviously, another source of exposure are the people who manufacture caprolactam in the first place.

OEHHA STAFF TOXICOLOGIST DODGE: Right.

PANEL MEMBER BLANC: You might want to say that.

OEHHA STAFF TOXICOLOGIST DODGE: That's what I meant by production of caprolactam. Yeah, I meant the

manufacture of the monomer.

PANEL MEMBER BLANC: I thought you meant the manufacture of the nylon monomer.

OEHHA STAFF TOXICOLOGIST DODGE: In there too.

PANEL MEMBER BLANC: You say polymerization of the monomer, but the step before the polymerization where you make the monomer itself?

OEHHA STAFF TOXICOLOGIST DODGE: Um-hmm.

PANEL MEMBER BLANC: I take it there's no monomer factory in California?

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: No.

PANEL MEMBER BLANC: Is there any polymerization in California?

OEHHA STAFF TOXICOLOGIST DODGE: I found places, yeah.

PANEL MEMBER BLANC: I mean, there are definitely places that use the stuff -- I mean, that make -- that use applications of it, but I'm just --

CHAIRPERSON FROINES: There is an application that's coming on -- apparently coming on line with nylon, where it is used in dry-cleaning. And that may be a source of exposure in the future.

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL:

There's likely to be --

OEHHA SUPERVISING TOXICOLOGIST MARTY:

Caprolactam as a dry-cleaning agent?

CHAIRPERSON FROINES: No, not caprolactam, but caprolactam obviously with nylon you have the potential for a monomer that's been in nylon.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Getting extracted?

CHAIRPERSON FROINES: Yes.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I see.

PANEL MEMBER GLANTZ: So should we make a motion?

CHAIRPERSON FROINES: I think I want to ask a question. I've already spoken at great length.

But in here you have the authors concluded that the irritant response threshold for the workers is at least or near 10 ppm. And that 5 ppm is 50 percent of the discomfort threshold, and quote, "...somewhat below the no effect level".

It seems to me that I have no idea where they got that 50 percent number. It seems like it's somebody taking it out of the sky, unless there's an experimental basis for it, in which case, I would say that it's not clear that the 5 part per million represents anything. I don't think -- I think it -- it's somebody's opinion rather than somebody's science, I think?

OEHHA STAFF TOXICOLOGIST DODGE: Yeah. That was their opinion. And it was partly based on the fact that

they did, you know, time-weighted average, threshold measurements of 8 hours. And, at one point, there was exposure of 7 parts per million, and the worker didn't --

CHAIRPERSON FROINES: Well, I think it would be worthwhile just to put in a sentence that says this is the views of the authors and not necessarily the views of OEHHA, because --

OEHHA STAFF TOXICOLOGIST DODGE: Okay. I'll clear that up.

PANEL MEMBER BLANC: Back to that quotation marks idea.

CHAIRPERSON FROINES: Yeah, because there are quotation marks in here that there -- you actually put quotation marks here, but you need your non-quotation mark comment.

OEHHA STAFF TOXICOLOGIST DODGE: All right. I'll clear that up.

CHAIRPERSON FROINES: I thought -- I'm still confused about exposure, but I won't raise it here. I don't think it's germane, but there's issues of the polymer and various stages of the polymer, which are -- would be an aerosol presumably -- also whether we're talking at times about caprolactam absorbing onto hair particles.

So I think that the issues of aerosols and fumes

and what have you is still an issue, but I can get back with you on that.

I do think when you have -- talk about air sampling, you talk about the process of sampling, where you have the 3 flasks and the flasks are filled with water and so on and so forth. But the analytical method is not here, so nobody knows what the analytical method that was used is.

OEHHA STAFF TOXICOLOGIST DODGE: Okay. I'll put that in. It was a gas chromatograph.

CHAIRPERSON FROINES: Gas chromatography, because you said a few minutes ago that they used HPLCs. I mean, some used --

OEHHA STAFF TOXICOLOGIST DODGE: Later studies.

CHAIRPERSON FROINES: Later studies.

OEHHA STAFF TOXICOLOGIST DODGE: Yeah, but these older ones.

CHAIRPERSON FROINES: Later studies. Yeah, I appreciate that. Just clarification as to the exposure methodology.

PANEL MEMBER BLANC: So I see a little bit of a complex issue here. I alluded to it before. There's two pathways we could be going down. You know, tomorrow you may get on the phone with Ziegler and he'll say I'm sending you a disc with the data or, you know, tomorrow

nothing may change or this week or whatever.

So obviously, it doesn't make sense for us to have a motion which tentatively accepts the document, but we don't accept it if you get the new data and that we would want to see what you do.

I think the more manageable approach would be to say that -- I mean, I think that the Panel's comments certainly document our overall acceptance with certain changes of the approaches used, and certain additions and new data that you've been given. But I would prefer not to have a motion that is a tentative acceptance at this time, bearing in mind that, at our next meeting, whichever version you bring to us will probably not engender a lengthy agenda discussion and can be dealt with at that time, you know, fairly easily.

I know that that does prolong or put in another round of comments from stakeholders, and so forth, because they'll be of a version that will subsume this version one way or the other, but I think that certainly in the scenario that you do get the data in and are able to generate an acute REL, then you certainly would want to have an opportunity for that stakeholder comment. And in the event that you don't, there probably is still enough changes that it's not harmful to have such an opportunity for comment.

CHAIRPERSON FROINES: I think that what's happened here today is that there has been an apparent general acceptance of the ideas in the document. But we've asked for quite a few changes. And I think that the magnitude of the changes makes it difficult to go in a different direction than you just suggest, but it's up to everybody, obviously.

PANEL MEMBER GLANTZ: Well, actually, I sort of disagree. I think there's been a lot of comments, but I have heard anything that makes me feel that there's a fundamental problem with the document. I mean, all of the comments I've heard have been -- except for this, if you can get the data from Ziegler have all been, unless I'm missing something, clarifications, improvements, things like that. I don't see any of these things being substantive changes to the document.

And I worry that this -- you know, we're dealing with someone -- with this Ziegler data who's been very uncooperative. And I'd just hate to see the process just keep dragging on and on and more stakeholder feedback and having to read it and then having to respond to it.

So I would much rather tentatively accept the document, subject -- as we've done many times, you know, and delegate to the Chair the ability to say the changes have been made correctly, with the caveat that within a

reasonable length of time, you can get the raw data, then we would hold open the one issue of the acute REL.

And if you're able to get the data and could get an acute REL, then that one issue would be open for public -- because I think if you do it, then it is legitimate to have public comment on that. And then --

CHAIRPERSON FROINES: I'd like to disagree.

PANEL MEMBER GLANTZ: And we've done this before on a couple of other documents, so that we can get the rest of it and be done with it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Can I --

PANEL MEMBER GLANTZ: And just have that one narrow question, if within -- you know, and I don't know what a reasonable time is you could get the data, a couple of weeks maybe, then we could approve the rest of the document, bring that one issue back after public comment, and then, fine. And if you can't get it within a couple of weeks, I think we should just be done.

CHAIRPERSON FROINES: No, let me --

PANEL MEMBER GLANTZ: That's me. Alan, do you --

CHAIRPERSON FROINES: No, I'm going to. Our job is to evaluate the science of the process in every document we look at, and that includes the intellectual elements, which has to do with the substance of the document and the substance of the science. It also has to

do, however, with the presentation.

And we have made fairly extensive requests for changes to the presentation. And I think that it's within that criteria that I would argue that Paul is right, that having the vote on acceptance when we haven't seen whether or not the document meets our -- we're comfortable with what is the end result, I think is important.

Melanie.

OEHHA SUPERVISING TOXICOLOGIST MARTY: I just want to make a couple clarifications. First of all, remember that the stakeholders can send you whatever they want. It was -- that was not an open public comment period. So we did not have an open public comment period.

If we get raw data and then can generate an acute REL, we would have a public comment period on that. And it can be a completely separate document. It doesn't have to be this document redux, it can be its own document.

PANEL MEMBER GLANTZ: Well, then if that's the case -- yeah, I agree with you about presentation, but I still don't see the things that have been talked about here as being a big deal. Maybe I'm misunderstanding something.

So if that's the case, if you can get the data for an acute REL and then just bring that forward as a separate document or in a -- which would basically addend

or replace part of this one, then I'd still like to move that we tentatively accept the document subject to, you know, them making the Chair happy. If the Chair is uncomfortable, you could always say I'm not happy and bring it back to the Committee. But I just -- I agree with the suggestions that have been made. I think they'll improve the document. I just don't think they're that big a deal.

CHAIRPERSON FROINES: I think -- speaking --

PANEL MEMBER GLANTZ: But if you're uncomfortable that, then --

CHAIRPERSON FROINES: Speaking as the Chair, I'd prefer that the Panel had a look at what the changes were, and they can communicate that very briefly in the next meeting and vote. We can do it in 10 minutes if it's -- unless there's a problem. I mean, so there's --

PANEL MEMBER BLANC: Yeah, I think it would help me -- I mean, I was one of the leads, and, Stan, you were de facto sort of another lead, so we clearly don't agree. But we've always managed to come to consensus as a Panel.

PANEL MEMBER GLANTZ: Okay, if that's what people feel, then that's okay.

CHAIRPERSON FROINES: Any other comments?

Shall we take a vote or is it --

PANEL MEMBER BLANC: I don't think there's

anything -- there's no motion to vote on.

PANEL MEMBER GLANTZ: Okay. Then I'll withdraw my motion.

PANEL MEMBER NAZAROFF: Sort of yeah, it was a hesitant motion.

(Laughter.)

PANEL MEMBER GLANTZ: I'll just withdraw my motion, we we're all parliamentarily clean.

CHAIRPERSON FROINES: So should we break for lunch?

PANEL MEMBER GLANTZ: I hope we can do this quickly though to some --

CHAIRPERSON FROINES: No, obviously, we want to do it quickly.

PANEL MEMBER BLANC: It's my commitment and my comment was predicated on it being a rapid discussion, presuming that there's not a new REL. And that if there's a new REL, we would have to discuss that.

I'm happy to break for lunch. What time are you proposing we reconvene?

CHAIRPERSON FROINES: I don't know where -- Peter, where do people eat around here.

MR. MATHEWS: Directly upstairs.

PANEL MEMBER GLANTZ: There's a Cafeteria.

CHAIRPERSON FROINES: So we can take 45 minutes,

do you think?

MR. MATHEWS: Easily.

PANEL MEMBER BLANC: So 1:15.

CHAIRPERSON FROINES: 1:15, and we'll do nickel.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: Okay. Melanie, are you set?

(Thereupon an overhead presentation was Presented as follows.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: So this afternoon, we'll start off with Dr. Joe Brown. Joe is going to go over the nickel reference exposure levels, the derivation, and some of the data behind it.

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OEHHA STAFF TOXICOLOGIST BROWN: Okay. Just we're talking about non-cancer RELs here. Just to remind everybody -- can you hear me?

PANEL MEMBER BLANC: Yeah.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. This slide just summarizes our authority under the Hot Spots Program Legislation and also the Children's Environmental Health Protection Act of 1999. Those are the two main laws that we're operating under. And those are the mandates that we have.

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OEHHA STAFF TOXICOLOGIST BROWN: Summary. Nickel. Actually, more than Nickel (II), as Dr. Nazaroff pointed out, causes a variety of non-carcinogenic toxic effects, including occupational contact dermatitis,

occupational asthma, and reproductive toxicity in humans.

Studies in experimental animals exhibit immune suppression, nephrotoxicity, pneumotoxicity, perinatal mortality, and altered gene expression.

The most sensitive effects appear to be in the lung and the immune system.

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OEHHA STAFF TOXICOLOGIST BROWN: Nickel has a high potential for exposure, widespread occurrence, numerous uses. Effects leading to differential impacts on infants and children, include adverse impacts on the respiratory and immune systems, including asthma, which is covered in sections 5, 6, 8, and 9, and increased perinatal mortality and a reduced birth weight observed in animal studies of reproductive toxicity. And that's covered in Section 7.2.

The basis of all the data that we've looked at, we make a conclusion that OEHHA recommends that nickel be identified as a toxic air contaminant, which may disproportionately impact children, pursuant to Health and Safety Codes Section 39669. This is the Children's Environmental Health Protection Act.

CHAIRPERSON FROINES: May I ask a question?

When we first did SB 25, the Panel was limited to five chemicals. And then we added indoor -- environmental

tobacco smoke. And the question is, what's the situation in terms of how many you can bring forward to the Panel under SB 25?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay, let me answer that. This is Melanie Marty.

The way we interpret the statute is we were limited to five only for the initial list. So we have subsequently added several, through this process, of looking at reference exposure levels for use in risk assessment.

So in addition to the ETS, we've added acrolein, acetaldehyde, formaldehyde, mercury, manganese, and arsenic. And just a reminder, especially for those who are not totally familiar with the air programs in California, nickel is already identified as a toxic air contaminant. We did a review of the -- primarily, the carcinogenicity at the time. So we are not dealing with carcinogenicity this time.

PANEL MEMBER BLANC: And is -- Melanie, just to clarify. Is that true for every -- will that be true for any carcinogen that you feel has significant non-carcinogenic toxicity that you have to re-review it for its non-carcinogenic effects?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. It's actually -- this is actually being done under the Air

Toxics Hot Spots Program, which is a risk assessment program that came into being well after the toxic air contaminant program. So we're using that process to look at the non-cancer health effects from a quantitative risk assessment perspective.

But initially, way back when we first started the TAC program, we focused on carcinogens. And obviously, many carcinogens also have other types of toxic effects. So there's very few actual TAC identification documents, where we did a quantitative risk assessment for non-cancer health effects, very few.

PANEL MEMBER BLANC: So do you anticipate this is the first of a group that may come?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, we have looked at arsenic, which is a carcinogen in 2008, I think it was. So we're just -- we're going along using the prioritization that we did way back in 2001. If you guys remember, there was a lot of chemicals that we looked at, that kind of ranked towards the top, but didn't quite hit the top five.

So we're going through those first. And we're also looking at chemicals that the Air Board and the air pollution control districts view as problematic for -- in terms of emissions in their area.

PANEL MEMBER BLANC: Okay. Because, you know, I

know that when -- certainly, when I was reviewing your overall more global ranking attempts, you know, my impression was always that what we were trying to do there was identify substances which we really hadn't looked at for any endpoint, rather than going back to do non-cancer health effects in something which already was a listed toxic air contaminant.

And certainly, I don't want to try to speak for others, just for myself, I think what I, you know, want to see or make sure that we don't miss are substances which we haven't dealt with at all for any endpoint. And at least that once we have identified something as a toxic air contaminant, there are certain things that flow out of that, even if we haven't looked at all the endpoints.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. Well, some of it -- the statute itself referred to chemicals that were already identified as TACs.

PANEL MEMBER BLANC: For the Children's --

OEHHA SUPERVISING TOXICOLOGIST MARTY: For the Children's list.

PANEL MEMBER BLANC: Right. That's where this is coming.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's why we're looking mostly at things that have already been identified as TACs, but we're slipping in other --

PANEL MEMBER BLANC: New things

OEHHA SUPERVISING TOXICOLOGIST MARTY:

-- compounds for reference exposures levels. We won't be able to do this process, declare it a TAC, unless it actually is one already.

PANEL MEMBER BLANC: Right.

