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STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
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1001 I STREET
SACRAMENTO, CALIFORNIA

UNIVERSITY OF CALIFORNIA, LOS ANGELES
SCHOOL OF PUBLIC HEALTH
CENTER FOR HEALTH SCIENCES, ROOM 46-060
650 CHARLES E. YOUNG DRIVE, SOUTH
LOS ANGELES, CALIFORNIA 90095

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DEPARTMENT OF MOLECULAR BIOSCIENCES
EVERSON HALL, ROOM 220
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SCHOOL OF PUBLIC HEALTH
2199 ADDISON STREET
BERKELEY, CALIFORNIA 94720

TUESDAY, APRIL 2, 2013

3:06 P.M.

JAMES F. PETERS, CSR, RPR
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A P P E A R A N C E S

PANEL MEMBERS:

John R. Froines, Ph.D., Chairperson

Jesús A. Araujo, M.D., Ph.D.

Paul D. Blanc, M.D.

Alan R. Buckpitt, Ph.D.

Stanton A. Glantz, Ph.D

S. Kathryn Hammond, Ph.D.

Bill Nazaroff, Ph.D.

Beate Ritz, M.D., Ph.D.

REPRESENTING THE CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY:

Dr. Gina Solomon, Deputy Secretary, Science and Health

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, Scientific Review Panel

Mr. Peter Mathews, SRP Support Administration

Dr. Linda Smith, Chief, Health and Exposure Assessment Branch

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Joe Brown, Staff Toxicologist

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

Dr. Melanie Marty, Acting Chief, Reproductive and Cancer Hazard Assessment Branch

A P P E A R A N C E S C O N T I N U E D

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. David Siegel, Chief, Air, Community and Environmental Research Branch

I N D E X

P R O C E E D I N G S

CHAIRPERSON FROINES: All right. So I'm going to open the meeting on -- which is July -- April 2nd, Tuesday at 3:00 p.m. of the Scientific Review Panel, and we should proceed with the roll call. Go ahead, Peter

MR. MATHEWS: UCLA, please.

PANEL MEMBER RITZ: Beate Ritz.

PANEL MEMBER ARAUJO: Jesús Araujo.

CHAIRPERSON FROINES: John Froines.

MR. MATHEWS: UC Berkeley?

PANEL MEMBER NAZAROFF: Bill Nazaroff.

PANEL MEMBER HAMMOND: Kathy Hammond.

MR. MATHEWS: UC Davis?

PANEL MEMBER BUCKPITT: Alan Buckpitt.

MR. MATHEWS: UCSF.

PANEL MEMBER BLANC: Paul Blanc.

PANEL MEMBER GLANTZ: Stan Glantz.

MR. MATHEWS: John, do you want to identify who's at the Air Resources Board for the record?

CHAIRPERSON FROINES: Yes.

DR. SIEGEL: David Siegel.

PANEL LIAISON BEHRMANN: Jim Behrmann.

DR. SMITH: Linda Smith.

DR. MARTY: Melanie Marty.

THE COURT REPORTER: Jim Peters, the court

reporter.

MR. MATHEWS: Peter Mathews.

CHAIRPERSON FROINES: Okay. We can proceed. And who is going to be the lead for OEHHA in terms of the presentation?

DR. SIEGEL: Okay. Dr. Froines, I'll be introducing the lead. My name is David Siegel, and I'll be introducing Dr. Joe Brown.

(Thereupon an overhead presentation was Presented as follows.)

CHAIRPERSON FROINES: Okay. Go ahead.

DR. SIEGEL: Well, good afternoon, Mr. Chairman and Panel Members. My name is David Siegel, and I'm the Chief of the Air, Community, and Environmental Research Branch of the Office of the Environmental Health Hazard Assessment. Last September, we sent our public review draft on the document of 1,3-butadiene reference exposure levels for acute, 8-hour, and chronic exposures to the SRP. And at the SRP meeting in October, you provided us with comments and suggestions on the document.

At the beginning of March, we sent you our revised draft document, with changes based on your comments and suggestions. Today, Dr. Joe Brown, the author, will present you the changes we have made to the document.

Joe.

DR. BROWN: Yes. There's a PowerPoint presentation. Can I ask if everybody has access to this?

