MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

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APPEARANCES

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Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, SRP

Mr. Peter Mathews

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Dr. Tobi L. Jones, Assistant Director

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Dr. George Alexeeff, Deputy Director

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

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

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PROCEEDINGS

CHAIRPERSON FROINES: This officially opens the meeting of February 28th, 2008. And we're going to have a slight change in the process.

The third item on the agenda that deals with priority setting, we're not going to hold that today. Roger Atkinson, who was going to be one of the speakers, has resigned from the Panel. And we will hold that at the next -- we will hold the priority-setting workshop at the next meeting and finish it off. But we need to obviously replace Roger in some capacity. So the third item on the agenda won't occur today.

And so we're going to start with Endosulfan. And I just wanted to -- I feel that the Endosulfan issue is -- it's like living again in 1962 with Rachel Carson. And I just wanted to read something from ATSDR, which says, "Currently the GABA antagonism mechanism of toxicity is the most widely accepted hypothesis." This is the same mode of action that ATSDR has identified for lindane, aldrin, dieldrin, and chlordane. These pesticides are no longer used for agriculture in the United States.

So Endosulfan is a compound which in a sense is at the bottom end of a series of compounds which have been eliminated. And so hopefully over time this compound will become even less used. So I wanted to just say that at

the outset to put it in context.

What I'd like to do then is to invite Tobi Jones from DPR to make a short presentation. And then I'd like to have a discussion among the Panel about voting on the document in terms of its being a toxic air contaminant and then to get on with the findings.

So, Tobi, please.

DPR ASSISTANT DIRECTOR JONES: This is Tobi Jones, DPR. I want to make a few introductory comments to review where we are on the Endosulfan risk assessment.

The Panel discussed earlier drafts of the Endosulfan report at its meetings in September and December. And the draft before you today incorporates changes suggested in those meetings.

We've provided you with a revised document -- and I hope that our annotations are clear in this copy that we provided you -- that address the areas discussed.

The current version includes: 1) Changes in the exposure estimates for bystanders; 2) more detail on the reported illnesses; and 3) certain changes in the occupational scenarios.

The fourth area is an expanded discussion of studies on genotoxicity and oncogenicity and includes an additional NTP, a mouse study. In this area we have attempted to maintain consistency with OEHHA's findings.

We are making some minor refinements in the executive summary and the risk assessment text beyond what you all have received regarding genotoxicity and tumor promotion based on some very recent discussions with Dr. Landolph. It would be acceptable to DPR if the Panel identifies further research needed in its findings.

The fifth area is an expanded discussion of studies that pertain to an additional uncertainty factor for age-related effects. We have not reached agreement with OEHHA on the rationale for this additional uncertainty factor. But we'll continue to discussion with them the approach that they've taken.

Should the Panel determine that it recommends the use of an additional uncertainty factor, DPR would welcome the Panel's guidance.

In conclusion, we believe we have presented a defensible case that Endosulfan should be listed as a toxic air contaminant. DPR and OEHHA are in agreement with the endpoints that form the basis of our proposal. We hope that the Panel agrees with our proposal and we look forward to receiving your findings.

Let me conclude by also expressing our appreciation for the Panel's review of the document and especially the helpful comments of Drs. Landolph, Hammond, and Atkinson in refining the risk assessment.

CHAIRPERSON FROINES: Thank you very much.

My own point of view is I think there's very ample evidence of Endosulfan being a toxic air contaminant. But let me turn it to Joe and Kathy, who were the leads on the compound, and get their perspective for the rest of us.

PANEL MEMBER HAMMOND: Thank you.

I would like to thank you, Tobi, and your staff for the work you've done, and OEHHA for the work that they have done. I think there's been a lot of work that's been done on this compound, and I think the staffs have been responsive to the comments from the Science Review Panel. And Joe and I have been working on some of the findings for that.

And do we want to go directly to the findings then at this point?

CHAIRPERSON FROINES: We're still at whether it's a TAC stage.

Paul last night asked me, "Don't we do TAC and findings at the same time?" But the answer is we generally vote on the document as a TAC and then go to the findings.

And I had one question for the two of you. Joe and Kathy, has everybody on the Panel seen the findings?

Oh, that's a serious problem.

PANEL MEMBER HAMMOND: Yeah, right.

CHAIRPERSON FROINES: Peter, do you have the findings.

PANEL MEMBER HAMMOND: So in terms of the toxic air contaminant, I think that it's our feeling, and I think I would like to move on behalf of the Science Review Panel, that there is ample evidence that Endosulfan is a toxic air contaminant.

Do I make that as a motion? Is that the procedure?

CHAIRPERSON FROINES: You can. But --

PANEL MEMBER HAMMOND: But that's the procedure --

CHAIRPERSON FROINES: No, but you -- I mean we want to hear what you think, and then you can make a motion as a result of that. I would make the motion after we've gone around the room --

PANEL MEMBER HAMMOND: Oh, okay.

CHAIRPERSON FROINES: -- so that everybody has a chance to talk.

PANEL MEMBER HAMMOND: All right. So there are several different endpoints where Endosulfan has been shown -- demonstrated to be a toxic air contaminant. And there have been some measurements in the air that indicate that the levels to which people can be exposed fulfill the

requirements of something being a toxic air contaminant. So there's both toxicity and exposure data that support that.

So I personally find the evidence compelling that Endosulfan's a toxic air contaminant.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yes, I pretty much concur with Dr. Hammond's discussion. It's a neurotoxicant. It's a genotoxicant. There's some suggestion that it does things in vitro which might lead it to be a tumor promoter. More work needs be done on carcinogenicity.

But I was particularly impressed that some of the applicators were occasionally getting neurotoxicological symptoms. And that worried me from the beginning.

So adding all these things together -- it also seems to be endocrine disrupter, it causes problems in development. So for all these reasons, I would second Dr. Hammond's opinion. My opinion is the same and I'm confident that, in an assessment from me, that it is a toxic air contaminant, yes.

CHAIRPERSON FROINES: So, Charles.

PANEL MEMBER PLOPPER: I don't have anything to add. I'd concur with that. I think there's pretty good strong evidence that it is.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: I agree with Charles. I have nothing to add. And I think their conclusions are very reasonable.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: Yeah, I agree. I think the leads have done a fine job on this with DPR and as well as OEHHA's input. And I also agree.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I think there are two parts to the formulation here. And I want to make sure that the record also indicates that not only is the chemical under discussion inherently toxic, but also that there is convincing evidence of airborne exposure to the toxin at levels which would pose a potential health risk even within the somewhat more restrictive guidelines of the DPR calculation approach. So that it's a two-pronged issue.

CHAIRPERSON FROINES: And the second prong is?

PANEL MEMBER BLANC: Well, the first prong, everyone said it's clearly a toxic material. The second prong is not only is it a toxic material, but there's airborne exposure at levels which make it a toxic air contaminant. After all, it wouldn't be a toxic air contaminant if it wasn't in the air.

CHAIRPERSON FROINES: There's actually some new data emerging on that issue. But it's not in the record

so I won't bring it up. But the point is actually getting stronger rather than weaker.

We went around the room so fast. I don't want to -- Melanie, are you comfortable with the conclusions the Panel has made as the OEHHA person?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

CHAIRPERSON FROINES: I don't know if we've ever had something quite so --

PANEL MEMBER BLANC: Well, again, I think that it's partly because some of the issues that -- some of the nuance that may come up in the wording of what the content of the findings -- our findings and interpretation themselves are probably still worthy of discussion. And I'd have to go back and look at the record. I'm actually not sure that we -- you know, that we typically have very much difficulty with the phase of the dichotomous yes/no. Some of the more protracted discussions occur related to content of the -- more emphasize in the findings statement.

So I certainly would be comfortable moving that the Scientific Review Panel concurs that the scientific evidence presented supports designating this compound as a toxic air contaminant.

CHAIRPERSON FROINES: Is there a second?

PANEL MEMBER HAMMOND: I second that.

CHAIRPERSON FROINES: Is there a discussion?

PANEL MEMBER BYUS: John, don't we -- at some point I mean I agree. But don't we also have to say whether the document is seriously deficient or not? Or is that part of the findings? Where is that?

CHAIRPERSON FROINES: We absolutely have to make that determination. And that will -- that is a requirement of our findings.

PANEL MEMBER BYUS: Okay.

PANEL MEMBER BLANC: And actually that's why I worded my motion the way I did, which is that whatever the deficiencies may be, I believe that the science is acceptable to the standard of the dichotomous designation of yea or nay to it being a toxic air contaminant.

CHAIRPERSON FROINES: Paul was actually making -- you see, we don't determine -- we may recommend that it be a TAC, but we absolutely have to determine the adequacy. And so that's what I heard him doing. And so if everybody understands that, then we can --

PANEL MEMBER BLANC: Could you read back the wording is that possible.

(Thereupon the record was read as requested.)

PANEL LIAISON BEHRMANN: Dr. Froines?

CHAIRPERSON FROINES: Yes.

PANEL LIAISON BEHRMANN: If I could just add very briefly -- I'm Jim Behrmann, Staff Liaison for the Panel.

The Panel most often meets in northern and southern California. And I want to thank the Panel for meeting here in Sacramento today. And for the benefit of the people that are here today that are not normally at a panel meeting, I wanted to just add -- and I'm sure you may even have alluded to it in your earlier remarks -- but lest anyone here in the audience think that the staff has not had to present much in the way of evidence or that the Panel hasn't really discussed this. This report has actually been the subject of two previous meetings, at which -- during which time there were hours of discussion by the Panel members, both in September and in December.

So I wanted to make sure that the people attending today that do not normally have the benefit of seeing this Panel, that they get the correct impression that this isn't an easy task to come before you.

Thank you.

CHAIRPERSON FROINES: What he's really saying is that "too bad, folks, but you've missed all the fun."

(Laughter.)

CHAIRPERSON FROINES: So all in favor?

(Ayes.)

CHAIRPERSON FROINES: Opposed?

It's unanimous.

So thank you, Tobi. You're done. We're in business.

Now the question comes, do we want to take a 10-minute break, 15-minute break and give people a chance to read the findings as they're currently written?

PANEL MEMBER FRIEDMAN: You know, I don't -- I'm sorry that I keep harping on this. But my experience in the past is the findings are not -- I just opened a page at random that says, "Since this was an older study a number of developmental markers were not as assayed including sperm counts, crown rump links, skeletal stains, vaginal opening, and preputial separation." That should not be part of our findings, I don't -- I think we should have a brief, maybe two-page document. And that was my experience in the past.

This is regurgitating a lot of the larger report. And I'm not sure that that's what's expected from us and what's helpful.

CHAIRPERSON FROINES: Well, my view is that we have -- I think -- by the way, Kathy and Joe would agree that this is too long. So that it's a friendly audience.

My view is that the findings should be exactly that. They should be findings. In other words, they should be the written justification for our decision of

the compound as a toxic air contaminant. In other words, we don't need extraneous material that doesn't pertain to the actual decision that we made. We made a decision to identify this as a toxic air contaminant, and there were reasons for that. And I think our findings should be those reasons.

PANEL MEMBER FRIEDMAN: I agree. But do we need all this detail?

CHAIRPERSON FROINES: No, no. No, we don't.

PANEL MEMBER FRIEDMAN: And I don't think we can read this in 10 or 15 minutes, frankly.

CHAIRPERSON FROINES: Well, what would you suggest?

PANEL MEMBER FRIEDMAN: Well, you know, in view of saving resources, I'm not suggesting that this be rewritten. But, you know, in the future I would like to see us go back to what we used to do and have like a two-page summary that justifies the conclusion that it's a toxic air contaminant and here are the reasons why.

CHAIRPERSON FROINES: I'll tell you this. I saw an Email from Joe in which he went through the process of how this has emerged. It went to Kathy, it went to Joe, it went to Kathy, it went to Joe. And so he went through that process. And then at the end he said, "And finally it will go to John." That's the -- "we're going to get

rid of it and send it off to Froines and let him deal with it."

So I'm happy to be the person -- well, I'm not happy to be the person. But I'm willing to be the person who will take what they have written and write an edited version, if that would be acceptable, based on what we're going to talk about today. And I don't know whether you want to take a break and talk about it or whether you want to leave it up to me or how you would like to approach it. But I'm going to -- I will do exactly what you want, because I think -- I think what we want is findings that give the context for the decision. And we are in complete agreement I think.

PANEL MEMBER FRIEDMAN: Okay. Well, you know, I hate to assign you work out, because I'm not in the position. But I think that would be great, if you take this and make it into the kind of findings we used have that were about two pages and had the main points of why it's a toxic air contaminant, why people are exposed to it.

CHAIRPERSON FROINES: See, I get $110 a meeting.

(Laughter.)

PANEL MEMBER FRIEDMAN: In that case, absolutely you should do it.

CHAIRPERSON FROINES: Yeah. See, I get the extra

10.

That's not true, by the way.

PANEL MEMBER BLANC: Can I just point out one nuance here to what's being discussed, which is that, Gary, although I would agree with you 110 percent in terms of the kinds of findings that we deal with with the proposals that come from OEHHA or, you know, the work that comes from them, I think that the Department of Pesticide Regulation, as we have been struggling to evolve to a common ground, it may be necessary for our findings to be somewhat less telegraphic than they might need to be for the other. So that there may be some bifurcation here.