OEHHA SUPERVISING TOXICOLOGIST MARTY: And we were able to use the ETS document to get ETS on that list, once it was identified.

CHAIRPERSON FROINES: But you have 180 some HAPs that are TACs.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Correct.

CHAIRPERSON FROINES: So you could look at those.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes. And some of them are -- we have been.

CHAIRPERSON FROINES: What's your status with respect to pesticides. Do you have authority for pesticides?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No.

CHAIRPERSON FROINES: Because Cory-Slechta has some nice work on perinatal effects associated with her studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: The statute specifically disallowed us from looking at pesticides.

PANEL MEMBER BLANC: Okay. Sorry for the diversion.

CHAIRPERSON FROINES: Go ahead.

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CHAIRPERSON FROINES: I think it's important, because I think people are new to the Panel, so this is helpful.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. Continuing on. Nickel sources. Air. The annual statewide average ambient air concentration for nickel 2002 was 4.5 nanograms of nickel per cubic meter. That's from the Air Board, 2008.

Soil concentrations throughout the U.S. range from less than 5 to 700 ppm, geometric mean of 13 plus or mine 2, from Geological Survey.

Drinking water general contains nickel at concentrations ranging from 0.5 to 25 micrograms of nickel per liter.

PANEL MEMBER EISEN: Excuse me. So nanograms of nickel, nanograms per meter cubed, is that micrograms?

PANEL MEMBER NAZAROFF: No. It's got to be nanograms.

OEHHA STAFF TOXICOLOGIST BROWN: Air is in nanograms. Water is micrograms.

PANEL MEMBER NAZAROFF: This is a correct

reporting.

PANEL MEMBER EISEN: Right. So how do I translate that to though to micrograms?

PANEL MEMBER NAZAROFF: Oh, divide by a thousand.

PANEL MEMBER EISEN: So that would be 0.004.

PANEL MEMBER NAZAROFF: 004, 005.

OEHHA STAFF TOXICOLOGIST BROWN: That figure is the average from the Air Board's monitoring network. So it varies from region to region

In food, the mean and median concentrations of nickel in combined dietary solids and liquids were 47 and 43 micrograms of nickel per kilogram respectively.

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OEHHA STAFF TOXICOLOGIST BROWN: Toxicokinetics oral absorption ranges quite a bit depending on water solubility from 0.5 to 40 percent. Also, vehicle, whether it's water or food or whether the animals are fasted or fed.

Inhalation. Fifty percent of soluble nickel chloride cleared from the lungs in three days. Insoluble forms are cleared much more slowly. For example, the half-life for nickel oxide in the lung of 12 and 21 months depending on particle size.

Distribution in all tissues is somewhat dependent on water solubility and dose. For nickel sulfate, the

ranking goes kidney greater than testes greater than brain greater than spleen greater than heart greater than liver.

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OEHHA STAFF TOXICOLOGIST BROWN: Excretion. Most nickel compounds observed from the diet and environmental media are rapidly excreted in urine, generally, as first order elimination candidates with half lives of 60, 50 hours in rats and 83 hours in rabbits. So you have a fast phase followed by a slower phase.

Excretion in sweat and milk are possible, excretion routes for humans.

A number of models were covered. Apparently, we missed a couple, which is sort of surprising, because I'm familiar within Dan Menzel's work on arsenic modeling, but I guess I missed his stuff on nickel.

Anyway, there is a section of discussion of that and some model code and an appendix for people that are interested.

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OEHHA STAFF TOXICOLOGIST BROWN: Acute toxicity in humans. There's an oral study from Sunderman 1998. Thirty-two workers consumed 0.5 to 2.5 of nickel, Nickel (II) as chloride and sulfate in drinking water. Twenty had nausea, vomiting, and abdominal discomfort, giddiness, lassitude, headache, cough, shortness of breath for a few

hours to several days

An inhalation study in occupational workers with asthma tested for lung function with 30 minutes exposure to 0.3 milligrams per cubic meter of nickel sulfate. Six out of the seven had significantly decreased FEV_1. That's Forced Expiratory Volume one second greater than 15 percent. That's Cirla, et al. study.

Now, this study is the basis of our current acute REL for nickel. And we're using it again with slightly revised uncertainty factors. I went back and read this study. And you'll notice there's inequality there. They don't actually give the actual values for the FEVs that were observed. They were all greater than 15 percent.

Also, the study is in middle-aged asthmatics. And I just wonder whether this study is adequately representative of children with asthma, whether children, you know, would have greater sensitivity to inhaled nickel than these middle-aged occupational asthmatics.

Yes.

PANEL MEMBER BLANC: I mean -- well, to the Chair, do you want us to have questions at all now or do you want us just to hold them.

OEHHA STAFF TOXICOLOGIST BROWN: Well, I just want to mention it and we'll come back to it, because this study is -- we're going to give the rationale for

developing an acute REL based on it, so we can discuss it again there.

CHAIRPERSON FROINES: We've generally said that clarifying questions should occur during the presentation, but the major discussion would occur subsequent. But if you have something that's important, I think it's relevant to raise, as long as it's within those guidelines.

PANEL MEMBER BLANC: I'll come back to it, because I think this is a major methodologic question, because I think you're using the study to do something which is not what you think you're doing with it.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. It's probably the weakest of all the studies that we're looking at here. But we've used it before, and there's not a better one that we can find.

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OEHHA STAFF TOXICOLOGIST BROWN: Acute toxicity in animals. Water soluble nickel compounds are more acutely toxic than water insoluble ones by the oral route. Nickel sulfate, nickel acetate, single dose oral LD_{50}'s range from 39 to 141 mg/kg in rats and mice.

On the other hand, nickel oxide, nickel subsulfide. Single oral LD_{50}'s were greater than 3,000 mg/kg in rats and mice. Much less toxic. On the other hand, if you look at inhalation exposures, 6 hour per day,

5 days a week for 12 days, 5 to 10 milligrams of nickel subsulfide caused lung pathology, mortality, and mortality at higher doses in mice and rats. So the insoluble ones are much more toxic by the inhalation route.

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OEHHA STAFF TOXICOLOGIST BROWN: Immunotoxicity was also observed in mice. The Graham et al. study, which we've use. Six-week old mice exposed from 0 to 490 micrograms of nickel per cubic meter nickel chloride, less than 3 micrometers in particle size for 2 hours.

Exposed animals gave significant decrease in antibody-forming cells after antigen challenge. A LOAEL of 250 was identified. NOAEL of about 100 by the author.

We did our own dose response on this and calculated BMDL of 164.6 micrograms of nickel per cubic meter, using a benchmark of a loss of 100 plaques per million cells exposed. And actually, there's a figure of this, I think.

Next slide.

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OEHHA STAFF TOXICOLOGIST BROWN: So this shows the linear response. Also reported by the author with a fitted equation, we'd applied the benchmark dose model here and got a BMDL of approximately 165 micrograms of nickel per cubic meter.

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OEHHA STAFF TOXICOLOGIST BROWN: Reproductive and developmental toxicity in animals. There's a 2-generation reproduction study in rats at 0, 0.22, 0.56, 1.12, or 2.23 milligrams of nickel per kilogram day by nickel sulfate aqueous gavage. Minimum of 70 days of treatment. This is an industry-sponsored study.

Dose related increases we're seeing in perinatal mortality. A LOAEL was identified as to 2.2 mg per kilogram day, and a NOAEL of 1.12 mg per kilogram day.

Another study was spermatotoxicity in mice, Pandey & Srivastava, 2000. Male mice orally administered 0, 5, 10 and 20 mg of nickel sulfate or nickel chloride per kilogram day, times five days per week times 35 days.

Observations were significant. Decreases in sperm count at 20 and motility at 10 and 20 milligrams per kilogram day. Increases in abnormal sperm shapes were seen at 10 and 20 milligrams per kilogram day.

And our benchmark dose value that we observed here fitting the data was 2.91 milligrams per kilogram day for sperm motility, for nickel sulfate, and 0.46 for nickel sulfate, and 0.34 for nickel chloride mg per kilogram day for sperm abnormality. That's our own analysis of the data.

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OEHHA STAFF TOXICOLOGIST BROWN: Reproductive and developmental toxicity in humans. There was a number of studies by Vaktsjold et al. One on spontaneous abortion, case controlled study in female nickel refinery workers. The odds ratio for association between nickel exposure and spontaneous abortion was 1.38, with a 95 percent confidence interval of 1.04 to 1.84. That's unadjusted.

When you adjust the data, the significance is not quite there, but it borderlines. The author said possibly a weak excess risk.

Semen quality. Another study by Danadevi. Semen quality in 57 workers exposed to nickel and chromium and compared to 57 unexposed controls. So there's co-exposure with chromium here.

Sperm concentration was reduced in exposed group --

CHAIRPERSON FROINES: Is this to the nickel and chromium --

OEHHA STAFF TOXICOLOGIST BROWN: Mixed, yeah.

CHAIRPERSON FROINES: -- metal?

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

CHAIRPERSON FROINES: It's not a solid.

OEHHA STAFF TOXICOLOGIST BROWN: I think it must -- well, let's see now.

CHAIRPERSON FROINES: It's not a solid, it

wouldn't be chromium 6, for example.

OEHHA STAFF TOXICOLOGIST BROWN: I don't think it's -- I'm not sure if it's Chromium-6 or not. It might be. I don't know. I'd have to check that.

CHAIRPERSON FROINES: Well, we need to know the valence state basically.

OEHHA STAFF TOXICOLOGIST BROWN: Yeah. Anyway, the chromium apparently didn't have any effect, because the reduction in sperm concentration to 14 mill from 62 million which is a significant drop. Rapid -- there's also a rapid reduction in linear sperm motility and an increase in sperm tail defects. The correlation was with increased blood nickel and negative with association with chromium. So I'm presuming this is inhalation exposure and they were tracking blood concentrations of nickel and chromium.

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CHAIRPERSON FROINES: I would guess there are design issues in that study.

OEHHA STAFF TOXICOLOGIST BROWN: This is another study looking at lung radiographic abnormalities defined as pulmonary fibrosis, or PF, in workers exposed to airborne nickel. This is the Berge and Skyberg study.

Odds ratio for PF and soluble nickel was 4.34 with a confidence interval 1.75 to 10.77. That's

unadjusted. And when they adjusted it for age, smoking, asbestos and sulfidic nickel, the significance dropped. So it was, you know, boderline 0.82 to 6.16.

When they looked at sulfidic nickel, the odds ratio was 5.06 unadjusted. It also dropped when it was adjusted to the same things, but in this case to soluble nickel instead of sulfidic obviously.

We did a benchmark dose on this and we found the dose response as 0.35 for soluble and 0.19 for sulfidic, using a metric of cumulative nickel exposure as milligrams of nickel per cubic meter per year. So it's questionable what's going on here. There's obviously somewhat of a dose response. Whether it's significant or not, I think this is a question. We're using it as sort of a supporting study.

The results indicate dose response for cumulative nickel exposure, and pulmonary fibrosis. Mean and median exposure periods were 21.8 and 21.9 years respectively.

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OEHHA STAFF TOXICOLOGIST BROWN: Chronic toxicity in animal studies. A study by Oller et al., using inhaled nickel metal now in rats at 0, 0.1, 0.4 or 1 milligrams of nickel per cubic meter. And these were particles with a mean diameter of 1.8 micrometers, 6 hours a day, 5 days a week, for 24 months. No NOAEL was observed.

Respiratory lesions included alveolar proteinosis, alveolar hystocytosis, chronic inflammation, bronchiolar-alveolar, hyperplasia, and bronchial lymph node infiltrate.

An NTP study, and there's a couple of these NTP studies, which are quite extensive. Chronic study of nickel sulfate, now hexahydrate in rats. Exposures of 0, 0.03, 0.06 or 0.11 milligrams of nickel per cubic meter as above same sort of regime.

They observed lung inflammatory lesions, macrophage hyperplasia, and nasal epithelial atrophy seen at 0.06 and above. And identified a LOAEL of 60 micrograms per cubic meter.

CHAIRPERSON FROINES: What was the size distribution?

OEHHA STAFF TOXICOLOGIST BROWN: I think it's on another slide. That certainly is part of our analysis that I'll be talking about later in the -- I'm pretty sure it was 2.5 with a standard deviation -- or a geometric deviation of 2.38, but I think that's on a later slide.

Anyway there's a LOAEL of 60, a NOAEL of 30, and a benchmark dose of 30.5. So you see, in this case, the benchmark dose at a 5 percent level basically matches the NOAEL that was observed.

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OEHHA STAFF TOXICOLOGIST BROWN: Continuing on with chronic toxicity animal studies. This is another NTP stud. This is now in the nickel oxide in mice exposed to 0, 1.0, 2.0, or 4.0 mg of nickel per cubic meter, 6 hours per day, 5 days a week for 24 months. Again, lung lesions similar to other studies, bronchial lymph node, hyperplasia evident in all nickel exposed animals.

A NOAEL was not observed. A LOAEL of 1 mg per cubic meter. And we did a benchmark dose and got 117 micrograms of nickel per cubic meter for the endpoint of alveolar proteinosis. And that's reported in the document.

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OEHHA STAFF TOXICOLOGIST BROWN: Are there any questions at this point, because I'm going to launch into the derivations now of the various values we came with up.

This is the one for the acute REL. Again, this is the Cirla study, which we acknowledge as sort of problematic in 7 metal plating volunteers with occupational asthma. Exposure was 0.3 mg of nickel hexahydrate per cubic meter. That translates to 67 micrograms of nickel for 30 minutes. LOAEL of 67 for 30 minutes for an FEV1. NOAEL was not observed.

For a 1-hour adjustment we adjust this to 33 and then we apply a LOAEL uncertainty factor of 10. And an

intraspecies of root 10, because this is to account for children as opposed to adult asthmatics. That gives us a cumulative UF of 30 and an aREL of 33 over 30 or 1.1 micrograms of nickel per cubic meter.

So do we want to discuss this study now or do we want to wait until I've gone through the derivations of all of the RELs?

Dr. Blanc, it's up to you?

PANEL MEMBER BLANC: No, I'm not a lead. I think it will be up to the leads to say you want to keep going and then does this all at the end?

OEHHA STAFF TOXICOLOGIST BROWN: Okay. This is the 8-hour REL. And here we're using the Graham study, the one where I showed you the linear graph of the dose response, also supported by the NTP 1994c study.

In this case, the study population's female mice exposure of 100 to 490 micrograms of nickel chloride per cubic meter for 2 hours. The effect noted was depressed antibody response to sheep red blood cells.

The authors identified a LOAEL of 250. We have a benchmark dose of 165. And the NOAEL of 100, I think, is questionable in this case.

The BMDL extrapolated from 165 is 82 for 8 hours. The LOAEL uncertainty factor we're applying here is root 10 for a BMR analysis. In other words, we did a dose

response analysis, so we don't feel we need to apply a full 10-fold here.

Interspecies 10 and intraspecies 30, which includes factors for both pharmacokinetic and pharmacodynamic factors, giving an overall UF of 1,000. And 82 divided by 1,000 is 0.08 micrograms of nickel per cubic meter. That's the value we're proposing for the 8-hour REL.

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OEHHA STAFF TOXICOLOGIST BROWN: For chronic REL for nickel and nickel compounds, except for the nickel oxide, we're using the NTP 1994c study.