PANEL MEMBER RITZ: I'm trying to find it in my thousands of emails. Can somebody tell me --

DR. BROWN: The first slide has 1,3-butadiene reference exposure levels draft on it.

PANEL MEMBER GLANTZ: The email was sent from Andy Salmon.

DR. BROWN: It would really help if you could find this and sort of follow along as I go through them.

PANEL MEMBER BUCKPITT: This is Alan Buckpitt. I have it.

CHAIRPERSON FROINES: Okay. Beate is going to sit next to Jesús and look over his shoulder at his screen.

We can proceed.

DR. BROWN: Well, let's go to the next slide then, which this gives the overall summary and these are the same values we had the last time. In other words, the revisions didn't involve any numerical changes in the values we were proposing.

The acute REL of 0.66 mg/m^3, the 8-hour REL of 28 $\mu g/m^3$, and a chronic REL of 7 $\mu g/m^3$.

Now, we have added some additional supporting

analysis for the chronic REL, and more explanatory material throughout the text, but the basic values have not changed.

Next slide, please.

Okay. This slide -- the top of it has MATES III if you're following along.

This table was requested to be a companion to the table we had on ambient values in the Bay Area. This particular table from the MATES III analysis is southern California values. And on the whole, they're about twice the values we see in the Bay Area. I think there was some concern that they might be a lot higher than that. But if you look at the values across the Board, they seem to be about twice as high.

We also added some material on photo chemistry, an expanded discussion of that. More I added on the environmental tobacco smoke, a study on Finnish restaurants. A wood burning study from Sweden also added discussion about that.

Next slide.

CHAIRPERSON FROINES: Can I interrupt?

DR. BROWN: Go ahead.

CHAIRPERSON FROINES: I just wanted to make a comment which is that there are a large number of PowerPoint slides and some detail, and I wanted to make

sure that the Panel is comfortable that we prefer not asking -- breaking into your presentation to ask questions, but if there are questions that will help clarify what's on this PowerPoint slides, they should feel free to ask them.

DR. BROWN: At this point, I'm just sort of listing some of the major changes, which generally, if you have a hard copy, these are all values that are -- are all things that are underlined in the text as being revisions. So you could sort of follow that.

If you think it would help, I might be able to give some page numbers, but sometimes that does not work.

Anyway, going on, we've added additional studies on indoor air, Logue et al. And this 2006 study by Marshall is based on about 20,000 commuters in the South Coast Air Basin. And he estimates that intakes are about eight percent of the chronic REL that we're proposing. So I think, based on that, there seems to be an adequate margin of safety for the values that we have.

We've added material on comparative butadiene metabolism from Bond et al. and also on adducts as biomarkers, Sangaraju et al. 2012.

Next slide.

We added the Khalil et al. 2007 a study on neurotoxicity, which was interesting, but we didn't find

it adequate for risk assessment.

We tried to clarify the --

CHAIRPERSON FROINES: I should comment that --

DR. BROWN: Go ahead.

CHAIRPERSON FROINES: -- I thought that that study was important from the standpoint of identifying neurotoxicity as an endpoint, and that there was evidence of acute and chronic effects.

DR. BROWN: Yes. And the authors identified it as -- butadiene as a neurotoxicant based on that study. So I think that is important, but I think for dose response assessment you need more information.

PANEL MEMBER BLANC: Well, maybe we can come back to that when we discuss the slides.

DR. BROWN: I try to clarify the acute toxicity dose response, and I hope that's done successful, but I want to know after you read it.

I added material on cardiovascular, because this was a specific request. I looked at the Penn and Snyder 2007 and went back and looked at the Matanoski occupational epidemiology information. And while there's data suggesting an effect here, it's not really adequate for dose responsiveness. There is some interesting information on Avian model, which is mentioned in the -- by Penn and Snyder as well.

Next.

Now, I've added a section, sort of a speculative specs, on mode of action. And this basically depends on sort of adduct formation on cellular protein, DNA adduct formation and oxidative stress. Now, this is largely speculative, but, you know, I think -- I don't think we're going to get a lot of arguments about that, but it's at least some idea of what might be going on here.

I tried to add more information of dosimetric adjustment factor how that value that we used was derived basically from pharmacokinetic modeling.

And I've added an Appendix A, an additional description, of why we even mentioned mutagenicity in genetox, it's because we think that mutagenicity is not only involved in cancer, but could also be involved in degenerative diseases.