Not that it has to be perhaps as elaborate as this. But I think that there are certain -- there are certain areas, for example, in which there was certainly considerable debate and in the end no final closure between OEHHA and DPR on key issues. And I think that although that's not going to prevent us from finding that -- it has not prevented us since we've just moved that this does meet scientific muster to establish it as a toxic air contaminant. In fact, it maybe quite important for us as a panel not to have our lack of explicit comment on certain issues be misinterpreted as leaning towards some particular interpretation of the approach.

I mean I hope I'm not being too long winded in

what I'm trying to say.

PANEL MEMBER FRIEDMAN: Well, I have no problem with that. We definitely should include our comments, but not regurgitate little reviews of studies and what --

PANEL MEMBER BLANC: No, no, no. But I'm just making the point that I think whatever this -- whatever John working with Kathy and Joe comes to terms with an edited-down version of this, it will still likely, I anticipate, be longer than the two-page ideal findings that you're referring to. Perhaps that would be reasonable in terms of certain of the other items that we've dealt with historically.

CHAIRPERSON FROINES: I should also add something that Tobi alluded to in her remarks and, that is, that our findings are going to have some differences between what we write and what DPR has written. We're going to deal -- we are going to comment on the children's safety factor, for example. Tobi alluded to the genotoxicity and carcinogenicity issue that Joe's raised in the past.

So there are going to be -- our findings are going to have our stamp of approval. They're not a watered-down version of DPR or OEHHA's findings; and that's what I really want to avoid for ourselves. I think our findings should have our stamp of approval on what we think about this chemical. And so that's what it will

reflect. And if that -- but I do think there are substantial cutting that can actually occur. And it may not be two pages, according to what Paul said, but it could be.

PANEL MEMBER FRIEDMAN: And I think -- well, I totally agree with you. And I think this will be a more useful document to the people -- to the Air Resources Board if it is cut and it's readable and our conclusions and our comments are clearly stated, rather than going through all this massive regurgitating literature.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah, I do have to apologize a little bit. It was a little bit difficult for Kathy and I and John to converge for various time constraints. So it's been a work in progress. And I was working on it yesterday for the second time at 11:30, and I think I finally Faxed -- Emailed it to John. So we view it as a work in progress shrinking it. And we just didn't get enough time to shrink it down further.

I don't think it's going to hit two pages. I agree with Paul. But it certainly can go down more from the nine. Maybe four or five or something like that. There's a lot of elegant details that we don't want to sacrifice. Some of it backs up the conclusions of neurotoxicity and genotoxicity, et cetera. But we

certainly can shrink it down more, no question about it.

CHAIRPERSON FROINES: And I actually think that the developmental and reproductive and neurotoxicity are the three central areas that -- in a sense the oncology and the genotoxicity has gotten the bigger play. But it's less -- in some level less important -- not less important but just has less evidentiary basis.

I guess what I'm saying is that we're going to take -- the three of us are going to take this document, do a new version, submit -- circulate it to the Panel. And when we come into the next meeting, we spend 30 seconds on approving it and that's it. So we basically do it by communication among the Panel as we go. And Gary -- so we'll have it down to a size that Gary won't come in to the meeting and say, "Whoops, you guys didn't listen to a word I said."

Is that -- so we won't try and take a 10-minute break or a 15-minute break, because I think you don't get good work that way. Is that reasonable?

PANEL MEMBER FRIEDMAN: And I'd like to add that -- you know, I don't mean this at all as criticism of the lead people who -- you know, you guys have done a tremendous job. You've found a lot of flaws and problems that have been, you know, dealt with by DPR, and I want to thank you for all the good work you've done. I sort of --

that's what one of my pet peeves in life is brevity. And I guess I'm bringing that here.

CHAIRPERSON FROINES: Tobi, are you okay with -- this isn't going to throw you off, is it?

DPR ASSISTANT DIRECTOR JONES: That's okay.

CHAIRPERSON FROINES: The good news -- the bad news, it will be moved -- it won't be finished till next time. But the good news is that it will be finished next time. And that's what we want.

PANEL MEMBER BLANC: I think what would be useful though since we're obviously going to be saving time here not taking a break and not having a lengthy discussion of this with the wording of the findings -- I think that it would be useful for me, and I assume for the other Panel members, to hear briefly from Melanie in a sort of highlight form -- they've provided us also with their findings. And I think it would be useful for me to hear in five minutes what OEHHA sees as the outstanding gaps between the two positions at this point, just so that I can put that in context.

CHAIRPERSON FROINES: Melanie, can you do a five-minute gap?

I should say, Paul, one of the things that's important to note is that when Melanie's finished this, George and Melanie and whoever else is going to present is

going to present the non-cancer risk assessment. And that won't be voted on today. But it has an extensive amount of discussion on the risk assessment vis-a-vis children. So that OEHHA's position is actually coming in about 20 minutes and it's in considerable detail.

Melanie.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Melanie Marty from OEHHA.

We did develop a revised findings recently to reflect the changes that DPR made in their document. I think it's safe to say that most of the things have been resolved. The outstanding area of disagreement is whether there's an additional factor is called for to protect early life exposure. So that's really all that is left.

We felt that the data say there's a lot of arrows pointing to inhalation being an important route of exposure, being different pharmacokinetically than orally. So that should play into your -- into how you're looking at the data in terms of exposure.

And then also there are many arrows pointing to potential developmental toxicity including potential endocrine disruption and male reproductive toxicity that came from a lot of different studies. And while none of those studies is perfect in and of themselves, if you take the 10,000-foot view and look at all the data, it really

is saying to us that Endosulfan causes male reproductive toxicity in gestational and perinatal exposures. So that's --

CHAIRPERSON FROINES: That's very useful, because Joe and Kathy and I can focus on those bullets and it will be in the transcript. So we'll have -- having bullets like that are actually quite useful, because it helps focus your...

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: And some of the other data indicates also that effects were seen on a variety of parameters related to testicular function at lower doses in younger animals than in adult animals. So, you know -- and, again, none of the data are perfect, so there's, you know, judgment that has to come into play. But we would say that the younger animals were more susceptible.

CHAIRPERSON FROINES: Would you send us some references if you think that -- or point out where in the document that those references are so we know -- to help us know where to look.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure. Yeah, we can just send you the references that we think point these issues out.

PANEL MEMBER BLANC: Do you think that an important piece of that argument is the very recent

caballero study, or was that just sort of an aside? Because clearly that was too leg breaking to be in the document, but we could easily make sure that that enters into our record.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, the caballero study, which just was published I think last month --

CHAIRPERSON FROINES: That's not Roberts', right?

OEHHA DEPUTY DIRECTOR ALEXEEFF: No. That's an additional study.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: No, it's an additional study. Which, you know, obviously DPR couldn't put that in their document. It wasn't published yet. But, you know, it does show developmental neurotoxicity.

It's sort of, you know, interesting endpoints and it's hard to know what it means. But it was clearly there. It impacted the neurotransmitter concentrations in various parts of the brain when Endosulfan was given during gestation.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Can I comment?

George Alexeeff with OEHHA.

I just wanted to say I think both OEHHA and DPR staff have spent a lot of time trying to break through new ground here, where in many cases factors are thrown in by

various organizations without a lot of justification. And a lot of effort was spent by both OEHHA staff, DPR staff, jointly and separately, trying to look at the data to really understand everything from the overt results, the results studied in guidelines studies, the results studied in much smaller university-based studies, and trying to put all the pieces together.

So I think what you see is probably both excellent approaches by both staffs in trying to -- I mean all the pieces are not there. So we're looking at a puzzle where many pieces are there and we're trying to explain the puzzle.

And so I think that's -- I think both staffs made excellent efforts in that line. And that's all I wanted to say.

CHAIRPERSON FROINES: That's great.

Thank you very much.

And I should say that I think Joe and Kathy really worked their tails off on this. And so as much as I agree with Gary about shortening it, they really read everything and they really did work very hard to get the findings for this meeting. And so it's no reflection on them that we're going to shorten it to some extent.

PANEL MEMBER BLANC: Can I just follow up. And I don't want to badger the issue, but I want to make sure

that I understand OEHHA's position in terms of this recently emerged data. I mean your findings suggest that were one to rely on the recent caballero study, it would generate an RCD that would be .06 as opposed to the .194, which is three times lower. That would seem to be a very cogent argument for a threefold safety factor.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER BLANC: And then you make a further argument that in fact that's an oral study, adding further uncertainty, which would seem to support an argument for a tenfold safety factor, simply based on alternative or emerging data that are there, leaving aside whether or not -- and if those data were confirmed in other studies, then you wouldn't need the safety factor because you'd have the sensitive age establishing. You'd just used that.

Is that -- am I understanding the thought process correctly?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, I think that's a good summation. You know, part of the issue of the caballero study is the first study that's actually done such a type of measurement. So we know it's neurotoxic to us. Anything that's neurotoxic raises a big red flag for developmental. I can't think of

any neurotoxin that's not worse during development than in adults. So that raised a red flag immediately to us.

This new study, which looked at neurotransmitters in the prefrontal cortex of the brain found a significant difference in the Endosulfan-treated -- the pups of the Endosulfan-treated dams relative to the controls.

So, you know, translating into that now what that means, you know, I can't say what that actually means. But, you know, neurotransmitters participate in neuro-development and they're very important signaling molecules. So that raises -- makes the red flag a little bigger, I guess I should say.

So I'm not sure we -- you know, it's hard for me to say we would base our number on that study.

PANEL MEMBER BLANC: No, I'm not saying that either. I'm saying that it's -- in support of the argument for the safety factor. If you were basing your numbers on this, you wouldn't have a safety factor because you would say this is what you've shown in the sensitive age range.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: Isn't that correct?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: That's right. If we had a good strong

developmental database, we would use that instead of an uncertainty factor.

PANEL MEMBER BLANC: Right.

And the other reason why I think it's kind of critically important that perhaps that be pretty explicit in the document is because apparently federal EPA has opted not to use a safety factor in their Endosulfan risk assessment, if I understand correctly.

CHAIRPERSON FROINES: That is currently being considered at this point. And they had proposed -- and their rationale for going to a one safety factor -- no safety factor was, in my view, slightly bizarre, and I won't go further, but it was very contradictory. So I don't know how it's going to turn out. But they're going to be under a lot of pressure to not stay with that position I think.

PANEL MEMBER HAMMOND: I'd like to state one of my view points on the question of childhood safety factor.

We --

CHAIRPERSON FROINES: Thanks, Melanie and George.

PANEL MEMBER HAMMOND: I think that that's an issue that we will probably need to be pursuing in the future and will simply be part of what we'll be looking at in the non-cancer risk assessment methods. And so these are new issues that we're looking at. They have the new

legislative mandates that the SRP is facing. I think they're very important issues. They perhaps increase sensitivity of children.

I think there -- even without having resolved those issues though, we can actually take other pieces of information. And I would say that there have been some testimonies that would indicate that you have to have experimental data proving greater sensitivity of young animals than adult animals in order to think that there's an age effect.

However, I think we do know enough toxicology that for certain systems such as neurotoxicology, we know that in general since the systems aren't fully developed that they tend to be more sensitive. And so we can without knowing what the safety factor is be aware that we would expect even without animal data that there would be more sensitivity of young humans than for adults. And so I think we can actually look at that. That's part of the science basis that we already have.

So I think the question of what level of evidence is needed, do we need it in this -- I would think at that point you would almost have to show that there's actually no difference between children and animals. But in the absence of data, I think one would assume that there's a difference.

CHAIRPERSON FROINES: Joe.

PANEL MEMBER LANDOLPH: Yeah, I was just rereading a document on the way up again. And I realized that there actually is data in here on page 39 that Endosulfan does cause tumor promotion in the hepatocyte foci bioassay. So that statement could be strengthened.

The other thing, that I puzzled by the gentox data, because some's positive and some assays don't work. And it turns out earlier in the document they indicated that Endosulfan can generate reactive oxygen species and they have an unusual and unique gentox profile. So that would rationalize some of this data. We'll probably put that in the findings too. Then we'll shortened it.

CHAIRPERSON FROINES: Do you have a reference on reactive oxygen species?

PANEL MEMBER LANDOLPH: They do.

CHAIRPERSON FROINES: They do?

PANEL MEMBER LANDOLPH: It's called Soan, et al., 2004. And they're looking in Saccharomyces Cerevisiae.

CHAIRPERSON FROINES: And do you know what they used as their endpoint?

PANEL MEMBER LANDOLPH: TBARS, thiobarbituric acid reactive substances, looking at lipid proxidation. And I'd have to pull a paper to get more detail on it.

CHAIRPERSON FROINES: Well, you know, there's

that big fat double bond that nobody's talked about yet that's going to potentially epoxidize and then form diols and -- and so that there are pathways that one could think would lead to reactive oxygen species. So that I've thought about that and just decided not to bring it up, because we've had enough complexity anyway.

But, I think that -- my feeling is the metabolism as we know it thus far is probably incomplete and that there are probably other metabolic pathways that could lead to other forms of toxicity.

PANEL MEMBER LANDOLPH: And the reason I brought that up was I was looking at the gentox profile again and it was a little -- it was interesting. And you get more chromosome breakage and less mutation. And that's true with oxygen radical species, because the assays don't detect their activity very well. So it's a consistent pattern.

CHAIRPERSON FROINES: Those are rigid molecules though, those more bornal structures. So it's not quite as simple as I just made it. But it's something that it would be nice to see some experimental data, you're not -- because I don't think they missed it. I think it isn't there. Don't you think?