Study population here is male and female rats. Exposure, discontinuous inhalation to 0, 0.12, 0.25, 0.5 milligrams of nickel hexahydrate per cubic meter. That Translates to 0.03, 0.06, and 0.22 milligrams of nickel per cubic meter. This is all 6 hours a day, 5 days a week for 104 weeks.

Critical effects were pathological changes on the lung, lymph nodes, and nasal epithelium. The LOAEL is 60. The NOAEL is 30. And the BMDL was essentially 30 micrograms of nickel per cubic meter.

The average experimental concentration was 5.4 micrograms of nickel per cubic meter. Now, to derive the human equivalent concentration, we used the MPPD2 model.

And using that model, we adjusted the 5.4 to 1.4 micrograms of nickel per cubic meter. There will be more discussion of this procedure a little bit later.

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OEHHA STAFF TOXICOLOGIST BROWN: Carrying on here. We applied and interspecies uncertainty factor of root 10. Intraspecies of 30. Giving a cumulative uncertainty factor of 100. And the cREL calculated at 1.4 divided by 100 or 0.014 micrograms of nickel per cubic meter. That's for nickel and nickel compounds, except for nickel oxide.

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OEHHA STAFF TOXICOLOGIST BROWN: For nickel oxide, we use the NTP 1994a study. This is in male and female mice, 57 to 69 animals per group. Exposure of 1, 2, and 4 mg of nickel per cubic meter, 6 hours a day, 5 days a week, 104 weeks.

Critical effects very similar. Pathological changes in the lung, including pulmonary inflammation and alveolar proteinosis.

The LOAEL was identified as 1 benchmark dose gave 117 micrograms per cubic meter for 5 percent of alveolar proteinosis. Average experimental concentration was 20.9.

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OEHHA STAFF TOXICOLOGIST BROWN: And the human

equivalent concentration was 2. And there's no MPPD model for the mouse, so we have to go to Hsieh et al., 1999 who did a deposition study for these very nickel compounds in mice, and we're using adjustment deposition factors from that study.

We used an interspecies UF of root 10, intraspecies of 30, giving a cumulative of 100. Two divided by 100 is 0.02 micrograms of nickel per cubic meter.

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OEHHA STAFF TOXICOLOGIST BROWN: Finally, the oral chronic REL. And here we use an industry study, NiPERA, 2002a and b. The study population is rats. Aqueous gavage with Nickel sulfate.

Critical effects, perinatal mortality in two generation study. A LOAEL 2.23, NOAEL of 1.12, mg of nickel per kilogram per day. Average exposure 1.1. Human equivalent 1.1.

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OEHHA STAFF TOXICOLOGIST BROWN: LOAEL UF of 1. I guess there was NOAEL.

Interspecies UF of 10. Intraspecies 10. Overall 100. Oral cREL is 1.1 divided by 100 or 0.011 milligrams of nickel per kilogram per day. This is the same derivation as used for drinking water PHG.

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OEHHA STAFF TOXICOLOGIST BROWN: Overall summary. The acute REL 1.1 micrograms of nickel based on FEV1 decrease in adult asthmatics. The 8-hour REL 0.08 micrograms of nickel per cubic meter based on immunotoxicity.

The chronic REL for nickel and nickel compounds, except nickel oxide 0.014 based on lesions in the lung. And the chronic REL for nickel oxide 0.02, based on alveolar proteinosis.

The oral REL, 11 micrograms per kilogram per day, based on perinatal mortality. The same basis as our drinking water, PHG.

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OEHHA STAFF TOXICOLOGIST BROWN: Now, should I go head and address this now or what do you think?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, we have one slide responding to the information that the SRP received from NiPERA. So I don't know you if you guys want to --

CHAIRPERSON FROINES: Go ahead. Go ahead.

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- hear what we have to say.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. This is the basic comment. It's about the dosimetry adjustment

that we used, particularly on the nickel sulfate. And the comment essentially is this. It says that, "OEHHA calculates the HEC based solely on the ratio of deposition fractions in humans and rats. A more precise calculation can be made based on the ratio of deposited doses".

And I followed here with an example. The method we applied, which we're calling a dosimetric adjustment factor for nickel sulfate is the fractional deposition of animals over humans, 0.089 over 0.348 giving a value of 2.64. This is the value we'd multiplied the animal value, exposure value by to get the human.

Now, NiPERA recommends using essentially what is EPA methodology from 1994, the so-called RDDR, which is the Regional Dose Deposition Ratio Rate. And this amounts to basically a normalization factor obtained my multiplying the ratio of the deposition rates, the FRA over FRH by a ratio of human to animal surface area -- lung surface area times the ratio of animals to human volumes. So this amounts to a normalization factor, which would adjust the 0.264 to 0.554 giving a doubling of the REL.

Now, the reason we didn't do this is because the normalization factors that are being used there are default adult values, and they're not child values. Whereas, the human FR used in our value is an average of

not only an adult model, but age-specific child models in the MPPD2 program.

So in other words, we took an average of deposition fractions from different age group met models from 3 months a age up to adult of 21 years. So in our view, that value up there, that 0.55 does not adequately captured the increased sensitivity of children -- the increased deposition of the nickel particles in the child lung.

If you look at the bottom there, all the child values -- child model values show higher fractional depositions than adult. The child ranged from 0.32 to 0.4 versus 0.25 for the adult. Now, one way of getting around this, we can go in and try to derive values -- normalization values based on child met volumes and lung surface areas.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: One of the tings I've been looking at an alternative approach using the MPPD2 model itself is to compare the retention of particle doses, if you like, for comparable periods of age in deposition and clearance simulations.

The MPPD model looks not only at deposition, but you can also run it in the mode of deposition and clearance. So you're actually looking at retention versus

time. And if you run these models for fractions of their age, say 10 percent of the age, and look at the retention defined here as micrograms of nickel sulfide retained in the lung per day per square meter of alveolar surface area, you find that you do get values that are quite different from those from -- provided by the adult human normalization factors.

So, for example, if you took the average of the values we obtained for three months, 3 years, 9 years, and 14 years, they would average 0.465. You know that would actually lead to a reduced dosimetric adjustment factor.

And this is a preliminary analysis, but I think it, you know, raises some questions about the adequacy the normalization factor the way it's being used.

So this is something that, you know, we can look at further in our revision to the document. Or at least what I should explain in greater detail the rationale for what we did and what the possible alternatives might be.

In this case, for example, we ran the 3-month model for 2 weeks, the 3-year for 6 month exposure, 9 years for one year, et cetera. So this is the way we did that, but there might be a more systematic way of doing it.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: So this is our,

you know, sort of response to their comment. If we do use some sort of a normalization procedure. It wouldn't be based solely on the human adults. It will be based on those child models as well.

PANEL MEMBER GILL: What's the definition of a child in the law?

OEHHA STAFF TOXICOLOGIST BROWN: Okay. The child models --

PANEL MEMBER GILL: No, by law, what's a child --

OEHHA STAFF TOXICOLOGIST BROWN: Eighteen. Eighteen, I think, isn't it?

OEHHA SUPERVISING TOXICOLOGIST SALMON: We don't use that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. We actually -- don't -- there isn't one in the statute that drives what we're doing. But we do have at least one pediatrician on staff. And we typically view the different developmental stages of children like a pediatrician would. So infancy is up to 12 months, then toddlerhood, older children, and then adolescence.

So we have done that. And you can actually find some age-specific surface area and then it - volumes if 4 brackets of those age groupings to apply, which is possible to do that.

PANEL MEMBER GLANTZ: Questions. In the end, so

what you're saying here is that even if you take the NiPERA approach, the children still have higher deposition?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER GLANTZ: Okay, but of the two methods, the 0.26 versus 0.55, I mean, do you still think you should be sticking with the original 0.26 or do you think they've made a good point to go to 0.55.

OEHHA STAFF TOXICOLOGIST BROWN: Well, they made a point in that the general procedure does use a normalization factor of sort of a depositional rate, if you like.

The question is which one should we use here where we're looking at child models? And I'd like to stick with the MPPD model, because that's what I've used to derive the deposition fractions. So I'd like to have the consistency of at least working in the same ballpark is something that's reproducible. It's a freely downloadable model that people can check the values on.

OEHHA SUPERVISING TOXICOLOGIST SALMON: I think it's also fair to comment that the RGDR and RDDR models, which they're advocating, and which of these ones which have been around from US EPA for quite a number of years as a sort of default approach, are things that we do have some significant reservations about how good they are

generally, and how reliable.

And we have, in fact, deliberately in other RELs like the acetaldehyde and formaldehyde things like that, we've deliberately used other deposition models for gases or particles, which we feel are superior to the original RGDR and RDDR type models.

So we have a policy of trying to use a more developed more analytical model, if we can.

PANEL MEMBER GLANTZ: And why do you think they're superior?

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yeah, for one thing, they are chemical and data specific. Whereas, the RGDR is just based on surface areas of lungs and things. It's species specific, but not chemical specific.

OEHHA STAFF TOXICOLOGIST BROWN: I agree with the comment, in that we have to provide more rationale and explain why we did it this way. I mean, that's a fair comment. I accept that. And I would like to provide at least a description of some alternatives that might be applied, even if we stick with a 0.264, which is between the two sort of extremes, if you like.

CHAIRPERSON FROINES: So is that an action item for a revised document?

OEHHA STAFF TOXICOLOGIST BROWN: Yeah. I would say so. I'd say it's on my -- it's certainly one of the

things I'd like to do on my own. Just responding to the comment, I think it's suitable.

CHAIRPERSON FROINES: Is that it?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yep.

OEHHA STAFF TOXICOLOGIST BROWN: Acute REL. So as I said this is a weak study.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So that's it for our presentation.

OEHHA STAFF TOXICOLOGIST BROWN: That's it for the presentation. Yeah, that's it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: So we can go back to the Panel for comments now.

CHAIRPERSON FROINES: So I'm going to go to Bill, who addressed exposure issues, and then Ellen. But, Paul, is that order, and then you, because you said you had.

PANEL MEMBER BLANC: Certainly the lead should speak first. I don't want to duplicate something they say.

CHAIRPERSON FROINES: Good. You're on.

PANEL MEMBER NAZAROFF: So thank you. I, about a week ago, maybe not quite that, forwarded a set of comments to OEHHA and to John and to our staff. And they've just been circulated, I guess, to the Committee. So the Committee has not had any advanced opportunity to see them.

What I'd like to do is just highlight the 5 main points that I've raised, which -- and I guess the best process here is not to engage in a dialogue, but I'll just present my comments in the same way that you presented your report.

And then I have an extensive list of very specific comments that I won't go through in full detail, but I'll pull some that I think are worth noting.

The first broad point is the issue of the environmental chemistry of nickel and its relevance in this story. We know that nickel can exist in many different chemical forms and in several different oxidation states. And that these characteristics are interrelated.

The chemical form and the redox state of nickel can vary among emission sources, it can have an impact on the environmental fate of nickel, and it can have consequences for health risks when exposure occurs.

The current draft document contains considerable information that pertains to oxidation state and to the chemical form. However, I don't find that that information is especially well organized, nor is every aspect that is important consistently reported, nor is the reporting done with perfect accuracy, even when it's done.

So broadly I would like to see a review of the

document with attention to the redox state and the chemical form. But let me give a few examples just to illustrate the nature of the concern.

In the opening paragraph of the summary -- well, actually it's the opening of the second paragraph of the summary on page 4, it suggests that the only concern is with nickel and oxidation state plus 2, but throughout the document other forms of nickel are referenced. There's nickel in valence state zero, nickel metal, and one of the chemical forms I think is oxidation state plus 3. It's Ni203.

And so this point needs to be brought out more clearly, if we're going to have an REL for nickel in all of its forms in any valence state, then that should be presented in that way. And, in general, it probably would be wise in the summary to just layout this issue that nickel can exist in these many states, and those states have impact on important factors like solubility, bioavailability and so forth.

On page 5, there is one compound in the table that -- I had to look these up some of them myself. I didn't know. But there's just a couple of things that struck me as odd. And the one was reported inaccurately. It's nickel carbonate hydroxide. So you should double check that. You don't have enough an ions to balance the

cat ion.

And then an important point is that the -- related to this whole story, the solubility of nickel in its various compounds seems to be of considerable importance in biological availability, and in the risk associated with it. And the topic of solubility arises at many places in the document, but it's not brought to the front in a way that would allow the reader to place the specific details in a broader context.

So there's a place at the bottom of page 9 where the relative solubility of several different nickel compounds is reported, subsidiary to ingestion as the pathway.

But that point is of much broader significance than just the ingestion pathway. So if -- the point is well worth making, but it ought to be brought out to a summary discussion of the environmental state of nickel.

The second broad point is -- well, actually, let me just make one other point. It's in the list of things later, but it's really worth calling out here.

And that is when a health study is being reported I think it's incumbent upon you to tell us to tell the readers what the chemical form, what the oxidation state of nickel was. And that's often reported, and it's often discussed, but there are many instances in the draft

document where that information is absent. It may have been absent in the original report. If that's the case, then you should call that out. But it seems so important to the issues that we're considering, that it needs to be consistency documented.

The second important point that I wanted to raise is the significance of particle size for respiratory exposure and respiratory tract deposition. For all exposures that occur by the inhalation pathway, particle size is a critical determinant of whether the particle makes it into the respiratory tract or not, the probability of deposition within the respiratory tract, and, if deposited, where?

And then the fate of the particles following respiratory deposition and consequently the risk of adverse health effects will be influenced by the size of the particles, by the chemical composition of the particle, and by the location of the deposit.

So, for example, it's been shown -- I don't know that it's been shown for nickel, but for some other metals, it's been shown that inhalation of ultrafine particles can result in deposition in the sinuses, and then translocation via the olfactory nerve into the brain when those particles are insoluble.

PANEL MEMBER BLANC: Well, I think that -- just

to clarify, I think that's really only been shown for manganese and it's not ultrafine manganese. In fact, it's larger particles of manganese.

PANEL MEMBER NAZAROFF: Okay. Well --

PANEL MEMBER BLANC: I understand the ultrafine manganese gets into the lung and gets into the circulation that way. But the amazing thing about manganese is that larger particles, which are generally blown off as being -- bad metaphor -- general discounted as not being so relevant to toxicity in manganese, that the large particles may actually matter more, because those are the ones that get taken up by the olfactory system and then get transported to the brain. I think that's it.

PANEL MEMBER NAZAROFF: I don't think it's right, but I don't have the literature at my finger tips. So I mean --

CHAIRPERSON FROINES: Well, the answer --

PANEL MEMBER NAZAROFF: -- I'm not disputing what you're saying, but the conclusion that that's the only important evidence about olfactory --

CHAIRPERSON FROINES: But we know -- let me weigh in, because this is part of our work. We know Günter Oberdörster at Rochester has shown ultrafines go through the olfactory bulb and into the brain. And so he's demonstrated it.

We have demonstrated that if you have exposed to ultrafine particles, that, again, the particles go through the olfactory bulb and cause chronic inflammatory processes. So there are two investigating teams that have shown that.

PANEL MEMBER NAZAROFF: And I want to use that as an illustration, in any case, of the broader point, which is that the size of the particle and the degree of solubility is quite important.

Larger insoluble particles that deposit in the alveolar region are likely only to be removed by macrophage engulfment. Particles that deposit in the tracheal bronchial region, if they're insoluble, will be cleared by the mucociliary ladder with different residents fines. Particles that are soluble and deposit deep in the respiratory tract have the possibility of the ions moving out, rather than having to have the particles move out.