Next slide.

I'v added another table in the appendix on the acute of the BMCL analysis on both the Hackett et al. and the Green et al. 2003 data sets. This is for both the total male and female, and also the male only. And I did this because it was requested that we have more information on that.

There is a difference of 30 percent in the 95 percent lower bounds. And we think that's well within the

ranges of our experience with this type of analysis. We also had the Green 2003 study reviewed by our staff biostatistician and it was judged in analysis by his review. So we think that study is okay to use.

Next slide.

Overall, we reviewed 65 references and added 32 in the paper. So we -- you know, we fleshed it out, added more references. It's heavier now. We hope it has more light on it at least.

You'll remember that right before the last meeting we were presented with a paper by Kirman and Grant on a meta-analysis. And so, you know, we've reviewed this paper. Toward the end of the document, there's about four paragraphs. I think -- I don't know exactly what page they're on, but they're sort of toward the end of the text right before the references.

The first two paragraphs basically are our interpretation of what the study -- what was done, in other words, what they seem to have found.

And the next paragraph sort of is, you know, what we think is wrong with it. Why we couldn't take the data or the conclusions of that paper and use them directly in our assessment. And that is basically because their assessment essentially assumes site concordance, in other words, what's happening in the mouse is happening in the

human.

And our basic philosophy of risk assessment is that we take the most sensitive effects that we can find in an animal study and we apply uncertainty factors for that, which we think are appropriate, and we assume, or we believe, that that will provide an adequate margin of safety for any effect in humans, including children.

So our analysis does not depend upon site concordance. And we think that their analysis, or their approach, does. And that's not to say that the methods they've used are wrong. In fact, we've actually applied one of their methods to our data sets to see what the difference would be.

Next slide, please.

I should say the last paragraph that's our answering the question what if we took their method and applied it to our data sets.

So basically, in order to compare their results with ours, we used their time-weighted average internal dose, which was based on an algorithm, which derived an average concentration of the diepoxybutane generated by butadiene exposure. And we conducted a multi-stage Weibull non-fatal analysis. This was a -- instead of a time to tumor, it was a time to effect analysis.

We did this using the new EPA software, which was

not used at all. We had to get some help from someone John Fox at the U.S. EPA. Thank you very much, John. And we chose to apply this to the same data set we used in our chronic analysis.

In that analysis, we applied it to all three time points the 9-, 15- and 24-month data. Here, we're applying it only to 24-month data, which is a small number of animals, 325. So here, we're using individual animal data for dose, time of death, the incident, which is they were found to have effects of ovarian atrophy and censored -- they were found not to have outside -- and the number of animals dying at that particular time.

And we obtained a value or 0.5 parts per million BD equivalent. This value is very close to the one part per million value we obtained in our time-weighted analysis. So we don't think it's really significantly different. It's basically supporting the effect we got. We have a larger number of animals.

Next slide, please.

PANEL MEMBER BLANC: Wait. I know we weren't going to go by pages, but there's a -- is what you're saying related to --

DR. SIEGEL: Could you please identify yourself for the court reporter.

PANEL MEMBER BLANC: Paul Blanc. Is what you're

saying related to Table 7 in the revision, page 41?

DR. BROWN: Yes, that's for -- that's Table 7.

PANEL MEMBER BLANC: Paul Blanc again. So the units in Table 7 are what?

DR. BROWN: Well, the units in the analysis are average the concentration of diepoxybutane generated from an algorithm. The algorithm is based on binding of diepoxybutane to form specific -- DEB-specific adducts of hemoglobin.

So if you look at their paper, and actually it's described somewhat in the text in my description of it, they use the algorithm to calculate the average concentration. They said they could not us a pharmacokinetic model, so they used this algorithm instead. So I took their values and ran the analysis on our data sets using their values --

PANEL MEMBER BLANC: Right.

DR. BROWN: -- to try compare, you know, what we would get if we applied their method to our data set.

PANEL MEMBER BLANC: So rather than concentrations, these are times?

DR. BROWN: Well, time is taken into effect. It's both dose and time. A multi-stage Weibull analysis. If you look at the footnote, it gives the equation for the response, the probability of response.

PANEL MEMBER BLANC: And that's why you have 0.5 ppm as your lower concentration ppm. That's dose equivalent.