PANEL MEMBER PLOPPER: Um-hmm. That's what I think.

CHAIRPERSON FROINES: Yeah, I think Charles and I would be on the same page on this one.

PANEL MEMBER HAMMOND: I have a comment about the findings, and just in their -- I actually tried fairly unsuccessfully to get some guidance on the findings and just what should be in them. I understood Gary wanted short findings. But I've also been unclear -- and I don't know whether this is a conversation to have here or elsewhere -- how much the findings need to contain within themselves the data or how much we just say that the data are in the report and we just make up, you know, like -- how would it be to say that there is evidence that endotoxin is a tumor promoter, period? Would that be a finding? Would that be sufficient?

PANEL MEMBER FRIEDMAN: I would be in favor of that. In fact, I would suggest that you read -- that Kathy be provided with some of our previous findings, that you're relatively new -- you know, if you could see what we've done before with some of the other chemicals.

PANEL MEMBER HAMMOND: But you would consider that a sufficient finding?

PANEL MEMBER FRIEDMAN: I would think that would be sufficient.

PANEL MEMBER HAMMOND: And would other members of the Panel feel that way?

PANEL MEMBER BLANC: I think it depends on -- obviously it depends on the spin that's in the document. If in fact what you're saying --

PANEL MEMBER HAMMOND: I think that's part of the problem.

PANEL MEMBER BLANC: Right.

PANEL MEMBER HAMMOND: That's the problem that we've been --

PANEL MEMBER BLANC: Right. So I think what you want to do is choose the things. So on the things in which there doesn't seem to be any heterogeneity of views and the data are straightforward, I don't think you need to -- we provide the detail. So, for example -- just a quick example, point number one, which is, you know, a full paragraph, I mean basically I think that can be two sentences because I don't think you need to recapitulate that. But if you're going to have a finding that more strongly emphasizes the potential tumor promoter potential of the compound which was only alluded to in passing in the document, then I think it's worthy to say although it was not strongly emphasized in the document, you know, we believe there was convincing evidence to suggest it was a blah, blah, blah.

CHAIRPERSON FROINES: Well, I have a question for people. Let's assume that we want to say Endosulfan is a

tumor promoter and so Joe wants to know if that's sufficient. One could say that the evidentiary basis is sufficient to conclude that Endosulfan is a tumor promoter and then put page numbers in parentheses where the actual evidentiary basis is found in the document.

What do you think of that?

PANEL MEMBER FRIEDMAN: That would be great.

CHAIRPERSON FROINES: That way you have your evidentiary basis but you don't have -- but you haven't said it in a million -- at length.

Paul

PANEL MEMBER BLANC: Again, I think it depends on the point you're trying to make. So, for example, this discussion we just had with Melanie about an article which doesn't appear in the report because it has only just now been published. I think that would require obviously more detail describing that publication should we -- should you choose to invoke --

CHAIRPERSON FROINES: Well, I don't know what the rules are. Can we in our findings put something in that's not in the record?

PANEL MEMBER BLANC: We can --

PANEL MEMBER HAMMOND: You mean not in the report?

PANEL MEMBER BLANC: I think we just put it in

context.

CHAIRPERSON FROINES: No, I mean the record. The record -- we could --

PANEL MEMBER HAMMOND: It could be in the record if we talked about it in here.

CHAIRPERSON FROINES: The record of the whole --

PANEL MEMBER BLANC: It's in the record because OEHHA's put it in their findings. So we were supposed to review OEHHA's findings too. So I don't see any problem with that. It's not something I found on med line.

PANEL MEMBER BYUS: I have now read the draft findings. I think they're an excellent first draft. I think they're -- it's got all the information in there. Now, all you have to do is edit it down. Take another view of it and make your points. I mean I think you made -- it's an excellent first draft for findings. So just edit them down. And whether it's two pages or four or six pages or however many it is -- I mean I think you're just speaking about tumor promoter. I think you've summarized the data quite nicely and made the right sorts of value judgments and conclusions.

So, again, you want to have it longer, a little shorter, I think is what you should do. So I think it's an excellent first draft for --

CHAIRPERSON FROINES: I still maintain that the

context or the purpose of findings is to describe the basis for your decision. And everything else is in the document.

PANEL MEMBER BYUS: And what they've done is pulled out of the document all of those key findings -- the key aspects and summarized them here in their first draft. So that's the decision. Do you want to leave them here or refer to them back in the document? But in your thinking, your thinking is all done. It's just a matter of where you put it as far as I could -- as I read.

CHAIRPERSON FROINES: Well, but you agree with Gary as well.

PANEL MEMBER BYUS: Um-hmm. I think it should be tightened up. I mean it's a first draft. So, yes. And so you've got all your -- the way I read this, you've pulled all of the document, all of the key aspects, reiterated them. So that your conclusions at the end of every paragraph were supported by the document and your thinking. So I mean it's just a matter of deciding to reference back into the document or leave them here in the findings.

CHAIRPERSON FROINES: You know what's clear about this discussion? Is that we are academics.

(Laughter.)

CHAIRPERSON FROINES: Only academics can take a topic and after a hundred meetings haven't resolved it yet.

(Laughter.)

PANEL MEMBER BYUS: If you read what they've said, I mean they've made some very -- they've made all the right value judgments as far as I can see. And it's here.

CHAIRPERSON FROINES: Now, the point is that as they and then me are working on them, what we would prefer -- what we would want of course is Emails to, say, Joe or -- say Joe just for the sake argument -- that if you have input, don't just wash your hands of it after -- in the next five minutes.

What?

PANEL MEMBER BLANC: Nothing.

PANEL MEMBER LANDOLPH: Mechanistically I think what might work is let Kathy and I take another crack at it from the electronic copy we gave to Jim, and let us work to shorten it. And then we'll send it to you and you send it to the whole committee. You want to do that? And then just send us back any comments you have and we'll be happy to put them in.

CHAIRPERSON FROINES: I really want to come into the next meeting with being able to start and take a vote.

Hopefully we can eliminate lengthy discussions.

PANEL MEMBER FRIEDMAN: But we'll get a chance to see it before the meeting, right?

CHAIRPERSON FROINES: You'll have multiple opportunities. It's embarrassing, frankly, that you didn't have it until this morning.

PANEL MEMBER BLANC: You know, Joe, I want to suggest a slight modification of that, because it's -- you guys have worked so hard on it and it's really, you know, hard to take a step back. I really would suggest that John do a big, big trimming and send it back to you guys for your vetting as the next step.

PANEL MEMBER LANDOLPH: That's fine. But I'd like to do just a few more things before he does that.

(Laughter.)

CHAIRPERSON FROINES: This is my friend Paul Blanc.

(Laughter.)

PANEL MEMBER LANDOLPH: I know that.

CHAIRPERSON FROINES: Yeah, I think -- I agree. I actually think that having a fresh face to work on it -- I think Paul's right, that I think I can bring a fresher face than you two can.

PANEL MEMBER BLANC: And, believe me, it's been a number of years since John was referring to as a fresh

face.

(Laughter.)

CHAIRPERSON FROINES: So are we done for this -- at this point we're beginning to drag it out.

PANEL MEMBER BLANC: Yeah. No, fine. I think we know what we're doing.

CHAIRPERSON FROINES: So let's take a ten-minute break and then start with OEHHA.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: We are starting with OEHHA.

And it is my understanding, Andy, that today you're making a presentation and then we're going to discuss it at the next meeting and that you're not anticipating a lot of feedback today. But is there any reason why we couldn't give you feedback if we wanted to?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: No.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I'll hand over to Melanie here. She was going to introduce the topic, so she can explain best.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: That's correct.

No, we'd be happy to take feedback at any point, today included.

I did want to just reiterate for the record that

we extended the public comment period upon request from a number of people. And so that threw us off a little bit timing-wise. So the Panel has only received the public review draft of the document. And we are going to give an introductory presentation today and answer whatever questions we can answer.

But we aren't going to go through the individual chemical RELs today and we're not going to -- obviously can't go through the public comment. The public comment period ended three weeks ago. So we have the comments now and we're going to be in the process of responding to them.

The normal process is you guys get the document, the comments, and our responses all at the same time. So it just got a little bit split this time.

So, yes.

CHAIRPERSON FROINES: When will the -- the document I notice was missing was Appendix D.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Appendix D was the individual reference exposure levels for the six -- I think we had six chemicals.

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

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: So --

CHAIRPERSON FROINES: They weren't in my package.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think we sent -- I think I -- I Emailed you them separately, I think, didn't I? But, in fact, what -- I think what happened is you were expecting all of the RELs in Appendix D. That's not what you're getting. What you're getting doesn't -- by design, doesn't include the existing RELs. It only includes the six new ones. So the Appendix D, as you have it, and as you will have it for the purposes of review, consists of the six new REL summaries. It doesn't include -- you know, when it's final, we would add in the existing RELs which have not been changed from the old document. Does that make sense?

CHAIRPERSON FROINES: Yep.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: At the risk of getting people to laugh, you noticed why I noticed that I was missing appendix D right away. Because that's the appendix that has naphthalene in it and --

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. Well, naphthalene is not one of the

first six. But it will be coming along obviously as an existing REL until such time as it's updated, which I think is likely to happen in the --

CHAIRPERSON FROINES: You realize that you have both Dr. Plopper and me on the naphthalene thing, so that that's the one you have to be really be careful about it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, that's why we didn't include it in the first six.

(Laughter.)

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: That was a joke, by the way.

Okay. I'm going to turn it over to Andy, and he will make the presentation.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. Now what I say actually I mean.

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. So I'm Andy Salmon. I'm with the Office of Environmental Health Hazard Assessment. And I'm going to move the microphone closer so you can hear me.

So this presentation is a summary of what we've been doing with this revised non-cancer risk assessment

methodology document. And I'll just start -- what I'm going to do is I'm going to basically concentrate on what has changed from the previous go-around. So some of the -- some of you will in fact recall the process by which we generated the original air toxics hot spots.

CHAIRPERSON FROINES: Can I ask a question?

Is there anybody here from DPR?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Lori.

CHAIRPERSON FROINES: Oh, so there are people from DPR? I just couldn't see around people's heads. I just wanted to make sure, because obviously some of the issues that came up in Endosulfan are going to come up right now. And so I wanted to make sure that there was communication going back and forth.

Go ahead, Andy.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. So essentially what has happened is that we have a mandate particularly from the Children's Environmental Health Protection Act, SB 25, to ensure that quantitative risk assessments are child protective. And part of that mandate is to reevaluate the methods for deriving reference exposure levels for non-cancer endpoints. And we are also taking the opportunity to

incorporate new scientific developments in risk assessment methodology since it's ten years since we last looked at the methodology documents.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The requirements of SB 25, basically that we take into account any source of difference in response of infants and children, does in fact also mention other sensitive subpopulations. But the emphasis is on infants and children. We need to consider differences in exposure patterns, differences in susceptibility of infants and children to the toxic effects.

We're also instructed to take into account the effects of co-exposure to other substances with common mechanisms of toxicity and interactions of multiple air pollutants. There is going to be some general guidance in that area. But unfortunately at this point the science doesn't give us a great deal of opportunity to address those last two issues in detail. But obviously where we do have that opportunity, we'll take it.

CHAIRPERSON FROINES: Does the special susceptibility include metabolic differences?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Absolutely. It includes any source -- as we read the statute, it includes any source of

differential impacts, including metabolic differences, physiological differences, and so on, as I will elaborate in due course.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Just by way of background, these guidelines are designed specifically to support the risk assessments undertaken under the Air Toxics Hot Spots Program. It's been mentioned by Dr. Froines, among others, that these guidelines certainly are reflective of how we do things generally and are looked at with interest by other OEHHA programs and other California programs and, indeed, outside of California. But the specific regulatory application of this document is the Air Toxics Hot Spots Program.

The previous guidelines to which I referred, basically the Parts 1 to 4 of the technical support document, which was an exercise required by statute that we produce formal guidelines and have them reviewed by the Scientific Review Panel, and these four existing parts are the ones which are currently in force.

The acute toxicity dates from 1999 and the chronic toxicity dates from 2000. The exposure -- the cancer potency was 2000 also. And the exposure assessment is somewhat more recent. I think that's about 2003 or

something, is it not?

CHAIRPERSON FROINES: Is there a document that addresses uncertainty on a quantitative basis and talks about Monte Carlo?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Some of that appears in Part 4 as regards the exposure assessment and stochastic analysis area. That's where -- some elements of that.

Other uncertainty-based considerations also appear in the non-cancer and cancer toxicity technical support documents.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: This presentation in this document refer to risk assessment for non-cancer toxicity. And in attempting to update the methodology for the reference exposure levels, we decided that the old guidelines -- we had two separate documents, one for acute and one for chronic. And we felt that the reasons and justifications for that were in fact largely historical, and that it would make more sense for this revision to tackle both acute and chronic toxicity in the same non-cancer toxicity document. So this proposed document, which you have in front of you, is designed to replace Part 1 and Part 3 of the existing TSD series.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: I'm just going to go through the changes, and I'm going to start with the changes in what I'm calling the general guidance principles.

The first and most important change is that children are explicitly identified as a critical target population in the guidelines. There was implicit consideration of children as members of the general population in the previous guidelines. But in response to SB 25, we are making -- it is identification explicit in doing actual calculations and other steps to take their characteristics into account.