My point is merely that each of those dimensions is of crucial importance in understanding any particular health study, the relationship between what exposure conditions were and what the pathways of biological insult and health risks might be. And so I just think they need to be consistently reported.

So again, particle size appears in many places throughout the document. And I'm not suggesting that you

didn't understand that, but it's not consistently enough reported to set a proper context for evaluating and understanding all of the studies that are reported here.

CHAIRPERSON FROINES: There's also the ultrafines can penetrate epithelial cells and are taken up.

PANEL MEMBER NAZAROFF: Yeah, ultrafine, if they make it into the --

CHAIRPERSON FROINES: Alveolar region.

PANEL MEMBER NAZAROFF: -- alveolar region or even in the tracheal bronchial, their transpleural transit is -- or whatever it's called -- has been documented in some studies.

There was also an odd mention, and I'm sorry I don't have the point in the document where it occurred at my fingertips, of respiratory tract deposition being somehow tied to the chemical composition of the particles. That is where the particles deposited or the probability of deposition, but deposition is, so far as I understand anyway, purely a physical process. And it would depend on the size and density of the particle, but not on its chemical makeup.

OEHHA STAFF TOXICOLOGIST BROWN: That's right.

PANEL MEMBER GLANTZ: Can I just interrupt for one second.

PANEL MEMBER NAZAROFF: Sure.

PANEL MEMBER GLANTZ: I mean, I -- well -- I thought that was great. And I had a really hard time with this report, because you didn't say what Bill was talking about. And given the multiple pathways that nickel is being absorbed, the multiple different nickel compounds that you're talking about, the sort of -- the role of ionic nickel versus other things.

I think the report would be a lot easier to read if you took the material we just heard and put that at the beginning. I realize you're not writing a textbook, but I think if you sort of presented that as a framework to hang -- because you just -- I just got totally bogged down in all of these 55 million individual studies.

And then you could say, okay, this is coming in through very fine particles. This is coarse particles. Here's where the ionic material is important. And that can be -- I don't think you'd have to write a lot, but I think if you could create -- that could create a framework that, if you carried -- if you kind of hung all of the individual studies on, it would have made the report a lot easier for me to understand. So I thought that was like really good.

And also John showed us, which I'm share he'll talk about, an Email a little bit about sort of cellular or subcellular mechanisms and pathways. And you do kind

of have that at the very end, where you're -- and I got to the end and I thought why didn't they put this picture at the beginning, because there's so many different details flying around.

So, I mean, anyway, I just -- thank you. That was great.

PANEL MEMBER NAZAROFF: So let me move on to now the third point, and that has to do with summarizing the State of knowledge of environmental exposure to nickel. I think -- and here, I'm treading on a little less comfortable ground, because I don't know the full context in which this document appears in a broader story.

But I found the early section that reported air and soil and food exposure to be lacking in sort of a critical summary of what we know today. The air part, in particular, doesn't cite anything more recent than -- well, actually no recent sort of archival literature. And the recent data that are cited, I actually have a bit of a question about anyway.

There's this odd character that the -- I went to the air toxics site of, I guess, it's ARB, and nickel is listed there being monitored. I don't believe the sentence literally as you've written it, that says that the 2002 number reflects the average ambient concentration above the State, because it just reflects the average of

the Samples that were collected, I presume, which are not, of course, statistically representative of all the air above the state. That's a fine point.

But I don't understand why the monitoring went from in 2002 a very low sensitivity threshold or detection limit to subsequently more recently, like I was wondering why are you citing year 2002 data?

The more recent data are almost all below the detection limit, but the detection limit has gone up to 9 nanograms per cubic meter for reasons that are not apparent to me at all. This is a weakness of the State's monitoring program, as far as can I tell.

So, you know, the last 7 or 8 years we have no sort of routinely gathered data that are being analyzed with sufficient sensitivity, so that we know what they are.

Anyway, I've provided a list of some, maybe 10 articles that I found in 30 minutes of looking, that report recent monitoring of air or near roadway concentrations of nickel in California or in conditions that are relevant to California, like in tobacco smoke. And I just commend them to your attention to strengthen that section of the report. I think it would be helpful to have some more modern context for understanding how important this contaminant is.

The fourth item that I point out is something that Ellen was on the distribution list, because we were co-leads, so she'll comment more substantially on this. But I just felt like the health studies didn't include enough attention to environmental epidemiology investigations. They seem to me to be biased towards being fairly thorough, I presumed, on occupational investigations, laboratory animals, in vitro studies in the laboratory, but there was a missed opportunity from taken a look at some recent work that looks at nickel in the environment and environmental exposures and trying to make some sense from environmental epidemiology of what the health risks might be.

And then my final general comment is actually coming back to something that Stan just raised. And the heading I put this under was flow balance and connectivity in the narrative. I also found this a very hard document to read. And in reflecting on it, I think part of the reason -- and the way I've written it here is you ought to tell them what you're going to tell them, tell them, and then tell them what you told them. And you didn't do a very good job of telling us what you were going to tell us, that each section when I entered it, I was -- I felt like frequently I was immersed in sort of a bottom up encyclopedic paragraph-by-paragraph description of

individual studies without a framework within which to understand it, and without much connective tissue to help me see how one study related to another study.

And by the time I got to the end of the report, I felt like I had plowed through 70 pages of dense narratives summarizing individual studies one by one. But then when I got to the part that I really wanted to have well developed, which was the explanation of how you took this literature and derived REL values, it was hastily -- I had the feeling of haste going through that; that there was not adequate discussion of how some studies were selected and others were excluded.

There was not enough discussion of what was in the studies, so that each of the studies, whether they were used to set the guideline value or not, were treated about the same way. It was like one paragraph on Cirla telling us about its merits. And there was one paragraph on 50 other studies as well. I needed to hear more about why that one study was the basis for setting the REL and the other 50 weren't.

PANEL MEMBER GLANTZ: Yeah, I really --

PANEL MEMBER NAZAROFF: I think I'll stop at that point.

PANEL MEMBER GLANTZ: I really, really, really want to second that. I mean, I felt like I kind of needed

a machete. And I just -- it was like just this bit -- there was all this detail, and I kept waiting to have it pulled together, so I could see kind of where is this taking me. And I felt very unadequate, but now I feel better.

(Laughter.)

PANEL MEMBER NAZAROFF: So I should stop there, especially in the interests of time. I've conveyed to staff, in addition to these broad comments, a list of 50 sort of line by line suggestions, some of which are quite trivial and others of which are more substantial, but they all are around these themes.

CHAIRPERSON FROINES: Melanie, do you want to respond or shall we go on?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Just to one of the points about the environmental epidemiology. It's kind of funny, because my other group who does the health-based recommendations for particulate matter for the ambient air quality standards has generated some of the studies that you're talking about.

But, you know, we kind of didn't want to get into the PM literature, which, as you know, is vast. So in as much as there's currently a couple dozen studies maybe that have done speciation of PM, and a subset of those that have looked at nickel. We could pool those together

and have a little section on it.

They're not super informative at the moment, because it's hard to do that kind of stuff, but we can put that in there. It's just kind of funny that we didn't.

CHAIRPERSON FROINES: I think you have to be very careful with the PM literature, because you don't want to in a way see nickel as the etiologic agent, when, in fact, there's a lot of other things that are important.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yeah. It's probably also worth saying, you know, maybe this is something that could have been explained better, but you know, the context of the proposed RELs is specifically in relation to point source emissions, not the general ambient environment. Although, what's observed in the general ambient environment is clearly relevant and important in understanding what the potential effects are. We need to have our recommendations to the RELs directed to a context which is relevant to the point source emissions situation in the Hot Spots Program.

PANEL MEMBER NAZAROFF: So, for example, would emissions from the Port of Long Beach be subject, at least of interest in this context?

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yes. Certainly of interest. But I think when we get into that area, we need to explain the context in which we're doing

it, which is that point, as I say, that it relates to point emissions rather than statewide ambient, for instance.

PANEL MEMBER NAZAROFF: That's fine.

CHAIRPERSON FROINES: Well, we know that the Long Beach Port, for example, the metals that we find most interesting are vanadium, iron, and copper, and nickel is another metal. But that doesn't mean that one can't make reference to the fact that nickel is one of the elements of concern.

OEHHA SUPERVISING TOXICOLOGIST SALMON:

Absolutely. But I just say, we need to have -- when we do incorporate that, we need to make sure that we reflect that context, I think.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. I guess the other thing I would say is, you know, that the older Panel members can tell you, we have sort of struggled with how much to put in these documents.

CHAIRPERSON FROINES: You should be careful about those older Panel members.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST SALMON: The more senior Panel members.

CHAIRPERSON FROINES: The experienced Panel members.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay, bad choice of words.

PANEL MEMBER GLANTZ: Well, speaking as one of the older Panel members, you know, I don't -- I think you could deal with a lot of this stuff without necessarily making the document a lot longer. I think it's more about -- you know, I think the sort of introductory stuff could be done in a couple of 3 pages. And then -- but to create a framework in which to hang all of the details in a context in which to interpret the studies.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Oh, yeah. No, I agree with that comment totally.

PANEL MEMBER GLANTZ: I don't think that would take a lot of additional pages. It might even shorten it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: No. I agree with that totally with having a framework in more context.

But in terms of how many of these studies to have a synopsis of, you know, if we had been doing this document 10 years ago or even 5 years ago, it would be a lot shorter. But we got a lot of feedback that it was hard to review a document like that, unless you happen to know a lot about the literature there are available on those chemicals.

So nickel is a hard one, because there aren't a lot of studies available, you know, of varying quality and looking at different things. So it did end up a lot longer than I thought it was going to end up.

PANEL MEMBER BLANC: Well, let me -- it's not my turn yet, but just wouldn't tabular presentations of some of it paralleling the table that you have Table 5a, wouldn't that, for some of these things that are going to end up being the studies that you're not using or certainly studies that you didn't even consider for more than a nanosecond as the -- deriving a REL could be summarized in that way and that would save space.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We could do that. And Dr. Froines also had a suggestion for me off line that maybe we can consider taking a lot of this and putting it into an appendix. So shorter summary/synopsis up front, longer detailed stuffed as intended.

CHAIRPERSON FROINES: Well, my suggestion -- I want to go to Ellen. But my suggestion was put what's important up front, put what supports the important studies next and then put everything else in an appendix and you'd have a smaller document as well.

Ellen.

PANEL MEMBER EISEN: Yeah. So I just reviewed your view of the epidemiology, and I really don't have

many points to make, except I'll make 3, I think.

I mean, most of the epidemiology wasn't very good. And the reliance for the acute REL on that Cirla study I found really, well, surprising. And I thought, well, this is -- I mean, it was a lesson in how EPA sets air standards to realize that it can be done on the basis of a single study, where there was just one does.

It wasn't like there was any dose response in the study. It was just the guy gave asthmatics -- occupational asthmatics, people who didn't have a prior history of asthma before they went to work in a nickel plant, challenge them.

MR. MATHEWS: Closer to the mic, please.

PANEL MEMBER EISEN: He challenged them with a particular amount of nickel -- and I don't remember what kind of nickel it was -- but anyway, with one dose level. And 6 of the 7 had a drop in their FEV1 of more than 15 percent. And so bing, that's the -- that was the level that you used. And I don't have anything else to offer. There wasn't anything else to use, but it just didn't seem very substantial.

And then in the -- I actually thought that the Skyberg and Berge paper was not bad. It was actually fairly decent, the pulmonary fibrosis paper, which you did end up using as a secondary supporting evidence for the

chronic limit.

But I did have a few -- I had a hard time understanding your Table 11 and how it corresponded to Table 5 in the Berge and Skyberg paper. In particular, I think the main -- so Table 11 is on page 101 in the document -- in your review.

You present summaries of their dose response results soluble nickel and this sulfidic nickel and present results for a crude model without adjusting for any confounding and then two different more fully adjusted models.

And I think what did you at the end of the day was used the crude model to drive your -- or to justify, to support the justification for the exposure limit. And I would just make the strong recommendation, that that's -- you know, you don't do that, that you always use the adjusted model, rather than the crude model, if you're going to --

PANEL MEMBER BLANC: I thought they used the raw data.

OEHHA STAFF TOXICOLOGIST BROWN: We used both, actually.

PANEL MEMBER EISEN: I also -- I didn't -- I can't -- I didn't understand also the -- I guess you use -- you're presenting in Table 11 on the far left

column that those these are means in the categories?

OEHHA STAFF TOXICOLOGIST BROWN: It's the mean of the dose interval. And that's put in a benchmark dose, which uses all the data to calculate a lower bound on a particular response level.

PANEL MEMBER EISEN: Right. I mean, I'm surprised that that's the procedure, rather than using the cut point for the category where you saw the effect.

OEHHA STAFF TOXICOLOGIST BROWN: I think that's the way we always do it with benchmark does. We've done that with arsenic and other points.

OEHHA SUPERVISING TOXICOLOGIST SALMON: It's how the software is setup to accept the data basically.

OEHHA STAFF TOXICOLOGIST BROWN: Lean and mean.

PANEL MEMBER EISEN: It's still sort of peculiar to me. I don't know why you would use the mean if you have a --

OEHHA STAFF TOXICOLOGIST BROWN: Mean and standard deviation.

PANEL MEMBER EISEN: -- lower cut point for that exposure category.

So then maybe we can come back to that discussion. But the third really point was really that I -- I do know that there's a little bit of PM literature looking at metal components based on these boilermakers --

from the occupational literature looking at at PM2.5 exposure in boilermakers where they have looked at particular metals and cardiovascular effects.

And so there's nothing on cardiovascular effects in here. And I don't know necessarily that you want to go there, but it did seem like something was --

OEHHA STAFF TOXICOLOGIST BROWN: There's no dose response data, but I think there is a few comments on cardiovascular effects of nickel in the document.

PANEL MEMBER EISEN: In your review?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, there is. It was added late, but I think it's in this draft.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It is.

PANEL MEMBER EISEN: Is it human data?

OEHHA STAFF TOXICOLOGIST BROWN: I can't recall if it's human or not. It might be.

PANEL MEMBER EISEN: Because I missed it if it was human data.

And then I actually did review some of the epidemiology that Bill had found on PM. And there was one study in particular, which I really think is actually probably better than anything else. And it's the study by Michelle Bell, where they looked at low birth weight.

So they looked at low birth weight in, you know,

70,000 births in Massachusetts and Connecticut and looked at PM2.5 and 6 metal components. And it was a pretty well done study. And they actually found effects for all of the metals that they looked at. Actually, I think they looked at 50 elements, but they report results for -- positive results for 8 metals, and nickel is 1 of the 8, where there was an 11 percent increase in low birth weight over the follow up period associated with an interquartile range, which was like 0.002 micrograms.

OEHHA STAFF TOXICOLOGIST BROWN: That's a published study?

PANEL MEMBER EISEN: Yes. It's published in Epidemiology in 2010.

It's a PM.

OEHHA STAFF TOXICOLOGIST BROWN: A PM paper, okay.

PANEL MEMBER EISEN: But it does seem relevant, in part because of the outcome. And it's a good study. I don't really -- and they used the air monitors. And so I mean, I can't -- so it's ecologic. It's not individual level exposure. And I don't really know how good, but judging from the authors -- judging from the authors, it was state of the art, sort of, you know, PM2.5 studies in 2010.