DR. BROWN: For all of these you have to workout what the external BD equivalent is, whether there's a dose response curve or a standard curve to try to get -- to go from the internal to the external.

In doing all that, we get a value that's very close in value if we did it by a different analysis. It doesn't involve individual animals. They use quantal data of aggregate data for each dose.

PANEL MEMBER BLANC: Right. And you're --

DR. BROWN: In other words 50 out of 70.

PANEL MEMBER BLANC: And that value is one part per million.

DR. BROWN: Yes.

PANEL MEMBER BLANC: So were you to use half a part per million -- just -- I want to make sure I understand -- which is half as much, then would your reference level be 1.5 parts per billion instead of 3?

DR. BROWN: Yes. In fact, I'll get to that in a minute, in the next slide. You're getting ahead of us here.

PANEL MEMBER BLANC: All right.

DR. BROWN: So basically this particular analysis

is based on 325 animals not 435. The original analysis, which is based on the applied dose, not the internal dose, right, gave us a value of 3, and its companion value of 4.8, which I'll also get to.

Go to the next slide.

MS. MATHEWS: Joe, can you speak up? The court reporter is having more difficulty hearing you.

DR. BROWN: Okay. Sorry.

MR. MATHEWS: Stat near the mic, please.

DR. BROWN: The mic is right in front of me.

MR. MATHEWS: Okay. Thank you.

DR. BROWN: Now, in addition to that, that's taking their metric, you know, applying their methodology and our data set.

Now, the next thing I did was I wanted to see if their assumption that they could not use a pharmacokinetic analysis was correct. You know we have a pharmacokinetic model that we use in other parts of the analysis.

So we went back and we said, well, what if we took the same type of metric, the average concentration of the DEB metabolite in the mouse model, PBK model, and used that? And so we went back and did that. And that's shown on this slide here.

This again is for the 24-month data. We're using an average -- we took the average -- the area under the

curve or 24-hour simulation, divide it by 24 to get the average concentration, and we used that in a dose only. So this has no time adjustment at all. And this gave a very good fit to the log-logistic model, in fact, a dose response.

Now, because of averaging, this gives a higher overall value for the cREL of 8.5, so there's no time adjustment here.

Next slide, please.

This shows the dose response. And you should be seeing a graph here with a log-logistic on the top. This is the dose response for five doses plus the control with the pharmacokinetic internal dosimetric of the DEB concentration. So that's a really extent dose response. It's one of the nicest ones I've ever seen for so many doses. In fact, Andy, you saw thought this was really good.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I was quite impressed by that. This is Andy Salmon here.

DR. BROWN: Okay. Next slide, please.

Now, to try to bring everything together, we have four different estimates. The top two are essentially similar, slightly different models. Specifically, there's not much to choose between them. We took the lower of

these two. These are based on applied dose, 435 animals, probit analysis of aggregate data. Note it is time-weighted, not individual animals.

The middle one, the MSW, is the analysis using the Kirman and Grant approach. This has fewer animals, 325. It has this algorithm derived metric, and it gives the lowest value 1.5 parts per billion. And then the final is the dose only analysis, 325 animals, using a PBPK metric and it gives the highest value of 8.5, but no time adjustment.

The geometric mean of those four values is 3.7, which is not really different from our analysis that's done.

So on the top we have applied dose, on the bottom two we have, you know, dosimetric based on some sort of modeling. And overall, we think we get a pretty good agreement between all of the values.

So we still think that the three part per billion is the best overall value. It's not the lowest, it's not the highest. It's in the middle somewhere, but we think it uses the most animals. It doesn't have the uncertainty of the algorithm or the pharmacokinetic modeling. So we'd like to stick with that as our best estimate.

So that's what I planned to give. Now, I do have more slides, which you may not want to get into. The

degree of fit business on the Multistage Weibull is a very complicated business. I have separate sides on that if you want to get into that. You probably don't. But if you do, we spent a lot of time on it. It has a separate program which you have to get through to get it.

We got, what we think is, excellent sets, we think, of the Multistage Weibull model. We can't get a regular chi-square on it like the other analyses. What we did get, a series of graphs, seems to indicate it fits pretty good.