A second change, which reflects -- basically updates in the methodology relative to last time is that the -- from the previous documents, you'll be familiar with the idea of using uncertainty factors in extrapolation. There's been quite a lot of work on developing explicit quantitative models, particularly in the area of pharmacokinetics, but for some other aspects as well. And so in order to take advantage of that, we are advocating that wherever possible uncertainty factors will be replaced with explicit models. Now, this is a general principle which will underlie the way we tackle the extrapolation parts of the risk assessment.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Another general change which we are doing is we are adding a determination of an eight-hour reference exposure level. The existing acute REL has an integration period of one hour. And the chronic exposure is designed to deal with long-term exposures, which will be eight years or longer, but typically used with a one-year time-weighted average exposure measure.

So the eight-hour is an addition which we -- it's been suggested that we provide this for a variety of applications in hot spots risk assessments, such as off-site work as children in schools and situations like that.

It's designed to deal with exposures which may be repeated on an ongoing basis, but would not be expected to be occurring on a lifetime basis. And obviously the exposure metric is the eight-hour time-weighted average.

There's an additional consideration in relation to this which is something actually which has come up during the public comment period, is that it's been suggested that we may in fact need to develop separate values for adults and for infants and children for this time-weighted -- for this eight-hour time-weighted average REL, because some of the situations where this would be

applied are situations where access by children is actually statutorily limited. It's like some work places. Whereas, other cases we do want to have children included in the population and consideration.

PANEL MEMBER BLANC: Andy, what is an off-site worker?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: If you have a -- well, a typical hot spots emission site is, you know, a factory of some kind. And if that is in, say, you know, an industrial park and there's another factory next door to it and it happens that your maximally exposed individual which you're using the base of your risk assessment is actually a worker in that second factory, that's an example of an off-site worker type of situation.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Just remember that these numbers are used in risk assessments of specific stationary sources. And so the requirements are to look at the dispersion of the air pollutant into the surrounding area. Sometimes a surrounding area is not residential. It's office buildings or another facility. And so the impacts are really to people who happen to be there eight hours a day off-site.

We don't deal with on-site workers, because then

we're stepping on Cal OSHA's toes. And that's why we call them the off-site workers. They're the ones that have the impact from the plume of whatever facility that is being evaluated.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I'll also interpose a comment here about this area, that obviously you're going to be hearing a great deal more about this sort of application of not only the eight-hour REL but the others as well, because you are in due course going to be seeing an update of the Part 4 technical support document, the exposure assessment part. And so a lot of the -- you know, the detailed considerations of how the exposure assessment is done, how the target individual or population is defined, and how the RELs are going to be used is actually going to be appearing in that document rather than in this one. This document is going to be just about how we -- how we derive the RELs, and we've set up some definitions of what they are in the document. But we don't in this document cover how they're going to be applied in any detail.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Excuse me. That was supposed to go -- okay.

Why am I going backwards? Sorry. It's all a

question of clicking the right button.

Another change in general guidance principles is in relation to the use of uncertainty factors. I've already mentioned this concept that we would be replacing the uncertainty factors by models. And part of the way that the people have been thinking about these uncertainty factors in the published literature, particularly over the last 10 or 15 years, is that the inter- and intraspecies uncertainty factors, which previously were more or less just seen as individual black boxes with a value of 10, people have been thinking about those as composed of two separate components: A pharmacokinetic component, in other words an area of uncertainty which addresses differences in absorption, metabolism, distribution, excretion and that part of the process; and then a pharmacodynamic or toxicodynamic component, which is actually differences or uncertainties in the response of a target individual.

And the way people have addressed these areas of uncertainty in extrapolating both between species and between individuals within a species has been to use models where they're available. We may well have a pharmacokinetic model but not a pharmacodynamic model. So it's convenient to separate out these uncertainty factors into these two subcomponents. And there's been a

considerable difference -- well, there's been a considerable discussion of this in the scientific literature. I'm not -- you know, I don't want you to think we invented this. But we've read it and we think it's useful.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Another change in general guidance principles is the use of benchmark concentration methodology where data permit. You have in fact seen this in several recent REL determinations which you considered.

It was mentioned as a possibility in the previous guidelines, but has been much more thoroughly developed in recent years.

And the benchmark concentration method is now, in fact, in our view, preferred wherever possible rather than the more traditional NOAEL/LOAEL method.

PANEL MEMBER FRIEDMAN: Would you mind explaining why that is preferred? Or would you rather wait till after your presentation?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I can explain now briefly. I mean essentially it's a statistical argument in that the benchmark methodology looks at all the --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: The next slide is a good thing to look at.

There you go.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: The method actually looks at all the data which you have. It looks at all the exposure levels. And taking that into account obviously produces a more robust result in statistical terms than just looking at the single point of the low end of the curve, which is what you're looking at when you're trying to find out what the NOAEL is. That's the essence of it.

It uses -- also it uses statistical curve fitting methodology to estimate the overall dose response curve, rather than just taking a single value. So it actually allows you to calculate confidence bounds. And so -- I mean you know the uncertainties there. But this gives you some measure of at least part -- the size of what that uncertainty is.

So I think that's in a nutshell why it's preferable. It certainly has properties of providing better independence of the actual study design and exactly where the dose levels were selected and things like that as well.

PANEL MEMBER FRIEDMAN: But if I understand it correctly, you select the dose that causes an effect in 5

percent of the subjects?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes, we do.

PANEL MEMBER FRIEDMAN: So that's really not a "no effect"?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, in fact, it is, in the sense that what you call a "no effect" -- remember, in the traditional method it's called a "no observable adverse effect level." And what you're actually saying is that -- you know, what you select as the NOAEL is the level at which you can no longer observe any effect. And if you look at the actual size of the studies and their statistical power, what you actually find is that if you had a response rate which was less than something around 5 percent, then you wouldn't see it unless you were very lucky. So in fact -- yeah, for a typical animal study.

We've actually done quite a number of these benchmark dose estimations now and we've compared what we would get using the benchmark dose methodology and selecting a -- it's the lower confidence bound on the ED05 is the proposed benchmark. And if we look at what we get by that method and then compare it to what we get by the more traditional NOAEL method, where we can determine a NOAEL, the NOAEL and the LED05 look very similar in the

majority of cases where we're looking at standard animal studies which have a quantal endpoint.

Now, this recommendation for LED05 does not apply to continuous data, because there are other different statistical considerations for statistical -- for continuous data. It also doesn't apply to analysis of epidemiological studies, because what constitutes an observable effect is a function in that case of the size of the study and the methodology. So those two situations we don't have a generic recommendation. We're saying you just to have look at the study and decide what would be an appropriate benchmark.

But for the -- for the quantal study in animals, the standard sort of tox data that you see most of the time, our experience is that the LED05 has similar properties to what is commonly referred to as a NOAEL.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Krewski did an analysis at one point and published it of the NOAEL and where that was on the response fraction. And it's anywhere between 1 and 20 percent for typical animal studies. One percent would be a pretty large animal study. So epidemiologists are used to looking at large numbers of people, and most of the tox data is not large numbers of animals

PANEL MEMBER BYUS: For what it's worth, I agree

with you.

(Laughter.)

PANEL MEMBER BYUS: It's the thing to do.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, as I say, we do have some experience with it now, which you have seen several examples of. And on the whole we agree with Krewski and others that this is a more robust method in situations where it can be applied.

PANEL MEMBER BYUS: You don't always have the data though. That's the problem.

CHAIRPERSON FROINES: Can you make available that reference.

I also think that the original Kenny Crump paper is still one of the best papers on this topic. You know, it really lays it out.

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

CHAIRPERSON FROINES: And it deals with quantal and continuous issues.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. We would be -- yeah, we have I think most of those references. I think all of them.

CHAIRPERSON FROINES: Well, that paper is -- it's probably like '83, but it still reads very, very well.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. Those are cited in the document. But I think we can get copies of those to you if you would like.

PANEL MEMBER FRIEDMAN: I would very much appreciate that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, certainly, we'll do that.

OEHHA DEPUTY DIRECTOR ALEXEEFF: George Alexeeff.

There was one other paper by Leisenring and Ryan that also looks at another kind of -- same analysis but sort of different perspective. So I think there's -- there's two or three papers that kind of looked at it from a probabilistic approach.

CHAIRPERSON FROINES: Well, then there's all the work that Dale Hattis did looking at -- and others looking at this factor of 10 and whether it's adequate or inadequate.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. I'm going to be talking about that next, or very soon, if you want me to do that.

CHAIRPERSON FROINES: No, go ahead.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. The next area I'm going to talk about is in fact, you know, how the extrapolation is going to

work, how we use the uncertainty factors, and what values they should have.

First extrapolation to consider is the interspecies extrapolation. And this is traditionally being handled by means of an uncertainty factor of 10 in taking the applied concentration in the test species to an equivalent applied concentration for a human.

And this somewhat complicated diagram is basically designed to indicate the stages of the extrapolation, at least conceptually, and the fact that these can in fact be, if necessary, individually replaced by quantitative models. And to the extent that we are able to use quantitative models, we would be replacing the uncertainty factor or some part of it with that model. But we might have to retain some of the uncertainty factor if there were other areas which were not being dealt with.

CHAIRPERSON FROINES: Andy, I have a question about that. Because it's one thing -- here's your uncertainty factor over here. And then over here you talk about the pharmacokinetic and pharmacodynamic aspects of models. But the problem is the pharmacodynamic part of that is very difficult and very, very uncertain, it seems to me.

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

CHAIRPERSON FROINES: So you've kind of got -- the danger is that you begin to mix all sorts of things that shouldn't be mixed. You know what I'm saying?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, that's one of the reasons why we tried to separate the two areas conceptually and to think in terms of two separate subfactors rather than an overall interspecies or intraspecies uncertainty factor. And it's also why we amused ourselves generating these complicated pictures, to try and emphasize that these were separate components and that, you know, dealing with one does not deal with the other.

And while I would certainly agree -- and I think it may even be in my next slide -- I say --

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- that we're well aware that there are few cases where we have good toxicodynamic models, but we do in fact now have some reasonable toxicokinetic models for certain cases. So this is one of the reasons for our laying out the idea that there are these two separate components of the uncertainty in extrapolation and that dealing with one explicitly does not deal with the other.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: I think it's also fair to say that there are cases

where the two are petty well intertwined.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. I mean obviously once you start getting into the area of talking about specific models, then it becomes very case specific and you're responding to what data you actually have and how much you understand of the problem.

PANEL MEMBER BYUS: What does the threefold mean there?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, basically that what we're saying here is that the traditional overall value of UFA has been 10. And as a default, for want of better information, we're assuming that the uncertainty represented by the toxicokinetic extrapolation and the uncertainty represented by the toxicodynamic extrapolation are equal in size. Which in the way that the --

PANEL MEMBER BYUS: How do you make that assumption?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, because we don't know what else to assume.

PANEL MEMBER BYUS: Well, I don't see how you can make that assumption. That's a false assumption.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, there are -- I'll come in a minute -- there are --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: This is what happens when a bench scientist looks at risk assessment.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah.

(Laughter.)

PANEL MEMBER BYUS: Well, I mean I don't -- just to pick the 3 out of air -- I mean I agree with you up to this point, that there are these two components. But depending on what you're talking about, you have no idea whether it's threefold or --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, there have in fact been some objective studies of how big the uncertainty factors need to be. And there is some literature suggesting that the overall traditional value of 10 isn't horribly wrong.

PANEL MEMBER BYUS: I'm okay with 10.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And also there is in fact some literature suggesting that the value of -- actually it's root 10, or 3.16 if you want to be picky about it -- there is some -- you know, there are some reports in the literature suggesting that that isn't too horrible. But --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: For the kinetics.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, mostly on the kinetics side.

But I would agree that these are, you know -- this is an arbitrary default to be used in the absence of data.

PANEL MEMBER BLANC: The reason you came up with these numbers is so that if you didn't have either, you'd be back to 10?

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

PANEL MEMBER BLANC: And that's why you're doing --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's part of logic, yes.

PANEL MEMBER BLANC: It's approximately 3 --

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

PANEL MEMBER BLANC: -- or something greater than 3? You're not saying that you're now going to have a maximum default of 9?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No, we're not. We're actually saying explicitly -- people, both ourselves an the EPA in

previous guidance, have rather loosely referred to it as about 3. But in fact if you're doing the -- you know, because there's a multiplicative sum, the way it's used is if you have two of these, quote-unquote, three factors, then it multiplies up to 10. In other words the actual value is the square root of 10, or 3.16, that's the assumption, so that it multiplies up to 10.

PANEL MEMBER BLANC: And you said you thought that there was some support for the toxico -- I'm sorry -- the toxicokinetic variability between species being something like a threefold --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, there is some support for that.

PANEL MEMBER BLANC: Because if I had to weigh the two of them, I would have thought that the bigger piece of the uncertainty was in the dynamic piece, where it's not that it's metabolized more slowly or cleared more rapidly, but that there was a mechanism of toxicity that differed between species and that's where the uncertainty was, and it didn't have to do with how much of the -- it wasn't that it was going down a different pathway in humans or something?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: There are most definitely those examples.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yeah, I think the point is that it's definitely -- it's case dependent. You know, there are some cases where the kinetic uncertainty is large, and there are certainly also some cases where the toxicodynamic uncertainty is large. But, you know, these are sort of median values for use when you don't know any better essentially.