And they used a -- they treated the variables as

continuous, I think, in the model, so there's no categorization. And they don't present the results of the models in ways that you would probably be able to use them easily, because all they do is present the change in the outcome per interquartile range, you know, no regression coefficients or anything.

But I bet those date you could get from the authors.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER EISEN: That's all. I mean, I thought, you know, the literature wasn't very good. And I thought you reviewed it okay. I mean, I don't disagree really with anything that Bill said.

CHAIRPERSON FROINES: Finished?

PANEL MEMBER EISEN: Yep.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: Let me start with the most recent study of the ones we've talked about.

I actually see a reverse problem with the fibrosis paper. And that is that they adjusted for age. Age is not related to pulmonary fibrosis. Age is very related to cumulative years of exposure. So I think they actually over adjusted.

PANEL MEMBER EISEN: You can't over-adjust.

PANEL MEMBER BLANC: Yes, you can, because if you

put in a surrogate for exposure as an adjustment factor, it will reduce the effect of your exposure. How can you say that?

PANEL MEMBER EISEN: Well --

PANEL MEMBER BLANC: Well, you just said it, but I don't agree with you at least. And I've seen --

PANEL MEMBER GLANTZ: I agree with Paul.

PANEL MEMBER BLANC: And I've seen studies where that's done. And also, by the way, smoking is not related to ILO graded opacities either. So I don't really care whether they adjusted for smoking or not. But I'm just saying, you have a good argument to use the unadjusted.

PANEL MEMBER EISEN: I mean, they have opacities in their reference group, you know, and they attribute that to smoking and age.

PANEL MEMBER BLANC: I understand. That makes it -- and they're not right. They're not correct. That's not the --

PANEL MEMBER EISEN: 2.3 percent.

PANEL MEMBER BLANC: I assume that some of their referents have other dusts that are associated with --

PANEL MEMBER EISEN: Like putting in nickel, because there's not --

PANEL MEMBER BLANC: So, you know, from that point of view, I don't -- it's an interesting study, but I

don't think you're forced to -- I think you can certainly make an argument that the age adjustment has its own set of problems.

But I think the issue with the asthma study -- let me get at it by asking you a question. If you were doing an REL for all toluene diisocyanate, would you use the dose response for bronchospasm in people known to be sensitized to toluene diisocyanate as your exposure metric?

Because this is not a study of people who generically have asthma and are they more responsive to nickel than non-asthmatics? These are people who have occupational asthma to nickel, who are responding to nickel. Is that the model that you want to use for an REL?

I think that that's got kind of a fundamental issue. You know, we know that people who are sensitive to TDI are 1,000 times more -- you know, they're at the level at which they'll respond. None of the -- certainly, none of the occupational standards are meant to protect people who are already sensitized to TDI from TDI. So I realize we're not talking about an occupational standard here.

But is this really a relevant, acute, effect model? Whereas, I fully agree that, let's say if you were looking at sulfur dioxide exposure, which we know

asthmatics, generic asthmatics, respond to it, you know, an order of magnitude lower than non-asthmatics, that that's completely appropriate.

OEHHA SUPERVISING TOXICOLOGIST MARTY: You know, it is an issue that we've batted around. For TDI, I'm not entirely certain we do it. But a couple of things.

First of all, those people who are nickel sensitized are part of the general population, so they are out there. They're running round. And there are a fair number of people who are sensitive to nickel from -- in terms of having a dermal reaction, whether those people also, if they happen to be asthmatic, are going to be more sensitive.

PANEL MEMBER BLANC: I want to come back to that in a second.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Okay. So, you know, what I'm thinking is, well, what if those people are also -- if they happen to be asthmatic are going to be more sensitive to nickel inhaled?

I don't think anyone can answer that. So, you know, it may be on the conservative side, but we didn't want to just discount it.

PANEL MEMBER BLANC: Well, I think there needs to be, in fact, some discussion in the document about contact dermatitis and what that means, and its potential

relationship to airway responses. But, in fact, it's a very poor correlation between nickel sensitivity -- skin sensitivity manifested as contact dermatitis, and nickel related asthma. You go so far as to quote Ben Nemery in that regard anyway.

But there's no coherent discussion of that. I mean, I think the whole issue of nickel is probably the most common skin sensitizer in the general population. And you quote a very interesting paper, which shows that the prevalence of sensitization actually appears to have a temporal trend. Those authors hypothesize that might be due to the prevalence of piercing with nickel-containing metals.

And I was glad to see that paper cited. The other discussion is lacking, but I think that you're -- I think you're making yourselves vulnerable, because it's just too far out there -- or if you want to stick with it, you would have to jump through a lot of hoops of making it clear that you better understood how tenuous the basis of using it.

I know you have your own trepidations. Frankly, this is one case, as opposed to the previous thing we discussed today, where I think if this is all you've got, then it would be better not to have an acute REL at all, than use this, because I think it's just -- now, there may

be other studies that you were closer to using. In your presentation, I know there were things you used to back-up the chronic REL, but I don't remember something else as your back-up for the acute.

OEHHA STAFF TOXICOLOGIST BROWN: No, there wasn't anything.

PANEL MEMBER BLANC: But I just think it's not -- I'm not sure it's the precedent that you want to set. And you know that my own tendency is to be conservative in these things, but I just think the model is not -- I don't know if it makes sense.

And, Melanie, if your answer to yourself is I wouldn't use the TDI example, then I think you have to be consistent.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. Well, I guess the reason I threw that out there is because I know that people who are sensitive to TDI can be incredibly, ridiculously, remarkably sensitive to the presence of TDI. I don't know that that's the case for nickel.

PANEL MEMBER BLANC: Well, it's generally true that once you're sensitized to something, the anamnestic response is quite impressive. I mean, orders of magnitude typically less than what people will respond to if you're talking about irritant versus an allergic mechanism.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yeah. The key issue is, I think, is how prevalent in the general population is at least some degree of respiratory sensitization to --

PANEL MEMBER BLANC: Yes.

OEHHA SUPERVISING TOXICOLOGIST SALMON: We don't know that, but I think in the case of TDI we have a number of reasons for supposing that the prevalence in the general population is pretty low. But in nickel -- there are certainly -- you know, there certainly are background exposures to nickel. So it's not inconceivable that they're --

PANEL MEMBER BLANC: Well, we know that nickel skin sensitization is extremely common and has become more common, but --

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yes. And so even if the nickel sensitization in the respiratory system doesn't correlate with skin sensitization, nevertheless it's not impossible that there's a measurable or even substantial amount of it there. It's just --

PANEL MEMBER BLANC: There's no evidence at all that there is.

OEHHA SUPERVISING TOXICOLOGIST SALMON: We don't have a good --

PANEL MEMBER BLANC: I mean, it's -- you know,

you're talking about a theory of a theory of a theory at this point. So I think you're -- I think you're just skating on pretty thin ice. Whereas, the model of this is something which asthmatics will -- generic asthmatics will respond to more than the non-asthmatic population, that's a different question.

Now, if you have any data at all that would suggest the prevalence of nickel asthma has increased, it's really an uncommon occupational asthma too, as far as that goes. You know -- and also, you know, our understanding of metal related asthma and all that it might be anyway. So, you know, it's a very complicated question.

OEHHA SUPERVISING TOXICOLOGIST SALMON: It's complicated and there's a lack of data, but it's also potentially quite an important issue, in terms of protecting public health. And I mean I know for a fact this exact same debate has come up in the discussion of platinum-induced asthma as well.

PANEL MEMBER BLANC: Yeah, but for -- well, yes, okay.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Which, you know, I mean, it's -- I'm not saying we have a good answer. I'm just saying it's a question that keeps coming up.

PANEL MEMBER BLANC: Yeah. So that's my 2 cents on that.

Just a few other small things. And I think it only dovetails with some of the organizational questions. But in this general source of exposure discussion, which you've already heard could be updated and a little clearer. And you have food and you have water and all of that.

And then sort of hanging out there, you have the paper about the prevalence of skin sensitization in the food section. What was the logic behind that? Why didn't you just have a skin section, then you can talk about exposure to the skin, if that's what you want to do? Or talk about that study when you talk about health effects. But I didn't understand that.

I also didn't -- also, as a question of sort of ubiquity of exposure, you have the sentence about nickel is present in mainstream smoke. I don't actually understand why for some things you give a one estimate and for some you give a range that may have to do with how the data you had, but it's certainly not obviously.

But does that mean you have no data on nickel in secondhand smoke. Because by only presenting it for mainstream smoke, it might be misread that therefore it's not in secondhand smoke. Is there no such data at all?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No, I'm sure there's data.

OEHHA STAFF TOXICOLOGIST BROWN: You know, he's probably given some --

PANEL MEMBER NAZAROFF: I sent them some references on that.

OEHHA STAFF TOXICOLOGIST BROWN: I think I got 25 references.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Okay. We can fill that one out.

PANEL MEMBER BLANC: And I assume by the way, this off hand thing about it may be because there's nickel in bunker fuel, that there's more in Long Beach? You know, that sort of parenthetic comment. Does that mean you don't think there's any nickel in diesel smoke and diesel exhaust?

OEHHA STAFF TOXICOLOGIST BROWN: No, but we do cite a figure in there from the South Coast Air Quality Management District on measurement of --

PANEL MEMBER BLANC: No, I know. And then you say in parentheses, "This maybe because of bunker fuel.

I would hazard a guess, that it's as much from idling diesel trucks, if it's in diesel exhaust.

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, it could be.

CHAIRPERSON FROINES: I think that the bunker fuel, we've actually pretty much characterized that and the issue with bunker fuel is vanadium not nickel.

PANEL MEMBER BLANC: I assume that nickel is not, in any way, an essential nutrient, is that correct?

OEHHA SUPERVISING TOXICOLOGIST SALMON: I think there is some --

OEHHA STAFF TOXICOLOGIST BROWN: I think it is.

OEHHA SUPERVISING TOXICOLOGIST SALMON: I think there is some use. Yeah, it's one of those ACDC ones, I think.

PANEL MEMBER BLANC: Can you comment at least on that in a sentence somewhere, if that's true or not true, in your food section or your dietary section.

OEHHA STAFF TOXICOLOGIST BROWN: I think it is, but I think there's probably been some arguments about it too.

OEHHA SUPERVISING TOXICOLOGIST MARTY: That's what I remember.

OEHHA SUPERVISING TOXICOLOGIST SALMON: It's one that people argue about like arsenic.

PANEL MEMBER BLANC: Somebody argues that arsenic isn't?

OEHHA STAFF TOXICOLOGIST BROWN: Oh, yeah.

PANEL MEMBER BLANC: I thought only if you're a

bacterium living on the edge of a volcano.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Only if you're a bacterium or certain --

PANEL MEMBER BLANC: I mean a human -- it's not a human essential nutrient, I don't think.

OEHHA SUPERVISING TOXICOLOGIST SALMON: I don't believe so, but some people disagree.

PANEL MEMBER BLANC: Anyway, those are my main comments. The thing I feel most strongly about would be that I personally -- my disbelief is not suspended about Cirla application.

CHAIRPERSON FROINES: Jesús.

PANEL MEMBER ARAUJO: Yeah. I don't really have much to add, other than curing about the need of updating, and including some of the population based studies and air pollution studies.

However, it is problematic also, because the role of nickel and in PM related health effects is still quite controversial. And even as much as I believe that you should include and mention about the cardiovascular effects, for instance, and even though there are studies and the studies from NYU that are pointing out to very specific effects, and there are other studies that are not confirming those same effects.

So I think that mentioning those, on one hand,

sort of to give the framework a stand is sane, but not in such a strong way as you will be taken then to regulate. So I think it is still early to take the air pollution studies as a base for regulation. But I think that it is important to mention them as a way of giving a framework.

And similar concepts, I would say, relates to all the concepts that we are having -- talking about the particle size and particle -- and the importance of lung retention. And as much as we want to believe in all these different concepts and the solubility of the particles and the soluble versus the insoluble and penetration and system translocation, et cetera, there is still so much information that it is controversial, that I don't think this would be the document to tackle that.

I mean, I understand that you having -- perhaps having that hesitation, because if you want to -- if want to tackle the role of nickel, and environmental exposures, so you're just getting to the whole arena of the PM, and I think that it is still premature to do that.

So it's a delicate balance. And I would move it, like you have it at the very end. I would move it up front. I would use it as a framework, but I will be hesitant in taking that data for regulation. Unless, there are very strong studies, like the one that you're mentioning with the low birth, that we feel that and --

PANEL MEMBER EISEN: Well, I think it would be useful actually to look at the exposure levels in this Bell paper and just see how they compare to what you're finding in the occupational and animal studies. I suspect they're a lot lower.

PANEL MEMBER BLANC: I forgot one thing.

You know, you have this comment a few pages in, "We won't be talking about nickel carbonyl.

OEHHA STAFF TOXICOLOGIST BROWN: That's right.

PANEL MEMBER BLANC: And I think that is reasonable not to deal with it, because you'd have a -- probably have an REL that was 100-fold lower. But what I would -- the way I would handle that is I would include nickel carbonyl in your table of nickel-containing materials, and then have an asterisk, and then say will not be considered further here. Because I looked at that table, and my first assumption is where is nickel carb. And then a few pages later, you know, it was sort of buried.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Or maybe we should put a REL for it.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Not now, Andy.

OEHHA SUPERVISING TOXICOLOGIST SALMON: Not now right now.

CHAIRPERSON FROINES: Jesús, are you finished?

PANEL MEMBER ARAUJO: Yeah.

CHAIRPERSON FROINES: I just will say, in light of what he said, I think you should delete that PM2.5 discussion on page 52 and 53. I think it's -- if you're going to do PM, you should do it. But if you're not, you shouldn't have this rather limp discussion of ROFA, which just doesn't fit. It's just apples and oranges, because it doesn't say anything. And when you're all finished, it doesn't say anything.

PANEL MEMBER BLANC: It spills over.

CHAIRPERSON FROINES: It's just speculative in a way that's not very helpful, I think, without -- unless one goes into greater depth about the issue and that's not what this document is about.

Alan.

PANEL MEMBER BUCKPITT: I don't have a lot to add to the discussion. But certainly some tables up front for me would have been helpful to tell me where you were going with the document.

Looking at the document, it seemed like a continuous consideration of each of the papers that had been published in an area. And it would have been nice to have some summary tables to kind of ground that discussion. So that would be my suggestion from the

report.

CHAIRPERSON FROINES: Sarjeet.

PANEL MEMBER GILL: I don't have much to add actually. Only 2 things, which I think will emphasize again. An overall framework would be very good. And secondly, the one actually -- the absence of actually a good study for REL. You'd rather not have one at this present moment. It looks like it's actually relatively weak for you to present one. And you yourself concur with it, so I would not actually present it, unless you have really good information with that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We're going to take a look again at the animal data. There are some animal studies that might end up being useful. In fact, we actually cite one in here, Graham. It's not the best idea. We had to use humongous uncertainty factor.

PANEL MEMBER GILL: But actually, Paul is correct, in the sense you have to be very careful in what you're doing. And you really otherwise again using the words Paul really difficult situation there.

CHAIRPERSON FROINES: Stan.

PANEL MEMBER GLANTZ: I don't have anything more.

CHAIRPERSON FROINES: Okay. Melanie, I'm the last one. And I sent you my thoughts. I think that you should not have the discussion on signaling pathways in

the immunotoxicity section. It should be in a mechanism section.