So I have those if you want to look at them, but its okay if you don't. That's all. That was the end of my planned presentation. As I said, I do have some additional slides, if you want to go through them, but it's not necessary for the --

PANEL MEMBER BLANC: Paul Blanc here. How many slides on the model do you have?

DR. BROWN: Six or eight.

PANEL MEMBER BLANC: Why don't you do them quickly, so that we can say that we've --

DR. BROWN: Let's do the first one.

This basically sets it up it. It says while there's no chi-square with a statistic -- you know this Multistage Weibull time. You know, with the new EPA software, there is this list of -- or this group of plots.

And there are basically four plots. There's the dose response plot, DR, a probability time plot, quantile quantile, and probability probability plots.

So you're looking at different things in different points. Let's look at the first one.

This is the probability dose plot. And what you're looking at here is the solid line is --

PANEL MEMBER BUCKPITT: Joe, I'm sorry to interrupt, but you need to orient this to where you are in the slides, because we need some coordinates that are more than just this slide.

PANEL MEMBER ARAUJO: The number of the slide, perhaps.

PANEL MEMBER GLANTZ: It's got a graph on it. And type BMD for Incident Risk at T equals 737.

DR. BROWN: It's a graph with a square in the upper left-hand corner.

PANEL MEMBER HAMMOND: And this is the graph that follows Goodness of Fit Plots, right?

DR. BROWN: It's the probably of incidental risk at T equals 737, which is days, which is the end of the study, and dose, which is in parts per million, butadiene.

And so the solid line is the Multistage Weibull prediction. And the points are a non-parametric analysis. And the goodness of fit is estimated to about how close

the non-parametric points are to the parametric points, which is a period. And so overall they say this is the most important of the various plots that they give, and part of this is a little bit.

Next slide.

Okay, this is the -- in the probability versus time plots, there's a plot for each dose. And so we've got six doses here, so there's six little plots. And in this series of plots, the line is the Multistage Weibull, and the dots are the non-parametric estimate. Again, how close the dots come to the line is an indication of the degree of fit.

So there's a separate one for each particular dose, and the doses are in animals -- it's animal average concentration of DEB.

Next slide.

That just gives the last two doses of the probability versus time.

Next is the time versus time. Now, this is a little bit different. Here is the Multistage Weibull versus non-parametric. And the line is just a line of equality between the two. So how close the points come to the line here is a measure of how good the fit is. You can see it's not very good. It's at about a zero dose. But if you go up in dose sort of go toward the line.

Next slide.

And the top two doses.

And finally, this is the probability probability curve, multi-stage Weibull versus non-parametric analysis, the same sort of idea. The line is the line of equality in the middle. And again, it's how close the points come to the line.

So that's it. Those are -- this is run on a separate program. It's called Goodness of Fit Plot. It's, you know, a command line thing, which is the open source system that we use.

But it's not that easy to use, but, you know, we've managed to get it to work. It's in there. It's not in the document. It's too, you know, complicated. But I wanted to at least present it to you, so you could see that, you know, we do have what we think is a good fit for all of these data sets. So that's the end of the presentation. We can go back and chew over particular slides if you like or --

PANEL MEMBER BLANC: So Paul Blanc here. John?

CHAIRPERSON FROINES: Yes.

PANEL MEMBER BLANC: What are you looking for from today's discussion. Often when we're this far along with the document, we anticipate ending the discussion with a motion for approval with the caveat that there be

certain specified items that are cleaned up, assuming that there are not -- it's not too big a laundry list. Is that what your anticipation and expectation is?

CHAIRPERSON FROINES: Yes. I think that you stated very correctly. So I would say, at this point, the first thing we might ask is are -- do people have particular questions before we go to the leads and then the Panel?

PANEL MEMBER BLANC: That was my only question on process.

CHAIRPERSON FROINES: Are there other questions associated with the actual presentation that people want to raise at this point?

I'm hearing no sound, so I'm assuming that there are no questions. So I think that we should now turn it over, people willing, to the leads on the Committee.

PANEL MEMBER BLANC: Who are the leads?

CHAIRPERSON FROINES: Jesús and Alan. So Jesús, why don't you kick it off.

PANEL MEMBER ARAUJO: Sure. Yes. Overall, I think that this is a very improved version of the previous draft. And it is -- this version includes some elements that the previous one didn't have and proven some others that requires some additional work. For example, there is a better description of the butadiene as an indoor agent,

and also as a component of the environmental tobacco smoking. There is improvement in the description of the -- some of the metabolites and originates from the butadiene the biomarkers of effect.