CHAIRPERSON FROINES: But as much as I understand what Paul just said, I actually would take the opposite view, which is that the heterogeneity within the toxicokinetics can be a very large number.

CHIEF SALMON: Well, I mean I think we're agreeing that you're both right. It depends which sort of -- you know, which compound you're looking at. In some cases that uncertainty, you know, will be biased in one direction, in other cases it will be biased in the other. But what we're saying here is if you had the information where you could say that, then you would be using that information. Even if you didn't have a good model, you'd be -- if you had information which even if it didn't give you a quantitative model, allowed you to say that "in this case I think the toxicodynamic uncertainty should be 10," then you would do that.

PANEL MEMBER BYUS: I guess I'm -- I think

everything you're saying is reasonable.

But let's assume you had the data -- I mean I'm just confused. Let's assume you had the data on the toxicokinetic differences in the individual model of the animal and it was fourfold. Now, are you saying --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: You'd use 4.

PANEL MEMBER BYUS: Okay. But then you would not use the 10X?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No, if --

PANEL MEMBER BYUS: You'd only use the 4?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, if --

PANEL MEMBER BYUS: And then you would pick this other one as the default 3 for the pharmacodynamic, is that what you're saying?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, if we had -- in any case if we have real data, we would be using the real data rather than the default.

PANEL MEMBER BYUS: If you only -- what I'm asking you is if you only have half of the real data -- in lieu of the tenfold uncertainty factor, say, you only have the toxicodynamic -- or toxicokinetic data or you have the

toxicodynamic -- I don't care which one --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. We would be using the -- but we are viewing those separately. So if we had the one but not the other --

PANEL MEMBER BYUS: So my question is: What do you do with the missing one? How do you apply it?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We're getting to that.

PANEL MEMBER BYUS: What is the value applied to the missing one?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We would have -- we're getting to that. In the next few slides you'll see that.

But we would not just replace the toxicodynamic uncertainty factor, because we knew something about the toxicokinetics.

PANEL MEMBER BYUS: That's what I'm saying. If you know something about the toxicokinetic and don't know anything at all about the toxicodynamic, what do you do?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, we'd use what we know to determine an appropriate value for a toxicokinetic factor and we'd use the default for the toxicodynamic, because we don't have --

PANEL MEMBER BYUS: And that number is?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Root 10,

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Root 10.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: About 3.

PANEL MEMBER BYUS: It's 3?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER BLANC: 3.1 something.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: 3.16.

PANEL MEMBER BYUS: And so say the toxicokinetic factor was 1.5X. So you would be using -- and so you would use 3 for the toxicodynamic --

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

PANEL MEMBER BYUS: -- and that would be less than the 10?

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

PANEL MEMBER BLANC: But it could be more than 10?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: It could be more than 10.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: It could equally well be more than 10.

PANEL MEMBER BLANC: Right, because if they had a value of 6 that they were pretty firm on for one --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: They are in fact -- although we're not going to be able to get to the discussion of the individual RELs today, you will see examples within that where based on at least partial compound-specific data or mechanism-specific data, we have chosen non-default values for these subfactors. But we do so independently. If we know one, we use the known version. If we don't know the other, then we use the default.

PANEL MEMBER BYUS: Well, let me -- and I'll just ask this one last question.

So if you -- say the toxicokinetic factor was measured and it was .5, and then you would use 3 for the toxicodynamic, and that would be considerably less than the 10.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes.

PANEL MEMBER BYUS: And I'm asking you: Is that in fact the way to do it?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, there's a very slight caveat -- there's a very slight point here, in that at least somewhere in the sort of the depths of our methodology -- I don't think we even necessarily lay it out in the guidelines explicitly. But there's a reluctance to use uncertainty factors of less than 1. But with that caveat, basically -- as I say, if we've got data, we use it; if we haven't got data, we use the default. That's the principle across the board.

PANEL MEMBER BYUS: I know, but the -- all right.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll have a little more discussion time because we're going to get into this same issue for the intraspecies extrapolation. So --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So if you knew that toxicokinetics was 1 and you didn't know anything about toxicodynamics, then you would use a toxicokinetic factor of 1 and a toxicodynamic factor of root 10. And this is in fact, as I'll show -- it may even be the next -- yes it is the next slide.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: This is actually what we've been doing all along in one particular case. But I'm going to actually

propose a modification of that case. But the point is, that is exactly what we've been doing all along in this particular case.

And the particular case is this so-called human equivalent concentration calculation, which we had in the old chronic guidelines. It's a methodology which was developed by U.S. EPA which considers basically deposition in the respiratory tract and uses the areas of various parts of the respiratory tract as a way of estimating what they thought would be the deposition of gases and vapors on the one hand or particles on the other in the various parts of the respiratory tract, and adjusts the equivalent concentration depending on where -- either in the respiratory tract or systemically the toxic effect is appearing.

So this is an established method developed by U.S. EPA. We used it previously for the chronic RELs. And it covers deposition. But I'd emphasize, it appears not to have any specific allowance for metabolism or elimination.

What we did in the chronic -- old chronic guidelines is where we had one of these calculations, we eliminated the interspecies toxicokinetic factor. We use -- and we'll change it down to 1. So we just used an interspecies factor of 3, which was representing the

remaining toxicodynamic uncertainty.

However, we have looked at this --

PANEL MEMBER BYUS: That's less than the tenfold?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, it is. It's 3 rather than -- or 3.16 rather --

PANEL MEMBER BYUS: The total was less than tenfold?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, the total is less than tenfold.

But we looked at this again, and we decided that because this doesn't cover metabolism and all those sorts of processes, that we would not in factor reduce the kinetic uncertainty factor to 1; we'd only reduce it to 2, because we felt that there was still some residual uncertainty due to the metabolism and elimination processes.

PANEL MEMBER BYUS: Which are the major considerates by far of the effective dose. I mean disposition is relatively minor, in general. In terms of drugs, it's relatively minor in an effective dose.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: It is. But I think what you need to think about --

PANEL MEMBER BYUS: Yeah, elimination and

metabolism are by far the major contribution.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, remember, we're talking about inhalation here. So, in fact, deposition processes can be rather significant, especially when you start talking about particles.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: So you're going from a rat's snout to a human. So that -- remember, this is going from an animal inhalation exposure to a human equivalent inhalation exposure. So the morphomatric differences in the respiratory tract make a fair amount of difference in the dose you actually get. So that was the --

PANEL MEMBER BYUS: Right, inhalation, I'm thinking --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, that was the point of this. And we used to just do what EPA did and just say, okay, that takes care of the toxicokinetic differences. But that clearly isn't the case.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So it's the change in response to the availability of an HEC calculation, which is -- you know, which what is new.

So, anyway, but that also -- that also

illustrates your point, that, yes, the overall factor in this case would be reduced from 10 to 6 if we still knew nothing about the toxicodynamics.

PANEL MEMBER FRIEDMAN: That last part you said you didn't -- you prefer the PBK -- I'm sorry --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, PBPK model. If we have -- there are now some actually much more complicated kinetic models which consider not only deposition but also metabolism and distribution or at least delivery -- yeah, and excretion -- or at least delivery to a specific site within the respiratory tract, where the effect is occurring. And then you know how that is -- that local concentration response. And there are a couple of examples. Again, you will in fact see an example of the use of such a model in one of the example RELs when you get to looking at that. That's one of the reasons why the example RELs are there hopefully to, you know, illustrate what we're talking about.

PANEL MEMBER FRIEDMAN: Does that replace the 3.16?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, that would replace -- that model replaces the 3.16, yes.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: I think it's safe to say though that we're still using uncertainty factors for the majority of chemicals because we lack the models.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. There are not going to be a lot of situations where we can do that. But where we can, we will.

PANEL MEMBER FRIEDMAN: So if 10 milligrams per kilogram causes some effect in a mouse, and you didn't have any of these models to transfer -- you say that you'd assume that the same thing happens for 1 milligram per kilogram in a human?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's the underlying assumption, yes.

PANEL MEMBER FRIEDMAN: And if it's a dog, it's still 10 to 1, and if it's a rat --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The guidance as we had it previously and as it continues is that it would be 10 for non-primate species and 3 for primate species.

PANEL MEMBER FRIEDMAN: But no matter what the species is?

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

CHAIRPERSON FROINES: Now, we're doing a lot of

work on interactions. And it's so strange to sit here and listen to this discussion, because when you start dealing with more than one chemical at a time, this is just bizarre. I mean it's like another -- it's like another world. I mean it's so complex that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, where we have an interaction situation to deal with, we will be looking forward to your guidance in that regard.

CHAIRPERSON FROINES: Well, it's clearly necessary, because, you know, since we have globalization, we don't have any factories anymore, and so we need multiple exposure methods.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I would certainly agree with that.

CHAIRPERSON FROINES: That was a joke.

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: But I'd still agree with it.

(Laughter.)

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The next one I want to talk about is the question of how do we handle the extrapolation within the human species. And here we're talking about the

extrapolating from the average human to either a specific sub-population or a specific individual or a type of individual. And the way this has been done in the past has again been to use an uncertainty factor of 10. But in the similar way to what you've just seen, we're proposing basically to subdivide the extrapolation conceptually into various subparts and that we would again be able to use models to replace either and/or the toxicokinetic and toxicodynamic parts with models. And, again, we're hopeful of having dynamic -- toxicodynamic models but seldom do. But we actually do in some cases have workable pharmacokinetic models.

The interesting point here of course, that there are a number of specific individuals or individual types that we would need to consider. But overwhelmingly what we find in practice is that we need to think specifically about children and especially infants, who of course both in overall size and also in physiology and biochemistry are probably most different from adults.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Now, the other question is, when we don't have a model, what do we do? And obviously we're going to have to use the uncertainty factor approach. And as I mentioned, the traditional default has been a UFH of 10

composed of two equal factors, one dealing with toxicokinetics and one with toxicodynamics.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Now, we have to consider infants and children. And this slide is an illustration of the truism that children are not -- they're not just small adults. They have considerable differences in anatomy, physiology. There are differences in particularly exposures like respiratory rate, dermal uptake due to both higher surface area and greater permeability. There are differences in excretion. There are physiological differences in body composition like body water and body fat content, which affect how things distribute. And there are different organ system sizes and blood flow, other flux terms likely gastric emptying. And of course, importantly, there are substantial differences in metabolism.

PANEL MEMBER BYUS: Let's back up.

You might add on that chart incomplete blood brain barrier for infants.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Absolutely, yes.

PANEL MEMBER BYUS: Children often times have higher rates of metabolism for some --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON:

PANEL MEMBER BYUS: -- particular drugs, not always lower. In fact, it's rather significant in children when they get to be five to ten years old can have actually on a per body weight higher rates of metabolism.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. And I apologize that this is a summary slide. But, yes, we -- and of course, you know, we've had the opportunity to discuss this with you at some length when we were considering the SB 25 prioritization process. So in terms of what we're going to be doing here, you may consider that everything that we said in that somewhat substantial document is included. And, yeah, you're absolutely right. And of course there are many other specific factors.

CHAIRPERSON FROINES: We have found that -- this is a little bit off topic, but let me just ask you about it. We have found that if you have an acute exposure to a reasonable amount of a compound, that very often it disappears very rapidly because of metabolism. But if you have lower dose over a period of time, you actually have more of that compound around to exert toxicity. So that the rate of when we're doing these kinds of experiments for these sorts of purposes, the actual administration of

the chemical affects the outcome because the metabolisms -- the metabolisms actually vary. And so that's something that nobody seems to take into account.

I can send you some data that I think you'll find interesting.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. I can envisage situations particularly where, you know, if you had a full PBPK model you would see slower compartments like the less rapid profused organs or the fat and so on. And if you have those slow compartments in the model, then you can have really quite considerable differences between the concentrations achieved at a target organ depending on whether you have a short sharp exposure, which does a sort of quick in, quick out, but mostly via the blood concentration, versus a perhaps lower but longer exposure, which has time to equilibrate the slow compartments.

And I'm sure there are other factors as well, but that's certainly possible.

CHAIRPERSON FROINES: It's important in air pollution where you have basically constant exposure at low levels. And so you have to ask what's the significance of --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, and that's one; also one of the

reasons why we have tended to think somewhat separately about the chronic exposures which reflect ongoing exposure versus the acute one-hour exposures and why -- actually one reason why I think we're asked to look at the eight-hour, because you could argue that, well, you know, in the interests of public health protection just use the chronic all the time and, you know, assume that the eight-hour is going to be like a chronic. But in fact it's not -- you know, it's not as simple as that because of these kinds of considerations.

PANEL MEMBER BLANC: Andy, can I just ask, or the Chair, a logistical question. I mean you still have quite a bit of material to go through in terms of the number of slides and how complicated they are.

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

PANEL MEMBER BLANC: It seems to me that if we don't take a brief break now, we're going to really be straining ourselves. I understand that you probably want to break -- you don't want to come back after a lunch break. But I still think we should take some time now.

CHAIRPERSON FROINES: My question is: How long do you think you're going to take, given this pace, to finish? And it has to do with whether we think we want lunch or not.

My sense is that we're not going to want lunch if there's a -- if we could go a reasonable time, then people could take off. But I don't know what people are thinking.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I'm about halfway through at this point.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. We can pick up the pace and then --

CHAIRPERSON FROINES: So you would say an hour?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, yeah. I would say hopefully less than that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, and hope -- well, depending on how many questions you have, of course.

PANEL MEMBER BLANC: But he certainly has 45 minutes left.