And I think that -- I've given you a simple chart that I think is relatively reasonable. And so I think that what you want to do is talk about MAP Kinase and transcription factors and EGFR as being activated or deactivated by reactive oxygen species or electrophiles. And that sets in motion a process that leads to cardiovascular effects and asthma and disease.

And so that the role of the MAP Kinase research really is in the context of mechanistic determinations and not in the context of immunotoxicity

And so you've seen my little chart there that I developed. So I'd leave that as a recommendation, but I think it deserves to be in a mechanism section rather than in immunotoxicity. There's other papers in that section that are immunotoxicity. But when -- I also think that we need a context for mechanism. And I think that what I wrote was reasonable if a bit oversimplified obviously.

I could have made a much bigger chart, but then that wouldn't have been helpful. And I do -- I think you should take out the genotoxicity section. You may have it in there for some reason, but we're not talking about cancer. So it doesn't mean that genotoxicity is only relevant to cancer. So maybe that's your reason.

But my sense is that the genotoxicity doesn't add anything to this document. And so there needs -- it needs to serve a purpose. And if it doesn't serve a purpose, why would we put it in?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I think you actually nailed it with what you said two sentences ago, that genotoxicity is viewed as relevant only to cancer, but that, in fact, isn't true.

So I think --

CHAIRPERSON FROINES: But if you --

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- that's one reason it's in there. And nickel has a lot of studies on genotoxicity. And it is --

CHAIRPERSON FROINES: But you have a cancer document where that's where it's particularly relevant. And the question is unless you connect genotoxicity with some consideration of mechanism of action, then it just sits there by itself and doesn't have a context. And that's what concerns me is I don't know what to do with that genotoxicity information. It has the -- everybody says ROS causes everything. And it doesn't, as we know. And so you emphasize the ROS role in genotoxicity, but I don't think that's really what's going on, or at least not solely what's going on.

And so my concern is that it doesn't serve a

purpose. It's just information for information's sake. And so that's what I think.

PANEL MEMBER BLANC: Are there any papers that you have where they looked at genotoxicity and adverse reproductive outcomes in some way. For example, if that's the -- I think that's where you're going with this as being the key non-cancer thing. So, I mean, if you had a paper that made that linkage for nickel that they were sort of parallel endpoints.

OEHHA STAFF TOXICOLOGIST BROWN: I can't think of one offhand, but I can take a look.

CHAIRPERSON FROINES: That's basically my point, that unless you connect it somehow, it sits out there on its own on a desert island.

PANEL MEMBER BLANC: Or you might, just what you said, which was move the table to an appendix, but then have two sentences in the text that say we provide in appendix a summary of the genotoxicity and we put it there because genotoxicity, in addition to being relevant to cancer risk, has been shown, in general reviews, to be relevant to adverse reproductive outcomes in particular, and therefore --

PANEL MEMBER GILL: Did you do a search of epigenetic effects of nickel, by any chance?

OEHHA STAFF TOXICOLOGIST BROWN: Yes. There's a

section in here on that. But that's not tied -- well, there's a few focusing on immunotoxic endpoints as Dr. Froines mentioned, but a lot of it is not specifically tied to a toxic endpoint.

But your discussion on the oxidative thing is useful, I think, with respect to the lung, because there it would be nice to have some more --

CHAIRPERSON FROINES: In our laboratories, we've shown that this pathway works. I mean, it's not -- I'm not making it up. It actually -- we've seen ERK, MAPK, MEK and everything.

OEHHA STAFF TOXICOLOGIST BROWN: Is there a cite on that?

CHAIRPERSON FROINES: What?

OEHHA STAFF TOXICOLOGIST BROWN: Is there something we cite on it?

CHAIRPERSON FROINES: Yeah, I'll have to send it to you. I'll send you the reference. I don't have it in my head.

OEHHA STAFF TOXICOLOGIST BROWN: That would be great. Thank you.

CHAIRPERSON FROINES: So where are we?

There have been a number of changes recommended, so we have to have the same discussion we had earlier.

PANEL MEMBER BLANC: Well, I think you

basically -- it's kind of the mirror image of the other one. You have to come to a decision about how you're going to handle this acute REL, and then we need to see the document so we can determine -- you know, have a formal resolution to comment on it. It's a scientific thing. I think it's premature for us to do that just yet.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly. So we'll come back to the Panel with a revised draft.

CHAIRPERSON FROINES: Okay. Okay. Well, thank you very much.

We're doing great.

Jim Behrmann?

Melanie?

Where is Jim.

PANEL LIAISON BEHRMANN: Yes.

CHAIRPERSON FROINES: Are you and Melanie prepared to spend a few minutes talking about what we proposed, about the proposal for the administrative issues with the leads?

PANEL LIAISON BEHRMANN: We could so, if that's --

CHAIRPERSON FROINES: I asked Jim and Melanie to discuss, amongst themselves, how best the timing should be for submissions from -- how best to handle the timing of the process, because we were getting things close to

deadlines, industry can always do that. There's no reason that they can't.

But in terms of the role of the leads, it seemed like we wanted to give the leads substantial time, so that they could actually give feedback to the OEHHA and in a reasonable time frame. So that's context for this discussion. So it's all yours.

PANEL LIAISON BEHRMANN: Thank you. Thanks, John. I'm Jim Behrmann. I'm liaison to the Panel.

We just used -- we can use the nickel document perhaps as an example. We had a discussion, an Email discussion, among several of us, including Bill, Ellen, John and myself, about what are appropriate time frames.

And I think it's going to be somewhat dependent upon the document that's coming forward. But I think we can give some general guidance or some general suggestions of what kind of time frames we would propose, at least from a staff standpoint.

And by different types of documents, let me just briefly say the types of documents that come before this panel, for the benefit of some of the new members, range from the type of REL documents that you saw at this meeting, which probably were on the long side for REL documents. They range all the way up to documents for toxic -- proposed toxic air contaminants, which are

actually probably 10 times longer. They're -- I don't want to use the word huge, but they're large.

And they're large -- as I've mentioned to some of you, they're large because the way State law reads the law specifies that the documents shall be an evaluation of all available scientific data regarding a particular chemical. And we've been advised by our legal counsel that to avoid possible legal challenge, the documents need to be truly that. They need to be an exhaustive discussion of a particular chemical.

Getting back to the proposed time frames that we've been discussing. The thought is kind of working back from a meeting date. We generally try to issue a public notice and release -- the Department would release its particular document approximately 30 days prior to the meeting.

We're required by law only to give a 10-day public notice, but we've found in the past that that's generally not acceptable, in that you've got stakeholders and people that are interested in a topic, and especially if they're traveling from distances, and finally, because we want to encourage them to comment to the Panel early, giving a 10-day notice is simply not appropriate.

So working back from a meeting date, we have a 30-day public notice and the document being made available

to the public. Prior to that 30 days then, we can set whatever time frames work for the Panel. In this particular case, I think we provided the document two weeks earlier, did we, Melanie?

OEHHA SUPERVISING TOXICOLOGIST MARTY: (Nods head.)

PANEL LIAISON BEHRMANN: -- to the leads? But we can adjust that. We can make it -- we can make the document available to the leads a month before the report goes public. So then we're talking about a two-month time frame.

I think that's probably the short -- roughly the shortest we want to make it. For a toxic air contaminant document, you want a much longer time period, where the leads are interacting with the staff for the Department that's authoring the report.

So the time frame then is say two to three months prior to a document coming to a meeting.

CHAIRPERSON FROINES: Did you say you're talking about a TAC now?

PANEL LIAISON BEHRMANN: Say a TAC document or any document. We would work -- I would work or we would work with the leads and with the Department that's responsible for that particular report to come up with a time frame, remembering or recognizing the fact that the

Departments actually are beginning work on these documents a year, even two years prior to them coming before the Panel.

The departments will go through this exhaustive evaluation. They'll go through a public workshop process, often multiple workshops. And the documents are made available to the public for their review and comment. The departments, over time then, will revise their draft documents, and with the end result or with the goal of producing an SRP, a Scientific Review Panel, review draft that would then come to a Panel meeting.

So I'm not sure how much...

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. The only thing I would like to just -- I think everybody would understand this, but just to sort of get it on the record, is that the SRP leads obviously should not be part of the process of developing the SRP review draft. That's done by the Department with public input.

PANEL MEMBER BLANC: Right.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Then it goes to the Panel leads. So we don't want you guys to get involved, prior to that, because then you're not really viewing it, you're helping build the document. So that's -- you know, we have to be a little bit careful there.

You know, like some of the REL documents have been really short, you know 10 to 15 pages. It doesn't take that much to review the chemicals that have hardly any literature. And some of them, like nickel, was probably the longest reference exposure level document we've ever done.

CHAIRPERSON FROINES: I would argue that for a REL document or some other document that has -- is smaller in scope, that having the leads get the document eight weeks before the meeting would be an appropriate lead time.

For a TAC document, I don't -- I think it's hard to set a date. Because with diesel, for example, the Panel had a workshop that we organized. And so diesel took 10 years, and that -- so that -- so we need -- the Panel needs to know when a TAC document like that is coming down the road far in advance of eight weeks, so we can make -- define a strategy for ourselves as to how we want -- do we want a workshop, do we not want a workshop, do we want to have more than one workshop, or whatever?

So that means that we need a time frame that gives us that opportunity. And I don't think we can set a date -- a timeline on that. But with that kind of goal in mind, we can operate that way, but I think the eight weeks for the REL-type documents is reasonable.

PANEL MEMBER BLANC: Melanie, do you feel there are limitations in terms of public meetings, such as this, for what you can say about what's coming down the pike?

OEHHA SUPERVISING TOXICOLOGIST MARTY: No. We can tell you what's coming down the pike.

PANEL MEMBER BLANC: So can you share that with us and maybe that would help give concrete substance to this discussion?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Sure. We have several reference exposure levels in various stages of development. The isocyanate we actually had a public review, but then we lost our staff person to a terrible accident. He died. So we haven't picked that up yet. That is next, after we get rid of caprolactam -- not get rid of, excuse me, after caprolactam is completed.

And then we have the last piece of the Air Toxics Hot Spots Risk Assessment Guidelines, which is the exposure assessment document, that's almost in the -- that has a special requirement to be reviewed by the Air Board and the California Air Pollution Control Officers Association. It's almost there, or is it there, Bob?

OEHHA SUPERVISING TOXICOLOGIST BLAISDELL: It's almost there.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It's almost there. So the next few days it will go to them.

They get a certain amount of time. Then it has to go through public review. Then we have to respond to the public comments, and then it comes the Panel.

CHAIRPERSON FROINES: Would that document be appropriate to have Kathy and Bill be the leads, because it's an exposure document.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

CHAIRPERSON FROINES: I'm not volunteering you. I'm just --

PANEL MEMBER NAZAROFF: No, of course you're not.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: I think we had -- I think we already had Kathy -- I think Kathy already knows that that document is coming, I think. Yeah, and Stan was one of the leads the last time. So this is a revision of the '99 --

CHAIRPERSON FROINES: So you want to stick with that, Kathy and Stan?

PANEL MEMBER GLANTZ: Yeah. I thought Kathy and I volunteered at some previous meeting to do that.

CHAIRPERSON FROINES: Okay. Bill is off the hook.

PANEL MEMBER BLANC: What else?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. And so then we have --

PANEL MEMBER GLANTZ: Unless Bill is dying to do it.

(Laughter.)

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have reference exposures levels for several other chemicals. They're not -- they haven't even gone through my review yet. So that's further out. So in the next couple of months, it would just be -- or between now and the end of this year, it just be the TDI MDI and the Hot Spots Guidelines.

PANEL MEMBER BLANC: And then what are the other things just generically, so we get a sense of what you're thinking about.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We have, I to have remember this, toluene, butadiene --

OEHHA SUPERVISING TOXICOLOGIST SALMON: Possibly benzene, possibly naphthalene.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Possibly benzene and possibly naphthalene, reference exposure levels.

OEHHA SUPERVISING TOXICOLOGIST SALMON: And possibly PCB numbers.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, maybe

OEHHA SUPERVISING TOXICOLOGIST SALMON: Maybe.

PANEL MEMBER BLANC: And then, just as an example, so in passing was the comment Andy made of metal carbonyls, nickel and others. I mean, is that something that would ever -- that would have to be something that would have to named a toxic air contaminant or is it already a toxic air contaminant?

OEHHA SUPERVISING TOXICOLOGIST MARTY: I believe nickel carbonyl is probably already a toxic air contaminant, because of the way the listing is, it's nickel and nickel compounds. So it's probably already a TAC.

PANEL MEMBER BLANC: So just from a process point of view, the reason why you brought nickel for a non-cancer endpoint document now was because you wanted to get it on the childhood list?

OEHHA SUPERVISING TOXICOLOGIST MARTY: It had ranked pretty high when we did that ranking in 2001.

OEHHA SUPERVISING TOXICOLOGIST SALMON: It was in the next 15 as opposed to the Filthy 5.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER BLANC: And are there any -- and you've done several others in the next 15. Are there any others in the next -- is the benzene and all of those, are those where that's coming from?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes,

that's where that's coming from.

PANEL MEMBER BLANC: And so to come back to a question I asked earlier in the day. Are there any substances for which there isn't currently -- which is not currently a TAC already, which you believe should be coming down the pike as a full-bore toxic air contaminant assessment?

OEHHA SUPERVISING TOXICOLOGIST MARTY: The Air Board is responsible for requesting us to do a health effects assessment. And I think you'll remember that the Panel, at one point, was working with ARB on a prioritization process.

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: For 12 or 13 years.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. And so it's up to the Air Board, who I can't really speak for, to finish that process, and then they would have a list of candidate TACs that they would proceed on and that they would ask to us do a health effects assessment on.

PANEL MEMBER BLANC: So that's the only way in which such a document would be initiated would be at the behest of the ARB?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Right, if it's not already a TAC. But we have all those HAPs that got listed as TACs years ago now that didn't have any

quantitative risk assessments, so there was no way for the ARB to look and say it's a problem, it's not a problem. So we've been slowly working through. They're trying to work through at least some of those.

PANEL MEMBER BLANC: Are any of those on your horizon?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I'm not sure what -- all the ones that are coming up are TACs. I'm not sure whether they're TACs because they're HAPs or they're TACs because they got listed as the first 23. Benzene got listed separately before that statute. But I think toluene and -- did we do a separate document on butadiene --

OEHHA SUPERVISING TOXICOLOGIST SALMON: Yes, we did.

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- as a TAC?

OEHHA STAFF TOXICOLOGIST BROWN: Yes.

CHAIRPERSON FROINES: Yes, we did.

PANEL MEMBER BLANC: Well, but I'm sort of asking about something which isn't on the childhood list, for example, particularly, isn't in that first 25 for children, but nonetheless is a TAC for which you've never done any quantitative risk assessment for which -- therefore, without which there's never going to be any

strategy from ARB to address. So are there any of those around?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah, there are a few, but they're not ready to come close to the Panel.

PANEL MEMBER NAZAROFF: John or Paul, can I -- I remember from -- regarding the ARB and the priority listing from the last meeting you had asked if I would serve, and I don't whether there was somebody else involved, as a liaison with ARB to help in a prioritization effort. And I was contacted by them, I don't remember who though, shortly before our spring break to have a meeting during spring break when I had planned to be away. And I said I couldn't make it at that time. And they were going to return, but the return never happened. So that's a link that I guess we're waiting still for the next action on.