There is incorporation also of some status in that looking to the cardiovascular toxicity and the neurotoxicity.

Overall, I think that, as I said, that there is a very important improvement of the draft. I have some -- a list of smaller points that I will mention like section by section. So in the first section, the summary, I don't really have anything to highlight.

On the second version -- on the second point which is the physical and chemical properties, so the only thing that I would add is that just like in the parameters that are mentioned like the solubility. It says it's very slightly soluble in water, 735 milligrams per liter. I just -- I believe that this coefficient or this solubility is at 20 degrees. So if that is the case, so please add it.

On the third section of the occurrence and exposure, it is an important addition on the sources of exposure for the butadiene. And, however, I do have a point on the first paragraph, where it is mentioned and towards the middle section of the paragraph that the,

"Butadiene is a component of the gasoline, as well as a product of the combustion of minor gasoline components, olefins, and cyclohexane". And then there is a description about how it is contributed from the different industries and motor vehicles.

It just gives the impression as if it is exclusively coming from gasoline. There is no mention about the diesel. And butadiene also comes from the combustion of the diesel. So I think it pretty much got all the combustion of all the motor vehicles fuels and wood generated.

The second is that there is only a small component or small proportion of the butadiene in the fuels, per se. It really concentrates at the combustion of the fuels, which is probably not stated. I mean, the very large amount of the butadiene that is released is again from the combustion of this fuels.

In the 4th section on the metabolism, I also think that there is an important improvement. However, from this and towards the end of the draft and probably even towards the section that talks about the mode of action. There is -- there are some points that may make the presentation of the data and the different things that I reviewed somewhat confusing.

And even though it is not clearly stated in any

point in the draft that all the toxicity is given by the auxiliary products or by the metabolites of the butadiene, and this is only disclosed at the end in that Section 7.3. It almost gives like an impression that some -- it wanders like it's going like -- in some cases it appears that you're given like all the burden of the effects, and so these metabolites and these other sections it is not clear.

And I think that part of that ambiguity and that difficulty in understanding the course of the statement is just because of what you disclosed in that paragraph in the Section 7.3, which is like the mode of action -- and I'm just going to read exactly how it is presented in this current draft.

You start that 7.3 -- I'm sorry. Correct. When I talk about Section 7.3, I am really referring to Section 7.4 or Mode of Action. So that section you cited by saying, "there is currently no accepted mode of action for the acute or chronic effects of butadiene exposure noted in this document".

And then you go into a whole list of the different modes of different ways how it can have an effect. And I think that at the end, and may be this is something it can be brought to the discussion among the panel, the mode of action on how is it that the butadiene

causes the different effects depends on the type of effects.

And like it appears to me that some of the genotoxic effects and those that lead to cancer and perhaps some of the effects on reproductive biology are most reduced to the metabolites, and some of the adducts that are created in between the metabolites and the proteins and the metabolites and the DNA.

However, some of the effects like, for instance, the vascular effects or cardiovascular effects, and we don't know if there are any neurological effects, may not relate then to these metabolites or the adducts that are formed with the metabolites so clearly.

So I -- what I could suggest is that even in that -- from -- in the initial presentation of the metabolism, there could be like a couple of sentences where this is disclosed, that there are different modes of action depending on the different effects that this will be discussed in more details in a section and you can name the section.

Some of the effects are due to the metabolites or the process of the metabolism that would be described in this section. Some of the effects may be viewed to other non or mechanisms that are not clear as they would be presented also in other sections and you can name also the

other sections.

So this will set the stage like for the person who is reading this draft that we understand, okay. So when we're talking about these products and maybe this can explain like some of these effects, but maybe not explain some of the others.

This is probably the biggest change that I could recommend just for clarity. I mean, I don't believe that you are really constructing or you are really following any means statement. I just feel that in the way how it's presented, it is just difficult for the reader to perceive that.

CHAIRPERSON FROINES: Can I interrupt you?

PANEL MEMBER ARAUJO: Sure.