CHAIRPERSON FROINES: Well, then we should take a break now.

But am I correct that people would prefer to finish rather than take a lunch break if he's got 45 minutes?

PANEL MEMBER BLANC: I think so. It's the last thing on the agenda.

PANEL MEMBER BYUS: Yeah.

CHAIRPERSON FROINES: Gary?

PANEL MEMBER FRIEDMAN: Sure. I'm hungry, but that's okay.

CHAIRPERSON FROINES: Well, you can run downstairs and get a snack.

PANEL MEMBER HAMMOND: When is the cake being served?

PANEL MEMBER FRIEDMAN: Oh, the cake, right.

CHAIRPERSON FROINES: So are we agreed that we're not going to take lunch but we're going to have a break now and then finish off and go our separate ways?

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: Okay. Let's take a break.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: Do we have a quorum?

PANEL MEMBER BLANC: Yes, we do.

CHAIRPERSON FROINES: And so, Andy, why don't you proceed.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. I'll start.

So, anyway, we were talking before the break about the intraspecies toxicokinetic extrapolation. The key question is, in view of all these differences between infants, children, and adults, is the traditional toxicokinetic subfactor of 3.16, is that sufficient to protected children as a default? And as we've seen, there

are a variety of differences between infants and children and adults.

So what we did, we did two things. Firstly, we looked at reports in the literature where there are well described differences in kinetics. And this is mostly in the area of drugs. And we also looked at PBPK modeling, both examples in the literature and also quite an extensive group of studies which we did in-house. Dr. Brown on my staff was a major player on that one.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So the analysis actually suggests that, firstly, there's notably lower clearance or higher -- longer half-life of certain drugs in infants. And the PBPK analyses indicate that many chemicals show a larger than threefold variability in either the area under curve or amount metabolized, which are the sort of standard tissue dose kind of measures that you get out of a PBPK model. And so those age differences tend to suggest that threefold may not be enough.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The PBPK modeling we undertook used PBPK models with physiological parameter sets for various ages between newborn and adults. Most of these were -- we

didn't necessarily have real infant-specific values for all the physiological parameters. So in many cases, like metabolism, we were forced to use the scaling relative to body weight. But when we did have specific parameters, we tried to use those. And the number of published models were used and looking at metabolites in various target organs.

This is obviously to some extent a work in progress, in particular in regard to the need to identify more extensive chemical-specific metabolism data as that becomes available.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: But, anyway, the upshot of this is that with a variety of chemicals as the sort of things which are interesting to the Hot Spots Program, certainly in some cases the predicted range of the uncertainty factor -- and this is determined by taking the indicator parameter and looking at the ratio predicted for the adult model versus the infant or child model -- for many compounds admittedly the existing value of 3.16 would be sufficient. But there's a considerable number where it's not. And not quite half of the examples we looked at had something in the range of 3 to 10. And there were several in fact where the number exceeded 10.

So I think the first conclusion from this is that the threefold or the 3.16-fold is not sufficient.

PANEL MEMBER HAMMOND: Andy, what's the asterisk in that table?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, I'm not quite sure. That table was copied from the reports. So there's a footnote, and Melanie will look it up for you.

But the -- anyway, the upshot of this is that we think probably that we should be using an uncertainty factor for the kinetic intraspecies components of 10 rather than 3.16. And this covers most, although not all, of the examples we looked at. And we just see those ones where it's greater than 10 as not unusual but at least the more severe cases of the situation, and that we would hope to identify those by specific analysis when we --

PANEL MEMBER BLANC: And on a theoretical basis, how are you handling fetal exposures in these conceptually?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We don't have a good handle on fetal exposures. And the kinetics -- there are some kinetics looking at uptake of xenobiotics by the fetus. But the data are pretty limited and they typically don't deal very well with the sorts of questions that you'd be concerned

about with, you know, the site of toxicity. You know, for instance, it's not just how much gets into the fetus as a whole, but how much gets into a specific area of the fetus and what metabolic capabilities in that area are. So the short answer is we -- at this point we don't really have a very good handle on that.

PANEL MEMBER BLANC: But for this kind of exercise, wouldn't it have made sense to see if the same -- whether the range is yet even greater?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: If we had the means to do that, yes. But I don't think at this point we have the means to do it.

PANEL MEMBER BLANC: Meaning there are no examples of chemicals for which you have fetal data?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: There are no good models that I'm aware of where we could use that. But I don't know -- you know, I mean -- you know, let's say that certainly if we came across an example where we had such a model, obviously that would be very interesting. But I'm not aware of a case where we have one that we could use in this way.

The objective here was primarily to determine the range of the uncertainty factor for the intraspecies extrapolation. So for that uncertainty factor, we're actually looking at, you know, how would we extrapolate

the concentration to exposure of that individual? The question of, you know, what's the exposure to the fetus via the mother is a much -- certainly a much more complicated issue. And I think the only good answer that we have at this point that is to say that we would hope to look at developmental studies.

PANEL MEMBER BLANC: No, but maybe I didn't understand what you did. I thought for this table you took examples of chemicals for which you had a series of data on the effects -- or the pharmacodynamics --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: On the kinetics, yes.

PANEL MEMBER BLANC: On the kinetics on these various age ranges.

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

PANEL MEMBER BLANC: And you showed what the difference in the area under the curve was or some integrated measure and then saw how different it was and you divided the range -- and you present the range here, isn't that right, by category?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, that is correct. But we don't at this point have the technical means to produce a very satisfactory answer for the fetus.

CHAIRPERSON FROINES: Well, how did you come up with the ultra factor -- the UF factor being greater than 10 for methylene chloride?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: By fitting a combination of measures and extrapolated infant-specific parameters into the PBPK model.

PANEL MEMBER BLANC: Well, I should think that something that would be of use in this would be looking and seeing what happens with carbon monoxide, since you do have fetal data on that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. Although I think there are --

PANEL MEMBER BLANC: I mean there must be some other examples then.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: There's not very much that we could use in the sense of having enough coverage to be able to produce a prediction of a usable default at this point. I think that's the object -- that was the overall objective of this exercise.

PANEL MEMBER BLANC: Well, wasn't the -- I thought the object was to show that there's enough things that fall beyond a default of 3 that that wouldn't be public health protective on an automatic basis.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes. And I think we have covered sufficient number of examples to demonstrate that. But there are clearly going to be many other specific cases of interest. But, as I say, as a general rule, I think it's fair to say we don't have as satisfactory and complete a kinetic model available of fetal exposures to be able to include consideration of that for this purpose.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Now, one of the key things that we were concerned about was this question of target organ sensitivity and the fact that the dividing and differentiating cells in children may be more sensitive to damage. So I think this is another -- I mean we've been talking about the kinetics. But now we're talking about things that might affect the toxicodynamics.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: So going on to consideration of toxicodynamics, there are certainly reasons for thinking that children may be more -- actually more sensitive at the tissue level target organ sensitivity. And this should -- by the way, I'm sorry, there's a typo in the title. That should read "toxicodynamic variability."

That's what I'm talking about here.

PANEL MEMBER HAMMOND: Shouldn't that be UFH-d?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That should be UFH-d, yes. I'm sorry, the title got copied across and then it didn't get edited. It should have been.

So we have a position that children may be more sensitive to toxicity than adults. But in general -- I mean and certainly there are specific cases where we know about this. But in general we lack quantitative information on how large that difference would be. And we have in the past assumed that the existing defaults is adequate. And in this particular context we are going to -- we're proposing to assume that the existing default is adequate, because we don't have evidence in general that it's insufficient. But we do recognize that there are some specific organ systems and toxic endpoints which have been identified as being of particular concern. And these -- this is a list of some of the, so to speak, red flag effects, which we particularly identified these in our SB 25 prioritization, for instance.

So these are things that we would tend to look at and say we think there's a potential for infants to be more sensitive -- quite apart from any kinetic differences, they would be more sensitive at the tissue

levels of these kinds of effects.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And what we hope of course is --

CHAIRPERSON FROINES: Andy, go back a second.

You don't think that respiratory disorders shouldn't be in there?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: They are. We put those in there in our prioritization document. I mean we -- this is not a complete list, for sure. The one example that we gave during the prioritization process was asthma as differentially impacting young children.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think that one got kind -- because this slide has only so much space, that probably got subsumed under the immunotoxicity heading. But it's certainly a substantial consideration and one which we hope -- you know, we intend to give full attention to.

So, anyway, what we're saying is, firstly, therefore, what we propose is that we would use a toxicokinetic component uncertainty factor for intraspecies extrapolation of 10 as a default, and that we would use -- the uncertainty factor for extrapolation of toxicodynamics, the default we would use is 3 or 3.16.

This would in fact increase the overall intraspecies uncertainty factor to a total of 30 by default.

PANEL MEMBER BLANC: Thirty-one actually.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, no -- oh, yes, 31.6 if you -- but the trouble is, yeah, we keep getting beaten up if we quote more than one significant figure. So this is why there's this constant flip-flop between is it 3 or is it 3.16 and powers of 10 beyond that.

PANEL MEMBER BLANC: Well, except here you're multiplying it then again by 10. So it's not so trivial a question.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. The answer is in every case when we do the multiplication, we will use the true value of the square root of 10 and we'll then round to one significant figure.

PANEL MEMBER BLANC: Okay.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's the procedure as defined.

PANEL MEMBER BLANC: Okay.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And so what we're saying, these would be the defaults, which we would use unless we have evidence to show otherwise or the ability to conduct an actual

model that would include appropriate infants and children's parameters.

PANEL MEMBER BLANC: So if I understand you correctly, this is actually a major policy change.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. This is the bigger -- one of the bigger changes that we're proposing, definitely.

PANEL MEMBER BLANC: And this will put you quite a bit at a divergence from current EPA policy.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, of course it depends which piece of EPA you're talking about, in that by doing this we're actually halfway between what the air program is doing, which I think is essentially not much at this point, and what they're doing under the FQPA factor, which is putting in a whole factor of 10 in addition, which I'm not saying covers only this or with this sort of compound. But, you know, for the pesticide area they're potentially talking about needing an additional factor of 10 rather than 3. But that --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Also, I think it's fair to say that EPA has added additional uncertainty factors where they felt there was a need -- there was a data deficiency, and primarily where there was a data deficiency in developmental toxicity. So

they have done that on many occasions.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, that's -- well, I'm going to say a little bit more about that in a moment.

But it certainly -- it's not the case that EPA has ignored this problem. But they have in fact -- you know, they've taken assessment-specific choices to address it rather than at this point having a policy default.

But you're right. This is the -- probably the largest single change we're proposing and also the one which has attracted a lot of comment.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Melanie mentioned the data deficiency uncertainty factor. This is something which --

CHAIRPERSON FROINES: You say it's generating a lot of comment. Are we seeing those comments coming in, or what's the situation?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We're in the process of responding to those comments and, if appropriate, revising the document. So the next thing the Panel will see is a revised document plus the comments and our responses to those comments.

CHAIRPERSON FROINES: And that you think is?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: It would be certainly before the next meeting, which we're hoping is two months.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So U.S. EPA has used this concept of the data deficiency uncertainty factor in a variety of cases. And they've certainly used it in cases where they were concerned about impacts on infants and children. But one of the most important areas is not only postnatal but prenatal developmental toxicity.

We have not used this factor in previous OEHHA guidelines. But we now see it as a useful addition, especially to address concerns for children's health. And we feel that it would be useful to include this as a policy option where we have concerns about developmental impacts, including the kind of concerns about prenatal exposures and the difficulties that we have in dealing with, for instance, the kinetic uncertainties of fetal exposure, which Dr. Blanc pointed out to us just now.

So this is one way that we would perhaps want to build in additional uncertainty to address things that we can't necessarily model well.

And of course what we hope is that we would have actual toxicological data which would address this concern. But where we lack that data, we propose to use this data deficiency uncertainty factor similarly to the

way it's been used recently by U.S. EPA.

PANEL MEMBER BLANC: But I think what's getting confusing here is what you're -- what you've said previously is that the intraspecies factor could be as large as 30 if you have no data at all upon which to make any estimate of the toxicokinetic or toxicodynamic --

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

PANEL MEMBER BLANC: And now you're saying that in addition it might be three times greater, it might be 90 in the case in which you don't have data, but you've already said that the reason you'd have the value of 30 is because you don't have any data. So how much more data can't you have?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, the 30 reflects the situation where we're using 10 to address the uncertainty in kinetics. But we're still only using 3.16 to address the uncertainty in toxicodynamics. So this would come in, for instance, in a case where we've got toxicity studies in adult rats which identify a particular kind of endpoint, you know, say, respiratory irritation or something like that, but we don't have studies either in young humans or young animals, and we're concerned that there's a possibility of a different toxicodynamic result. You know, that would be

one case where --

PANEL MEMBER BLANC: But isn't that where the 3.1 comes from?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I think what this is trying to do to have a data deficiency uncertainty factor is make it for the fact where you really have huge data gaps and that you have a suspicion that this thing might be worse from a dynamic aspect in early life stages. Then you can have a higher uncertainty factor than just the -- higher cumulative uncertainty factor than just the 30X for intraspecies. You could add an additional database deficiency.