CHAIRPERSON FROINES: Well, I think Jim could talk with Janette and see where that sits, because, as I say, it's one area of extreme frustration since they've been working on this prioritization for a dozen -- maybe up to 15 years now, and it's never come forward.

And so one could argue, as Paul I think is subtly arguing, that we need chemicals to be brought forward for TAC determination.

PANEL LIAISON BEHRMANN: John, just to clarify, I think as Janette and maybe Richard Corey explained in the meeting back in January, they had a prioritization process set up based upon the language in State law, which specifies certain parameters to be used by the departments to set priorities. That prioritization process, which has been in place and has been revised several times is undergoing this latest revision that you're referring to, which has been going on for some time.

Not to -- I think as they -- as the Air Board staff explained in the meeting back in January, they have placed a much higher priority over the last number of years on the regulation writing to actually reduce public exposure to toxic air contaminants that this Panel has already reviewed, primarily diesel and formaldehyde.

And I think it's become a much larger resource drain than they had ever expected. But a large number of staff work on actually reducing public exposure.

CHAIRPERSON FROINES: That's a good point, because diesel -- they clearly -- diesel was '98. And a lot of regulations had been written, as you say. But the issue is that we named diesel particulate as the TAC, and we need to go back and name diesel vapors and gases, because there's significant evidence that vapors are involved in diesel toxicity. So that's an issue that

could be taken up in the near future.

PANEL LIAISON BEHRMANN: And having a discussion with the Panel and with ARB staff would allow that issue to be raised.

PANEL MEMBER BLANC: Well, Jim, how would you feel about us having in early 2012 a formal one-day workshop on priority setting for identifying toxic air contaminants?

PANEL LIAISON BEHRMANN: Well, I personally think workshops work very well for this Panel. We've done it a number of times in terms of pesticides, in terms of diesel, as John had pointed out. I can take that message back to the Air Board staff. I think -- I'm not sure about how formally it would occur, if the Panel would --

PANEL MEMBER BLANC: We would initiate it.

PANEL LIAISON BEHRMANN: -- initiate or request it.

PANEL MEMBER BLANC: We would initiate it and we would bring experts that talk about when you have a whole group of toxic materials, how do you relatively rank, from a public health perspective, what should be targeted first? Is it volume of usage? How do you weigh volume of usage against inherent toxicity against vulnerable population toxicity against multiple roots of exposure?

I mean, there's a whole series of things that

we've talked about on the Panel. And sometimes we're at a loss. It's not as if we sat around right now and threw out a bunch of chemicals that we think some action needed to happen on. I think we would be doing it in a qualitative way, but that would be hard pressed for any of us to say this -- you know, A, B, C, and D is why that one matters more than another one. But it would be great, I think, to have some outside people come and present their views on -- and that in itself might stimulate --

PANEL MEMBER GLANTZ: Well, you know, actually there are a couple of prioritization documents that we approved. I mean, it's been awhile. For the one people talk about the 5 and the next 12, those were chemicals with special effects on kids.

But I mean, wouldn't a simpler first step to be to ask the ARB to go, and whoever, to take a look at the last prioritization document, which has been more or less been followed, I think, and just come back to us with an update, and say -- because a lot of the information you're talking about was in there --

PANEL MEMBER BLANC: Well, it seems to --

PANEL MEMBER GLANTZ: -- and just update it and bring it back, and then we could have a discussion of that and --

PANEL MEMBER BLANC: Since they haven't done it

in -- they've been working on it for years and years and years.

PANEL MEMBER GLANTZ: No, but I think if you -- what I'm just saying is if we could ask them to sort of bring it back in early 2012.

CHAIRPERSON FROINES: Well, I think that this has been very difficult for that group of people. And they've done -- worked very hard at it. And so they deserve the credit, but they've gotten side-tracked with other responsibilities within ARB.

I think Paul is -- I think it would be important to have Janette and her staff make presentations at a workshop like Paul is talking about, but I think we need people from the scientific community who can have ideas about what sorts of things are important and benefit from external input. For example, I mean I would like to argue that there are 100 Michael Addition compounds that are neurotoxic, and one should be taking the Michael Addition compounds up.

So, I mean, there are lots of people who have lots of ideas about these kinds of issues. And so I think a workshop would be quite reasonable.

PANEL MEMBER GLANTZ: That actually is a good idea to have Janette -- I mean, do what I was talking about --

PANEL MEMBER BLANC: In that context.
PANEL MEMBER GLANTZ: -- in that context. I think then you get the best of both worlds.
PANEL MEMBER BLANC: Both.
CHAIRPERSON FROINES: Do you know about -- anything about DPR bringing things forward?
(Laughter.)
OEHHA SUPERVISING TOXICOLOGIST SALMON: If we did, we wouldn't say it.
PANEL MEMBER BLANC: The record does not have to show laughter.
(Laughter.)
PANEL LIAISON BEHRMANN: Well, actually OEHHA and DPR have been the two departments that have been regularly bringing items before this Panel over the last several years.
CHAIRPERSON FROINES: But do you know right now whether they have plans for some?
PANEL LIAISON BEHRMANN: I do not know what their next TAC pesticide will be or proposed TAC pesticide will be.
CHAIRPERSON FROINES: Melanie, do you have -- are you planning anything further on your document on chloropicrin?
OEHHA SUPERVISING TOXICOLOGIST MARTY: No.

CHAIRPERSON FROINES: No. We have a situation where OEHHA has disagreed with the risk management document that DPR prepared for chloropicrin, which this Panel declared a toxic air contaminant. And when the risk management document was produced, it was contradictory to what OEHHA and this Panel had found.

And so the question becomes should we hold a hearing on chloropicrin, which is going to be very controversial?

PANEL MEMBER GLANTZ: Yes.

PANEL LIAISON BEHRMANN: Yeah. Just to clarify, John, again for the new members here, the Department of Pesticide Regulation proposed identifying chloropicrin as a toxic air contaminant. And so this Panel reviewed that proposed listing. The Panel approved the report. It sent findings to the DPR Director. The DPR Director subsequently listed it as a toxic air contaminant.

Now, in State law, that initiates then a second part of the process, both for DPR and also there's a parallel structure set up in State law for the Air Board. Anytime a toxic air contaminant is listed for the Air Board or by the Air Board, State law specifies that a Needs Assessment will be done.

In other words, an encyclopedic listing of all the ways in which ambient concentrations of a particular

chemical can be reduced. And they start the regulatory process of developing regulations on sources to reduce ambient concentrations, such that the risk to the public is reduced. And that's why there's been this lengthy effort in terms of diesel and formaldehyde, for example.

Now, on the DPR side, similarly they do a Needs Assessment, and they look at all the potential sources of chloropicrin, you know, whether it's label requirements, buffer zones, the use of alternatives or whatever.

And so DPR, by law, prepared a Needs Assessment and a Risk Management Directive, they call it, and by law had that directive reviewed by OEHHA. And I think what you're referring to is that there was some disagreement between DPR and OEHHA in terms of the specifics of how best to reduce the risk to the public.

But I only caution you in that the Panel's role when it comes to risk management is not existent. The Panel's role is to advise the departments in the risk identification for a particular chemical or a pesticide.

The risk management side is where, not just DPR, but the Air Board as well, they will weigh costs and benefits. They will basically make a decision or multiple decisions about how best and most cost effectively to reduce the public's exposure to a particular chemical or pesticide.

And as you can expect, there is always a wide range of opinion and agreement and disagreement about how best to do that.

CHAIRPERSON FROINES: Let me cut you off, because you're taking it to a place where I never said we would want to go, and that is to their risk management decision-making process. But if the Panel, this Panel, decides that chloropicrin was a carcinogen and of significant importance, and OEHHA had the same conclusion, and the risk management directive that's written says that carcinogenicity is equivocal, you have a contradiction between the findings of OEHHA and the SRP.

And the question is, should we look into that issue. It's not -- it has nothing to do with all the things you said about setting regulations with buffer zones and tarps. It has to do with the conclusions of the SRP versus the conclusions of DPR on very important issues, for example, the carcinogenicity.

PANEL LIAISON BEHRMANN: Again, just a suggestion from my position as liaison to the Panel is that a similar -- you could bring a similar perspective to the regulatory efforts, the risk management efforts of the Air Board. I just --

CHAIRPERSON FROINES: We've never had a situation like this in 30 years I've been on this Committee. We've

never had a situation like this. And I don't want to take it up unless there is some agreement that -- that we would pursue it. We can drop it, but there is an issue that we need to decide about.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, maybe I can put it in a different way. You know, DPR develops these risk management documents that are political decisions. They do weigh cost, technical feasibility like all risk managers do. And all risk management has a certain amount of political decision making that's involved.

The risk assessment is done. And we weighed in at risk assessment stage and the Panel, by law, weighs in at the risk assessment stage. Their risk management document, while it does have stuff that is contradictory to their own risk assessment document, is still a risk management document.

PANEL MEMBER GLANTZ: Yeah, but I think, Melanie, that the issue here -- and again, I want to reiterate what John said, is we're not regulators. That is a political decision. It's not a scientific decision. But the thing that really bothered me about what happened here, is we went through this whole long process to come up with a risk number, okay. And what DPR did was they just ignored that and said, well, we're going to write a regulation

assuming a lower risk.

And I think, you know, that -- you know, the way I've always described this process to people who have asked about it, is our job is to give people the best risk number we can. And then there's a political decision about what do you do about it.

You know, but I can't ever either, also as the second longest serving member, remember a case where people just said, well, we're going to just say that the risk is less than you did, and then write a regulation, which is then to the public understating the consequences of the political regulatory decision.

And I mean, if they are going to be doing that, then why do we bother with all of this. You know, because essentially -- my understanding of this whole process was it was to try to insulate the risk estimate from politics. And so then if the regulators wanted to go out and expose the public to very high risks, for whatever reason, that was their decision, but at least people would know it.

And so I was just -- when I saw this stuff come around, I was just completely shocked. You know, if they want to say we're willing to expose the public to this much cancer risk because we think it's economically justified, that is there business. That's not our business.

But for them, after this whole process, to say well, we are going to understate the risk, so that we can make our political economic decision and people won't think that they're being exposed to this level of carcinogenic risk, I mean, I think that's really appalling.

PANEL MEMBER BLANC: I think that --

PANEL MEMBER GLANTZ: And I think it just goes to the whole idea of the whole process and why we're -- we spent all of this time, you know, arguing about these numbers.

PANEL MEMBER BLANC: You know, I don't hear Melanie or Jim disagreeing with that.

PANEL MEMBER GLANTZ: I know.

PANEL MEMBER BLANC: But I think their point was, if I understood it correctly, is that they don't see the mechanistic vehicle through which we could revisit it, unless for some reason, the Department of Pesticide Regulation were to bring it back to us, is that what I heard you saying?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yes.

PANEL MEMBER BLANC: And so I guess a question in follow up to that, I would ask you to think about, but not necessarily say something, you know, standing on one foot, is for you to look carefully and see if thinking a little

bit out of the box there is any vehicle. For example, because it's a pesticide, you're precluded from looking at the pesticidal risk, except to the extent that the Department of Pesticide Regulation asks you for input, at that stage, like you did, right?

If something has both pesticidal and non-pesticidal exposure roots, can OEHHA, in any way, independently look at the non-pesticidal exposure piece of it, non-pesticidal uses?

Let's say we were talking about hypochlorite, which is used as a biocide, but also, of course, has many other uses.

CHAIRPERSON FROINES: Well, in this case, Paul, the question is there's a lot of fumigation that goes on at the Ports of Los Angeles and Long Beach where products are treated with fumigants before they're sent overseas. And so there is a non-farm related use.

PANEL MEMBER BLANC: I think structural pesticides are still -- I mean, I'm not sure that would be the way around it. It would -- I think it would have to be is it a byproduct of some other -- is it a hot spot, you know, is it manufactured at all? Is there a hot spot source or some other way around this that would allow you to bring it to us?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well,

even -- all of the statutes that we operate under for TACs, hot spots, SB 25 --

PANEL MEMBER BLANC: They exclude --

OEHHA SUPERVISING TOXICOLOGIST MARTY: -- they exclude pesticides.

PANEL MEMBER BLANC: The pesticidal use of a chemical. Does it exclude the non-pesticidal use of the same material?

PANEL MEMBER NAZAROFF: And example would be limonene. It's not a TAC, but it is used as a termiticide, and it's used as a solvent. And those are completely distinctive uses. And it's not clear -- I mean, the question that Paul raises is an interesting one.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Well, I'm not a lawyer, but all I can say is that the one chemical that we were allowed to look at as a fugitive emission from fumigation was Methyl Bromide. And it's because a judge made a decision in San Diego that that particular -- that once it comes out of the stack it's no longer a pesticidal use. But the judgment was limited by the judge to methyl bromide as a fumigant.

PANEL MEMBER GLANTZ: Well, you know, Maybe -- you know, the one thing that this is sort of bringing back is lead, where we had -- you know, where there was a huge political mess. And as I recall, what the Panel did was

ask the Department to simply come and make a presentation to us about, in that case, it was why they weren't doing anything. But maybe the thing to do is to invite DPR back to simply explain why they ignored the Panel.

PANEL LIAISON BEHRMANN: And let me --

PANEL MEMBER GLANTZ: And just see what they have to say, you know.

PANEL LIAISON BEHRMANN: I honestly do not believe the Department intentionally or even unintentionally tried to go against your advice in making its decision.

I have to just tell you, I'm struck by the conversation or the discussion, because it reminds me so much of actually one of the reasons I find myself sitting here, after my career here at the Air Board. My reason being a professor of mine at Berkeley, Bob Sawyer, was appointed by Jerry Brown to the Air Board. And I came to Sacramento to work with him on his staff.

And I still remember being in class in Berkeley and having this discussion. It was a very frank discussion about what it was like to go from being an academic researcher to now being a regulator. And the struggle that I can tell you, not just that he had, but that our current Board has over what to do about the ongoing high levels of risk to persons living around the

ports, around the railyards in California, they're levels that I'm sure this Panel would be concerned about.

So it's not just DPR, it's actually the Air Board as well.

PANEL MEMBER GLANTZ: Yeah, but the Air Board, I'm not familiar with the case where the Air Board in doing their risk management decisions changed an estimate of the risk associated with the exposure. I mean, I've never heard of them changing a unit risk that was approved through this process. And my understanding is that's essentially what DPR did.

PANEL LIAISON BEHRMANN: Well, I'm --

PANEL MEMBER BLANC: Twice.

PANEL LIAISON BEHRMANN: I'm not familiar with the specifics of what they did.

PANEL MEMBER GLANTZ: That's why I think maybe the next thing is to still invite them to come and explain it.

PANEL MEMBER BLANC: Jim, what I'd -- I mean, I don't object to Stan's suggestion, but what I also would like your commitment is to formally go back to your legal counsel and ask your legal counsel for a specific decision on whether the methyl bromide court decision could be interpreted by OEHHA to apply to other fumigants. And I'd like that legal counsel to say explicitly yea or nay or as

most lawyers do on the one hand, on the other hand.

Because, if, in fact, we take that narrow approach and more broadly interpret the methyl bromide decision that we do have the option of reviewing fumigants as potentially being air pollutants that are not exempted by being pesticides once they escape, then I would suggest that you do bring us chloropicrin. And I would also suggest that you bring us methyl iodide as well.

OEHHA SUPERVISING TOXICOLOGIST MARTY: We actually have looked at -- we have a chloropicrin reference exposure level. We already looked at it.

PANEL MEMBER BLANC: Well, bring it back.

PANEL LIAISON BEHRMANN: So just to clarify, you're asking that we --

PANEL MEMBER BLANC: Ask your lawyer --

PANEL LIAISON BEHRMANN: -- ask our legal counsel whether or not the methyl bromide decision in the San Diego case, where I believe the air district was allowed to regulate the emissions from these chambers, whether or not that decision can be applied more broadly to other fumigants?

PANEL MEMBER BLANC: Yes.

PANEL LIAISON BEHRMANN: And thereby?

PANEL MEMBER BLANC: Allow us to look at chloropicrin and methyl iodide, too, for that matter.

PANEL LIAISON BEHRMANN: And by us being?
OEHHA SUPERVISING TOXICOLOGIST MARTY: OEHHA independent of --
OEHHA SUPERVISING TOXICOLOGIST MARTY: I mean, I would argue that we've done that. We've done the risk assessment for chloropicrin and we worked with ARB staff on their methyl iodide document. I don't think -- and that was within our risk assessment context and the Panel looked at those documents.
CHAIRPERSON FROINES: Not methyl iodide.
OEHHA SUPERVISING TOXICOLOGIST MARTY: You're right. It wasn't the SRP. It was a specific panel.
CHAIRPERSON FROINES: Just some of the players are --
OEHHA SUPERVISING TOXICOLOGIST MARTY: Some of you guys were on it.
PANEL MEMBER BLANC: And in both cases the DPR simply changed the numbers.
OEHHA SUPERVISING TOXICOLOGIST MARTY: During their risk management phase, I guess that's the -- you know --
PANEL MEMBER GLANTZ: Right but gravity is still --
OEHHA SUPERVISING TOXICOLOGIST MARTY: During the risk management phase they decided to go against their own

staff, but I don't think that this Panel, which is the risk assessment reviewers, is the correct forum to go after that.

CHAIRPERSON FROINES: I understand, but the thing that troubles me, the numbers issue is very troubling. And you can argue that it's part of the risk management. But what bothers me the most is we stated unequivocally that chloropicrin was a carcinogen. There was no debate on that issue.

DPR says, in their document, that the data on carcinogenicity is equivocal and it doesn't appear to be a serious issue. So they absolutely contradict the findings of you and their own risk assessment people and this Panel. And it's -- so my concern is, is if we say it's a carcinogen and they say don't worry, it's equivocal and therefore not an important question, you're going to a fairly fundamental contradiction that's occurring. And we can forget risk management and risk assessment, we're talking about some level of integrity in the process, I think.

PANEL LIAISON BEHRMANN: And I think my only caution from having skimmed this risk management directive just twice is that I think it's very important to look at the context for the phrase that you stated. I think the context may provide a little bit more explanation perhaps

of what they meant by equivocal.

CHAIRPERSON FROINES: I don't -- so we'll -- I think we will not proceed further in any sense on this. I think that, based on Paul's suggestion, that we'll wait to hear from Melanie and you on where things are at. And the Panel may choose to not go forward in any kind of way or it may choose to go forward. I think it's a wide open question.

It's just an issue that I thought needed to be brought up, because there are contradictions. And so how we handle it -- I don't think we should do anything that threatens the integrity of this Panel. And especially with all the new members, that I think that we don't want to get into controversy that's not appropriate for the Panel to do so.

PANEL LIAISON BEHRMANN: I would agree with everything you said, John. And I hope that you've taken my comments in the same light. I think this Panel, or certainly my experience over the last decade or so, is that this Panel takes its independence and its integrity very seriously. And I think there have been numerous examples of that over the years. I appreciate your --

CHAIRPERSON FROINES: I don't want -- I just want to say, I don't want to do anything that compromises this Panel's ability to do its job. So that's the bottom line,

I think. But there is an issue and we need to have some resolution of it.

So Paul?

Oh, Bill, I'm sorry.

PANEL MEMBER NAZAROFF: No. I just -- I want to change the topic, if that's okay, back to the -- well, actually to come around back to the issue of process and the role of the leads and the timing.

I don't recall the date at which I got the REL document for nickel. I don't think it was six weeks ahead of the meeting. It might have been a month.

PANEL LIAISON BEHRMANN: No, it was not. It was about a month.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It was a month.

PANEL MEMBER NAZAROFF: Yeah. What I did in this instance was about what I think I could reasonably do, given that time frame, which is to provide comments close to a week ahead of time to OEHHA, which doesn't allow much time for absorbing and responding.

I didn't include a distribution to the rest of the Committee, which means the rest of the Committee heard my comments for the first time today. I don't know whether that model is the right one. And, you know, we've talked about having an earlier available time for the

leads or more available time for the leads, but I'm still not clear, at this point, what our best concept is for how to engage the pre-meeting review and communication of findings and so forth.

CHAIRPERSON FROINES: Let's assume that the leads have 6 to 8 weeks before the meeting to review the document that's available. When you write your comments, it's my view that I should take the comments -- Jim and I should take the comments and send them to the rest of the Panel. But we don't want to get into an Email exchange once they have them, so that the Panel members should have them to read and learn from, but it shouldn't generate activity that's not -- wouldn't be appropriate. So I think that's it more or less.

PANEL MEMBER BLANC: What you did was above and beyond the call of duty, really, I mean to have written comments in advance. Very, very often the comments are given at the time of the meeting. And so I would say we're ahead of the game if I get comments from the two of you two days ahead of the meeting.

CHAIRPERSON FROINES: But he won't start sending you Emails then

PANEL MEMBER BLANC: I for sure won't, in any event. But I think that's more than enough. I think the real question is, let's -- presuming that you're going to

send your comments back to OEHHA a week before, which I think they just need to have a heads up as to what the kinds of things are you're going to bringing up at the meeting. But I don't think our expectation is that they will have already revised the document in light of your statements, you know, prior to the meeting, because they need to hear from everybody else. And there may not be -- there may be a heterogeneity of views.

PANEL MEMBER NAZAROFF: Sure.

PANEL MEMBER BLANC: So it's really just to give them a heads up. If there's one specific thing for them, you know, they don't want to be, you know, caught unawares completely. But that's more than they usually get. So I think that's fine. I think the real question is for you to be able to read the document in a comfortable fashion and, you know, do it, you know, an hour here and an hour there in a busy schedule. Then the more time you have it, it's better from that perspective, but not because your then delivery date should somehow be moved back particularly.

PANEL MEMBER NAZAROFF: Well, it's also helpful to just know, because of course the new members to the Panel don't have any historical context in which to understand the expectations or norms.

PANEL MEMBER GLANTZ: Right, but the whole idea

though of having the leads is to be working with the OEHHA and the ARB and DPR when they're involved, to help them to kind of knock the rough edges off the document before. I mean, that's why we created the lead thing.

I mean, some people, like you did, have provided written materials others talk to them. You know, but I think -- the whole -- again, the idea -- I mean, I know we were talking about this a little bit at lunch. If you go back to the olden days, for us old people, you know, the documents would come to the Panel and have a lot more trouble. And so the whole idea of appointing a couple of leads was to work with them to try to identify problems before they got to the full Panel.

And I think different people have done that in different ways, in terms of preparing written comments or not. So that's -- I mean, it's been kind of an informal process.

CHAIRPERSON FROINES: Melanie?

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah. I was just going to say that it's really helpful for us to get comments in advance. You know, since --

OEHHA SUPERVISING TOXICOLOGIST SALMON: Written or verbal.

OEHHA SUPERVISING TOXICOLOGIST MARTY: For example, US EPA's peer review process is much more

formalized that they get comments in advance, than it helps to come to the meeting knowing what your issues were, if we've had a little bit of time to dig up some more information that would address those issues.

CHAIRPERSON FROINES: And so if Peter schedules the meeting at a time when you and Ellen say can have 6 or 8 weeks, then that just makes your life easier.

PANEL MEMBER NAZAROFF: Sure.

CHAIRPERSON FROINES: And that's the goal.

OEHHA SUPERVISING TOXICOLOGIST MARTY: It is -- there's a little bit of tension of scheduling the meetings way in advance and having the agency have -- be able to get the documents out two months ahead of that meeting. So, yeah, I don't know have a suggestion for dealing with that.

PANEL MEMBER NAZAROFF: Well, I mean, this time -- this is a really busy time and still a month was enough time to have done the job. That was fine, as long as the expectation was no more than what we were able to deliver.

CHAIRPERSON FROINES: I think, Melanie, that what we're saying is if we can get 6 to 8 weeks, that's the best of all possible worlds. If it turns out that you don't -- you haven't -- you know, somebody breaks a leg or there's an accident and it can't get done, nobody's going

to complain. It's sort of setting a goal, rather than saying that everything must be this way.

PANEL MEMBER BLANC: And for example, I would suggest with this nickel thing, you're going to go back and look at the animal studies. You're going to see if there's one that lends itself to an acute thing -- acute REL. I mean, I'd run that past your leads as a sort of iterative process. And I'm sure you're going to do that.

OEHHA SUPERVISING TOXICOLOGIST MARTY: Yeah.

PANEL MEMBER BLANC: You know, just like we were in communication about --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Exactly.

PANEL MEMBER BLANC: -- the acute REL on --

OEHHA SUPERVISING TOXICOLOGIST MARTY: Caprolactam.

PANEL MEMBER BLANC: -- caprolactam.

PANEL MEMBER ARAUJO: I think there is benefit also of keeping the format as we have it now, where you send the comments to OEHHA, and none of the other reviewers knew anything about what you guys feel, because in that ways we -- the other members of the Panel would not have any bias and approach. If you end up like reading the comments of the lead person before reading the material. So we're coming here totally unbiased to discuss independently.

PANEL MEMBER GILL: I agree with Jesús actually. That's much more useful, rather than having them reviewer comments, I can form my own individual opinion.

CHAIRPERSON FROINES: Are the two of you suggesting that we not send the written comments to the Panel ahead of time?

PANEL MEMBER GILL: Yes.

PANEL MEMBER ARAUJO: Yeah.

PANEL MEMBER GLANTZ: Well, the other thing is you can send them --

PANEL MEMBER NAZAROFF: You can ignore them.

(Laughter.)

PANEL MEMBER GLANTZ: -- ignore them.

PANEL MEMBER NAZAROFF: Don't open the file.

(Laughter.)

PANEL MEMBER ARAUJO: The issue would be so big.

(Laughter.)

PANEL MEMBER BLANC: I also think, Melanie, your point was very well taken, that we certainly don't want to go to a situation where Panel members are involved with an evolving document to the extent that there's a blur between the creation and the review. So we've generally taken the approach that once a document is very far along, that we might have some of that exchange with the leads.

And we've certainly taken the view that once you

present it once, then there could be very active involvement in certain ways, but I think your point was right on.

CHAIRPERSON FROINES: Paul, I'm sorry.

PANEL MEMBER BLANC: No, that's all.

CHAIRPERSON FROINES: There were four people. Ellen, Jesús and these two over here, who said, yes, they would not -- they would prefer not to receive the documents ahead of time. And so what's --

PANEL MEMBER GILL: The review documents.

CHAIRPERSON FROINES: The review documents -- the review from the leads.

PANEL MEMBER GILL: Yeah.

PANEL MEMBER BUCKPITT: Right.

CHAIRPERSON FROINES: And is that -- do we need to take a vote on that or how do you want to -- what's your pleasure? I mean, we can send them and you can not read them obviously, because that gives an opportunity for the people who want to read them to read them. So by not sending them, we actually rob some people of their desire to read them.

PANEL MEMBER GLANTZ: So why don't we send them to the people who want them and don't send them to the people who don't want them.

(Laughter.)

CHAIRPERSON FROINES: No. We've got to do it one way or the other.

PANEL MEMBER GLANTZ: Why?

PANEL MEMBER ARAUJO: More often than not, you're going to be running out of time. I don't think that anybody has the luxury of saying that you have read the document like two or three weeks ahead of, and then you have --

CHAIRPERSON FROINES: Well, let me just tell you that I told Jim to send the bills and Ellen's comments out Monday morning, precisely because I didn't want you to have them before the weekend. I was actually taking the conservative point of view, that if you took them, got them on the day before, that only those most interested would actually read them. So I actually am sort of caught between two positions.

So, Stan.

PANEL MEMBER GLANTZ: Well, I don't -- I mean, it's --

PANEL MEMBER ARAUJO: It's hard because of the process of the reviews for papers or grants, I mean, you -- nobody really has access to what the other peer member says, right?

PANEL MEMBER GLANTZ: I mean, I've always -- the times that they've been circulated, I've always found them

interesting, but I have my own opinions. But anyway, I don't care.

CHAIRPERSON FROINES: Well, I think people who want them should be able to have them, I think. That seems legitimate.

PANEL MEMBER BLANC: Well, first of all, there may not always be written comments in advances.

PANEL MEMBER GLANTZ: Right. Like I've almost never prepared written comments.

PANEL MEMBER BLANC: So what I think -- I think what you had proposed is a reasonable middle ground, which is if there -- that, A, we don't command that there be written comments. B, if there are written comments, they should go to OEHHA in a reasonable time frame, which would be a week to 10 days. And they should be circulated to the Panel a couple of days beforehand, if there are written comments, and people can have them with them. And then it's our expectation that since we're sending the documents to people a month in advance to the whole Panel, that the whole Panel should have read them more than two days before the meeting.

Something like that. You know, the best of all possible worlds, and then it meets your criteria and that you've read it.

CHAIRPERSON FROINES: Is everybody willing to

live with that?

PANEL MEMBER NAZAROFF: I think that's a good model.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER BLANC: Bearing in mind, that sometimes people may not write written comments in advance.

PANEL MEMBER NAZAROFF: Yeah, yeah.

CHAIRPERSON FROINES: Yeah, yeah.

PANEL LIAISON BEHRMANN: And I owe John an apology. And that when he directed me to send the comments to the rest of the Panel --

CHAIRPERSON FROINES: Don't worry.

PANEL LIAISON BEHRMANN: -- I wasn't in the office on Monday morning. And by the time I was, people were already on planes.

CHAIRPERSON FROINES: That's okay. Nobody suffered.

PANEL MEMBER ARAUJO: When did you send it, the night before, right?

PANEL MEMBER GLANTZ: Anyway, I think you're making too complicated.

CHAIRPERSON FROINES: Sarjeet.

PANEL MEMBER GILL: I just have one comment. When I -- this comes back as a document in itself, and I

ask an epigenetic issue. I read the whole part of the epigenetics while you were all talking about it. There's only one paragraph on epigenetic. The rest is a gene expression analysis. That's not epigenetics.

Just change the title to gene expression, there will cover up, because there's only -- the study is epigenetics. The rest is not.

CHAIRPERSON FROINES: Some of us have to catch a plane, soy I think we should draw a -- Paul, do you want to make a motion.

PANEL MEMBER BLANC: I'll move that we end the meeting, adjourn the meeting.

CHAIRPERSON FROINES: Second? Somebody second?

PANEL MEMBER GLANTZ: I'll second.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: Unanimous. Thank you.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 4:07 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 16th day of May, 2011.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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