PANEL MEMBER BLANC: I understand what you're saying. I think I'm having difficulty understanding some examples that would help me pinpoint a scenario in which -- because you're basically having two classes of uncertainty. There's an uncertainty that I don't really care about and then there's an uncertainty that I'm really -- you know, I'm sort of uncertain and now I'm really, really, really uncertain or something like that. Because in the EPA versions since they don't have the tenfold, basically they could get up to 30, which is where you are as a sort of baseline, right? They could get up to the same value as you if they put in the threefold uncertainty factor.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: They could put in -- and actually they could if they chose to, put in an uncertainty factor of 10 as well, you know. These are all default values depending on the case. But, yes --

PANEL MEMBER BLANC: Well, I understand that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: If I -- can I --

CHAIRPERSON FROINES: What we don't understand is this factor of 3 -- UFD 3.

PANEL MEMBER HAMMOND: Is that for developmental specifically or is it for --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No, it's not exclusively for developmental. But we -- what we're saying here is that that is probably the most likely -- what we're saying is in general we would want the ability to apply an uncertainty factor to reflect concerns where we feel that there's something which is not covered by the available data. And if I can give you just an example of how this might play out.

Supposing for the sake of argument we have a solvent which causes respiratory irritation. We're trying to set a REL which is going to be applicable to not only adults but infants and children. We only have a study in animals, say, or in humans, for that matter, if -- say

it's a worker study, we have a study which tells us what is the critical exposure in an adult mortal exposure.

So we look at that. We apply a tenfold UFH-k because our study is in healthy adults. And we feel that we need that thirtyfold uncertainty to extrapolate the kinetic uncertainty to infants and children.

But then we also realize that this particular solvent has some central nervous system effects. Perhaps, you know, in adults those are happening at about the same level as all the other things we're looking at. So they won't necessarily, the critical effect even in the adult. But in any case, if we're looking at this neurotoxicity in the adult, it's going to be expressed by, you know, anesthesia, possibly nausea, and effects on color vision or something. But, anyway, some temporary reversible neurotoxicity, which we certainly wouldn't ignore.

But if we look at the neurotoxicity of quite a number of these things in infants and children, or at least in infant rats, and if we look at what happens in in utero exposure, we see that -- we're seeing things like irreversible changes in neurotransmitters, we're seeing persistent behavioral alterations in the exposed offspring and things like that. So that's actually a different and significantly more sensitive endpoint than the things that we're seeing in the adults.

So then what we're saying is in this particular compound, we've got the adult numbers, we've done all the usual things and we've got what we think is going to be a reasonable protective level based on those adult effects, but we suspect based on the nature of the toxicity and so on that there may be in this case, say, a neurodevelopmental effect to which the fetus or the infant in particular is going to be much more sensitive. And because we don't have any data about that at all, we're concerned about it.

And so we're proposing to use this UFD to add in an extra safety factor to provide an extra degree of protection against that possibility. That would be the kind of example that we'd be thinking of.

Does that make sense?

CHAIRPERSON FROINES: No.

PANEL MEMBER BLANC: Well, what I have to say is that I think it's -- in principle I think you should have a safety valve that would allow you to be more conservative in situations where you think the stakes are higher and by --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: That's really what this is.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's what it is.

PANEL MEMBER BLANC: -- and by analogy. But I think that for the sake of consistency and transparency and understandability down the road, so that when it comes to the point where there's a critical toxicant for which in fact it's because you chose a ninetyfold safety factor that it has sort of public policy -- potential public policy implication in terms of how many hot spots are exceeding -- likely to exceed your REL, you are going to have to have a better explication of your rationale.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, we would on -- yeah, in any specific chemical toxicity summary we go through why we've applied that.

PANEL MEMBER BLANC: I understand that. But I think in your master document you perhaps should think through how to tighten your description of the safety valve. And I do think that you're on firmer ground when you're talking about, you know, developmental issues. And I think that -- you know, Kathy mentioned earlier the sort of generic issue of CNS toxins and the presumed risk that develop in nervous system in that situation. And there could be some other examples. But I think I would go back, look at it carefully, and make sure that your generic argument is as clear-cut as it can be.

You know, in a way what you're actually saying is

that, not that it's a threefold uncertainty factor, but in fact you're substituting a factor of 10 for the toxicodynamics with a factor of 30.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER BLANC: That's really what you're saying. And that to me would make more sense as the argument.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: And, in fact, that's what we explain in a few of the sample RELs. There are a few where asthma was a concern. They're respiratory irritants. They're known to trigger asthma. Asthma's the worst disease in kids. So we added an additional uncertainty factor for that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: But I think the difference between increasing the value of the UFH-d as opposed to putting in this data deficiency factor -- no, the distinction as I see it is on the one case we're looking at a measured endpoint which is -- you know, for which we have some data, say, in adults but we suspect that the children will be more sensitive to that endpoint. Whereas, the purpose of the data deficiency uncertainty factor is to also address a consideration where we think we know something about the endpoint we see in adults. And we don't

necessarily have to be able to say that the children are going to be dramatically more sensitive to that endpoint. What the UFD here is addressing is the case where we suspect there may be another and different endpoint. That's the difference between increasing UFH-d and then the case where we would optionally where we had that concern.

PANEL MEMBER BLANC: Well, is that true for the four chemicals which in your previous table had the uncertainty factors greater than 10. Were those in fact uncertainty factors that came out to be greater than 10 because there was a different end organ?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No.

PANEL MEMBER BLANC: Or was the very same --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Those greater than 10 are purely the kinetic component. They're not about what we're discussing here at all.

CHAIRPERSON FROINES: Yeah, they would have to be greater than 30.

PANEL MEMBER BLANC: Oh, I'm sorry. You're right, greater than 3 to --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, but that table is about kinetics

only.

PANEL MEMBER BLANC: Right, right. I'm sorry.

I see. So --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It's conceivable that we would have, you know, a value of -- an overall value of UFH. The intraspecies factor could go as high as a hundred due to selection of larger factors than default or based on evidence or concerns.

CHAIRPERSON FROINES: I understand. But I'm very curious to see an example at some point, because I think that it's very vague at some level. But it's sort of rhetorical --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, I think the problem with this is this is not something that we're doing all the time. It's something which we are proposing as an option to be available in specific cases. And the specific -- you know, the justification for using it would necessarily have to be presented in the specific case where it would be applied.

PANEL MEMBER HAMMOND: But, you know, I think many of us understand what you're struggling -- you're struggling with something that we're also struggling with. But there is that sense of, first, the term "data deficiency," you

know, when Paul started out talking about, "Well, isn't that data deficiency you're talking about in the other factors?" And they are data deficiencies, right? I mean that's why you have the uncertainty factors for the K and the D.

And then it turns out sometimes it's the endpoint, we're looking at a particular endpoint where we know that the child is more sensitive. So that's a different kind of reasoning. And at some level you're saying there are many reasons that we might need to do that. And I think we agree, but I think that that probably needs be more carefully articulated.

CHAIRPERSON FROINES: Well, I think it needs to be carefully articulated because somebody who is in your opposition is going to focus on it. And it's going to have a -- it's going to have a potentially negative impact in terms of how OEHHA is seen in terms of uncertainty factors.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, I think there's a clear intention to only use this additional factor, you know, when we can provide a rational case-specific narrative to defend it, which would go someway to -- you know, to address --

PANEL MEMBER HAMMOND: You know, maybe -- in that case I would suggest maybe you in fact say that

explicitly, that there could be uncertainty factors for other cases that are carefully explicitly laid out. In which case you may not want to say that the default value is 3. You may actually want to pick up of the value that seems appropriate for the type of outcome you're talking about or whatever the reason is for that uncertainty factor.

So you might want to rather say there are many reasons -- there are other uncertainties that enter. Talk about some of those, talk about what you know about those, and say that if one were to introduce another uncertainty factor, you would have to have a strong case made in any particular case. So you might leave the door open that way. But I think leaving it open in this kind of there's going to be a defined default of 3 for multiple reasons that could be there, and it begins to seem like, "well, I just want to have this extra thing in my back pocket."

CHAIRPERSON FROINES: Andy, you know what I think would be useful -- and I'll take you at your word here. You say on the slide used by U.S. EPA for some time, more recently with clearer criteria. So that means to me that there are some examples.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, there are.

CHAIRPERSON FROINES: And it would be useful if

we saw one or two of those examples, because that gives the impression that it's not yet to come.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah.

PANEL MEMBER BYUS: And I do think in the written document, which is clear, you can sense this, your language has to be a lot more precise than you're saying right now. I mean incredibly more precise. And I mean if you want feedback, that's the feedback I'm going to give you.

So I mean I think all of this is well and good. I mean I think it's well intentioned. I agree with all the premises that you've laid out. I just think the language that you've presented today is soft. And if you write it that way, it's not going to carry water. So let's hope that the written document is much more carefully constructed and the language is very precise. And I agree with John, some examples -- and you tried to give us one off the top of your head, and I don't think that maybe you -- but an example or two or three as you're going along is also a good way to clarify the precision of what you're saying.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. The only thing I would say to that is, you know, we have to -- if you get overly precise, you paint

yourself in a corner. And it really --

PANEL MEMBER BYUS: But the language has to be clearer than what you're saying. Much clearer. You know, we're all university faculty. We live by these words, papers, manuscripts, whatever, teaching, lectures. Words are very, very precise. And I think -- as I said, I understand the premises here. I think they're all well and good. I think you're really -- this should definitely be done. And I tend to agree with you. But the language is what's bothering me.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

CHAIRPERSON FROINES: Well, in the long run it's going -- it seems to me to have -- you know, we're supposed to separate risk assessment from risk management. But if I had something -- if you came in to something and you said to me, "This chemical X has to have an uncertainty factor of 100," I would say maybe we should consider not using that chemical in California, because it's probably very, very toxic. And so it's -- the risk management issue is not trivial when you've got something that obviously has -- you felt compelled to come up with numbers like you're talking about.

Although we're talking about data deficiency, so it's not necessarily -- that's the contradiction, isn't

it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, maybe one of the things we can do is actually dig out what U.S. EPA currently says about this one, because they -- I say they have in fact been doing this for some time. And some of the things which I've attempted to lay out, obviously unsuccessfully here, are based on what they've actually been doing. So --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, we'll go back and look at the language.

PANEL MEMBER BLANC: But again if I understand the context of the EPA doing it, EPA is doing it in a situation where otherwise their default value would be 10.

CHAIRPERSON FROINES: Right.

PANEL MEMBER BLANC: And this uncertainty factor brings them only up to where you are at your default level. And this is part of what triggered my line of questioning. So when you do this new uncertainty factor of 3, it's going to take you from a default level, which is actually the maximum except in some extraordinary circumstance for the EPA, and you're going to be then three times higher than that. Right?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Possibly. It really -- it very much depends on how they've interpreted the data.

PANEL MEMBER BLANC: Right. So therefore your trigger for invoking the uncertainty factor of 3 would seem to me to require a kind or sort or degree of uncertainty which isn't exactly the EPA's degree of uncertainty, because the EPA is really just arguing that, well, 10's not good enough. But you're arguing that 30's not good enough for certain chemicals.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I don't think that EPA is using it as a response to the perception that 10 is not good enough. That's not what they're doing.

They're doing it in response to their perception of a specific area of data uncertainty where some desirable information is lacking, such as the suspicion that there may be a developmental endpoint which hasn't been examined or something like that. They're not using it as a "let's bounce up the number by a factor of 3 because we don't think it's stringent enough." And that's not how we would be using it either.

CHAIRPERSON FROINES: Let's go ahead.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. Well, this one's the same as before, so I'm going on.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The other thing we're proposing as a change is that the Haber's Law adjustment -- this is again something which we have been doing in the past. It's a way -- essentially when considering acute exposures, the general finding is that in fact concentration is more important than duration as a factor in determining the extent of result.

The concern is how do you extrapolate from the duration of an experimental acute tox study to the one-hour period of interest for an acute reference exposure level.

We've done this before. This so-called modified Haber's Law uses an exponent of N, which is a weighting of the concentration term. The default we used previously was 2. But we're now proposing to change this default to 3, which increases the weight of the concentration term relative to the time term. This is consistent with what U.S. EPA now does and also consistent with the more extensive data which are now available.

The value of N has in fact been determined for quite a number of these chemicals. So there's a known range of values of various specific chemicals. And where we had a measured value, obviously we'd use it. But we're talking about what's a good default here.

So that change of N from 2 to 3 is one difference from previous guidance. The other difference from previous guidance is that we're proposing not to use this adjustment at all for developing acute or eight-hour RELs based on sensory irritation. And the reason we're proposing this is that sensory irritation is basically a concentration-dependent response. We have looked at the time scale of the response for a few irritants for which there were data. And the general finding is that it plateaus after some exposure time, which varies from seconds to a few minutes. And it then in fact stays level for a period of up to several hours. There may be some -- actually some sensory adaptation at the end of the exposure -- longer exposures. But at least we don't see a continuing increase in response with time at all.

So what we're proposing for specifically the sensory irritation endpoint is not to use the Haber's Law approach at all but to base it purely on concentration.

I'd emphasize that this is for the sensory irritation endpoint only. It's not looking at endpoints which involve tissue damage, development of cellular changes, inflammation or anything like that.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So that's the extent of the differences

from the previous document.

The timetable for what's been going on and what's proposed here: This draft has been reviewed by the Air Resources Board and CAPCOA. The public comment period, as you've heard earlier, has taken place and has been extended until quite recently.

We're starting your review with this meeting. And we are obviously looking at a subsequent meeting when you will see not only responses to the public comments but also, as far as we can, initial responses to your comments today. And with a view to potentially winding this up some time in the middle of this year.

And we've also developed some new RELs which we're not going to be able to deal with today. But you'll hear about those in due course as examples of this process.

CHAIRPERSON FROINES: Is this list those new RELs that we're not hearing about today and that you want lead Panel members on?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That is right, yes.

CHAIRPERSON FROINES: And so that's -- would those RELs come up in mid-2008?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, they're -- you should have copies of them already in the materials that you received. So hopefully then at the next meeting we'll be able to get more into the meat of what we just presented as well as the actual chemicals.

CHAIRPERSON FROINES: So, Melanie, when do you intend to bring the cancer methodology to us?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: It's about to undergo internal ARB review. Then next month in April we'll start a public comment period. We'll have to do at least 60 days. Then we respond to comments and then we send it to the Panel. So it sounds like to me fall for you guys to be looking at that

CHAIRPERSON FROINES: So when we talk about lead persons, we don't need to actually -- do we need to assign somebody, person or persons, for that now or should we just deal with this?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: That would be great if you can assign people for the cancer document now.

CHAIRPERSON FROINES: Now.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, that would be good.

PANEL MEMBER BYUS: The non-cancer document? Or

is it cancer --

CHAIRPERSON FROINES: No, the cancer document.

PANEL MEMBER BYUS: I'm confused.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: John's talking about the next document.

PANEL MEMBER BYUS: Oh, I'm sorry.

CHAIRPERSON FROINES: The next document that's coming down the road.

PANEL MEMBER HAMMOND: But we haven't assigned these -- for these yet.

CHAIRPERSON FROINES: I know.

PANEL MEMBER HAMMOND: But the non-cancer document.

CHAIRPERSON FROINES: I'm trying to look at the whole panoply of work.

PANEL MEMBER BYUS: John's way ahead of us, as usual.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: So I should say, because the other Panel members may not know, but Stan Glantz was the lead on this current non-cancer REL document.

PANEL MEMBER HAMMOND: Oh, we did have a lead.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes. And so we worked a little bit with him already. But he -- typically for the individual chemicals

we've had additional leads.

CHAIRPERSON FROINES: Well, doesn't it make sense to assign Stan, since he's not here --

(Laughter.)

PANEL MEMBER BYUS: Yeah, I like that.

CHAIRPERSON FROINES: -- for the cancer document and assign Joe, since he's theoretically an oncologist, for the cancer document? And then 1, 2, 3, 4, 5, 6 -- there are six here, so everybody should take one.

PANEL MEMBER BLANC: Which one -- I would like to do manganese myself.

PANEL MEMBER HAMMOND: I'd like to do manganese.

CHAIRPERSON FROINES: I knew you'd like -- wait.

PANEL MEMBER PLOPPER: You know, and I'll take the formaldehyde.

CHAIRPERSON FROINES: Charles is formaldehyde. Paul is manganese.

PANEL MEMBER FRIEDMAN: Which one has the most epidemiologic data? That's the one I would like to take.

CHAIRPERSON FROINES: Well, certainly arsenic.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Arsenic.

PANEL MEMBER FRIEDMAN: How about if I take that then?

CHAIRPERSON FROINES: Arsenic is more -- has

enormous amount of -- and so that leaves acetaldehyde, acrolein, and mercury. And we're missing --

PANEL MEMBER FRIEDMAN: I'll do one, whichever one you want.

CHAIRPERSON FROINES: Pick one.

PANEL MEMBER BYUS: And I'll do acrolein, unless you want it.

CHAIRPERSON FROINES: I'd rather do acrolein than mercury. How about taking mercury?

PANEL MEMBER BYUS: You want me to take mercury?

CHAIRPERSON FROINES: Uh-huh.

PANEL MEMBER BYUS: All right. I'll take mercury.

CHAIRPERSON FROINES: And I'll take acetaldehyde since I'm the air pollution guy here.

PANEL MEMBER BLANC: You're taking two.

CHAIRPERSON FROINES: Oh, wait. Kathy. What did I almost do?

So you're acrolein or acetaldehyde.

PANEL MEMBER HAMMOND: You take which one you want. I'll take the other one.

CHAIRPERSON FROINES: No, no. You take what you want.

(Laughter.)

PANEL MEMBER HAMMOND: I said manganese.

CHAIRPERSON FROINES: Yeah, but he's got a thing about manganese.

PANEL MEMBER HAMMOND: I do -- research on that.

CHAIRPERSON FROINES: Oh. Well, what do you want to do? Do you want --

PANEL MEMBER HAMMOND: I'll do -- which one did you want to take?

CHAIRPERSON FROINES: Well, I don't care what I do.

PANEL MEMBER BLANC: Who's doing formaldehyde? Did I miss that?

CHAIRPERSON FROINES: Charles.

PANEL MEMBER BYUS: Which ones have the biggest changes in the RELs?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Acrolein is one of the bigger ones actually.

PANEL MEMBER FRIEDMAN: Are the documents the ones that are in this book that you'd like us to review?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, they are.

CHAIRPERSON FROINES: And I'm acetaldehyde.

So you realize that the acrolein one you have to do EGFR activation, you know, for the endpoint. You don't get to use these old fashioned endpoints. You have to do

PTP1B inactivation.

PANEL MEMBER HAMMOND: Maybe you should pick the lead on that.

PANEL MEMBER BLANC: Let me just -- coming back to the topic that we beat to death about uncertainty. Let's just take for a moment arsine, which is a subset of arsenic, which causes hemolysis. And neonates deal very poorly with hyperbilirubinemia. So that's something you took into account in some kind of uncertainty factor?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Actually the way the arsine data worked, we looked at the hemolysis data and we also looked at a number of endpoints including data from the epidemiology. And that covered -- the other endpoints were all very considerably more sensitive than the hemolysis data that we had. So hemolysis -- so what we basically said was that we needed to use the all-arsenic endpoints for arsine rather than looking at hemolysis as the critical endpoint for arsine.

PANEL MEMBER BLANC: For acute effects?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah.

PANEL MEMBER BLANC: That seems biologically implausible to --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Well, that was -- I'll have a look and see -- you know, I don't think we --

PANEL MEMBER BLANC: I don't want to dwell on it now. I just pick as --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. But the answer is we considered a range of endpoints definitely.

PANEL MEMBER HAMMOND: May I ask, are you expecting the REL documents to change as you do the changes for the overall approach document?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We have not got -- well, we've not got anything in line at this point. There might be some corrections or -- the other thing is we might, I suppose, need to consult with the leads if we identify a problem through the public comments.

PANEL MEMBER HAMMOND: So you've received -- and that's what this is. You've received public comments on all of these?

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

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER HAMMOND: So there may be changes in these documents?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It' conceivable, yes.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: Well, these are interesting compounds.

PANEL MEMBER BLANC: These are the ones that made it on to that top list, right? Isn't that where we're going back to?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, all except acetaldehyde are somewhere in the first or second tier of the SB 25 prioritization. So that's certainly, you know, one key reason why these were selected. The other was -- there was a degree of, we selected ones which we felt exemplified principles or problems that we wanted to exercise the new guidelines with.

PANEL MEMBER BLANC: Okay.

PANEL MEMBER HAMMOND: Are the guidelines likely to change in any way that would lead to changes in the RELs?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, that may be up to you.

(Laughter.)

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah, that -- yeah, we would have to be iterative, because if the -- if you guys want changes to the guidelines or somebody brings up some important points in the public comment period that result in a change, then we would have to see how that reflects on the individual reference exposure levels. It may or may not, depending on what the change is.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, but clearly --

PANEL MEMBER HAMMOND: Now, the public comment period closed four weeks ago though?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER HAMMOND: So you had a chance to at least look at them?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We've had a chance to look at them.

PANEL MEMBER HAMMOND: You don't have a sense yet then how much they might change?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: I'd have to say, no, we don't have a sense.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No.

CHAIRPERSON FROINES: You don't have the what?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: We don't have a sense of how it's going to impact the RELs at this point.

CHAIRPERSON FROINES: When would you like -- Peter just gave me a note essentially asking when the next meeting should be. And it should be I think based on when you're going to be comfortable having completed everything.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: End of April would be great, or early May, avoiding certain weeks that are bad.

CHAIRPERSON FROINES: And according to Peter, for reasons I don't know, he said Bay Area.

PANEL MEMBER BLANC: Well, we were in Orange County.

PANEL MEMBER HAMMOND: Southern California.

PANEL MEMBER BLANC: I guess it would be fair to have it in the Bay Area.

CHAIRPERSON FROINES: And do we have a place in San Francisco?

MR. MATHEWS: Not yet. I'm working on it.

CHAIRPERSON FROINES: So we'll plan the first two weeks in May. And Peter can poll people. And we'll plan to have it in San Francisco or Oakland.

You know, Stan's not here, so -- stan always complains about Oakland meetings.

PANEL MEMBER BLANC: What about Stanford? Do you have any facilities?

PANEL MEMBER FRIEDMAN: I'm, you know, a consulting professor. I don't have a lot of clout there in terms of --

PANEL MEMBER BLANC: But you have that nice conference room.

MR. MATHEWS: I'll try it again.

PANEL MEMBER FRIEDMAN: Yeah. And you have to deal with the administration, not with me.

MR. MATHEWS: Well, I've dealt with them on --

PANEL MEMBER BLANC: I mean it's just as close for you from the airport.

CHAIRPERSON FROINES: Doesn't matter to me.

MR. MATHEWS: I'll give it a try.

CHAIRPERSON FROINES: So thank you, Andy. That was -- this is going to be an interesting process.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: A long, strange trip perhaps.

CHAIRPERSON FROINES: That's one of those statements that says that everything's not quite perfect but we're heading towards that.

PANEL MEMBER BLANC: Well, I'd like to make a motion that we adjourn.

CHAIRPERSON FROINES: Yes.

PANEL MEMBER BYUS: Second.

PANEL MEMBER FRIEDMAN: May I ask a question?

Are we expected then to have reviewed and given our feedback to the OEHHA with regard to these six chemicals by then? Is that the plan or what?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: Yes. But also the next meeting we will be discussing the amongst the Panel are our views of the document. So it's not one of those where we walk in and vote, because we've had no -- we've had limited discussion. And if there's no discussion, then we'll just vote. But otherwise we'll have a --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We'll have to present public comments as well.

PANEL MEMBER HAMMOND: My impression here though is that these chemicals were chosen because they helped to illustrate some of the issues and the challenges that lead to the developing of the new document.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Partially and --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: That's one of the factors, yes.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF

MARTY: Partially because they were prioritized high when we looked at children's health issues.

PANEL MEMBER HAMMOND: But they particularly bring us -- we get to confront some of the children issues by looking at these materials. So I do think this question of its being an iterative process might -- that sounds pretty likely. And I think that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, absolutely.

PANEL MEMBER HAMMOND: -- how much we come to conclusion by the next meeting with either the RELs or the document is less clear to me, and that may take some time.

CHAIRPERSON FROINES: Melanie, I had a question for you that is not meant as a criticism.

But when you talked about OEHHA's priorities for chemicals that will come up in the future, maybe TACs or whatever, you spent most of your time talking about what's going on in Canada, if I remember correctly. But you didn't -- you did not give very much in the way of specific chemicals that you think would be appropriate. When we have that meeting, can you give us some ideas of where you are on that question?

Am I asking a difficult question?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, that's a difficult question. I mean I think,

you know, that we have our ideas of some chemicals that we think are petty important and that should be looked at. But, you know, it has to be integrated with ARB's process of prioritization. So, you know, they have their candidate list of TACs and the information that goes into their prioritization process.

CHAIRPERSON FROINES: I don't know if I agree with that. I would argue something different. I would argue that you as scientists have views of what's important. That has nothing to do with ARB's prioritization process. If I talk about quinones, that's because I'm a scientist who deals with quinones. And it doesn't have anything to do with ARB. In fact, having some fresh ideas outside their prioritization process may be useful. They're not going to come up with ultrafines, I guaranty it. I might.

And so the point is, why do we need to -- my notion of putting this workshop together was to get ideas -- to get scientific ideas, not necessarily government. And then we have to figure out how the science relates to the prioritization process. It seems to me that that's a process that we have to talk about.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, you know, we have --

CHAIRPERSON FROINES: Tobi's going to have

compounds and so am I and so is Roger or Roger's replacement.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH CHIEF MARTY: We have a lot of ideas that we want to move forward on. We don't have a lot of time or bodies. But, you know, one is to look at what Canada did and how they prioritized, and whether any of those chemicals would be expected to be in the air. And the other is to look at some of the work we've already done with atmospheric transformation of emissions from tailpipes, run those through SAR -- existing SAR models and see what little flags pop up on some of those. We have not had the time to do that yet.

So I don't know that we could do that between now and May. But we can come up with additional ideas.

CHAIRPERSON FROINES: Well, we see you as, you know, in general, as the lead agency on risk assessment. And so getting some substantive ideas would be valuable. And the timing doesn't have to be May, but it would be useful. But also your thought process about approach.

PANEL MEMBER BLANC: Can we call the question?

There's a motion on the floor.

CHAIRPERSON FROINES: Well, are we finished -- are there any other issues that we should talk -- we should raise with OEHHA while we're here?

Anybody?

Okay. All in favor?

(Ayes.)

CHAIRPERSON FROINES: We're adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 1:06 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, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 10th day of March, 2008.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063