CHAIRPERSON FROINES: Could you clarify a little bit when you say that some effects may be the results of other pathways. I'm not quite clear on what you're thinking about. I would argue that the toxicity of butadiene, whether it be with proteins or DNA, is a result of oxygenated metabolites or atmospheric chemistry products, and that we're dealing with, for example, hydroxymethyl vinyl ketone is an alpha, beta-unsaturated ketones, and one would expect that to carry out Michael Addition Reactions and that would be a pathway to binding with protein.

So I wasn't -- so I'm -- I think that the hydroxylated or ketones products that follow are very important, as well as the epoxides and the -- so I won't -- I think we need to be clear on what we mean by other effects may occur.

PANEL MEMBER ARAUJO: Sure. Yeah. You're going right to the point that I'm trying to go over or discuss. And I agree with you, John, I think that most of the effects are really due to oxidative biology. The confusing part is that the auxiliary products of the -- that are generated that come -- result in the information on some adducts and with the DNA or the protein. And this -- and adducts and cancer as biomarkers of exposure, and in some cases as the biomarkers of effects, but it depends on the effects.

So we're talking about like a genotoxicity and perhaps reproductive biology. So, to me, they may serve as biomarkers of effects. But if we talk about like vascular effects, and whereas they both mentioned, perhaps neurological effects, maybe those are not biomarkers of effects. It could be biomarkers of exposures or may not even serve as such. We just don't know.

And the reason why I'm saying this is because in one of the studies that is mentioned also in this graph, there -- I don't know if I can locate it, but they

say -- yeah, this is in page 30 in the last paragraph of page 30, when they refer to the studies of Penn and Snyder 1996 and 2007, "...found that the atherogenic effects of butadiene exposure was apparently not associated with either of the two principal epoxy metabolites of butadiene, 1,3-epoxybutene and 1,2:3,4-diepoxybutane. Neither of these metabolites was increased by butadiene exposure in avian liver in contrast to mouse liver".

And this goes back to the discussion that we had a few months ago when this was first presented, because it was the impression that all these metabolites could be leading and explaining the toxicity, but then we have these other reports where apparently that was not so clear.

And even though they do present it, and even though they do have this paragraph in the 7.4 Section, it is still not clear, maybe because it just requires an additional refining of the few sentences here or there. Because that's why I suggest that maybe even up front and even before they start describe the whole metabolism, you just do like a couple of sentences on this, or what I mentioned, it could help on the perception.

CHAIRPERSON FROINES: I think that's very important, because there has been debate among the mouse versus rat models in terms of epoxide formation and the

relative rates of those formations, so that I think what you're suggesting is very important, because there are other pathways that may be significant over that which has been part of the major debate.

PANEL MEMBER ARAUJO: Yeah, absolutely.

So let's continue. So then in Section 7, even though I've been jumping between 4 and 7. I'm sorry. But let's just go now to Section 7. In the first subsection, 7.1, so they talk about the standardized mortality ratio. And they do a good description of the status and where that is used, since that is on page 27.

Not everybody knows what SMR is. So maybe they could define it. It's just a suggestion, because otherwise the result -- even the reason that is familiarized with the toxicology literature may not necessarily be familiar with SMRs.

In the second paragraph, when they refer to some status of butadiene in atherosclerosis, they refer to study, Salama et al. in 2002, and that it studied 120 atherosclerotic AR subjects. And I couldn't commit to the use of that abbreviation is -- even if it is used by the authors, which I'm not sure, it is not a standard abbreviation. And it's like confusing, and you're not really using it later on in the document, so I think that it's unnecessary.

In the Section 7.3, where you include new studies about the chronic toxicity in experimental animals suggest in adding some of the studies that talk about the cardiovascular toxicity. However, you do mention, and got most of the data from the reviews from Penn and Snyder 2007. You even mention the year of the originally cited from Penn and Snyder in 1996, but don't really cite it and don't really take the data straight from there. So I think the original study should be cited and also should be included in the bibliography, which at the moment it's not, and not just based it on this course of yours and segments and based on the review.

And I think that in the Section 8 in the derivation of reference exposure levels, I don't really have much to say. Just a very little point. Maybe it is bigger, which is just that in section 8.4 -- I'm sorry in Section 8.3, in the page 37 on the third paragraph, you talk about butadiene causes non-cancer effects following chronic exposure, the most important of which appears to be reproductive toxicity.

So I would change that "most important" to the most studied perhaps, because it may be that some of the other types of toxicity, like a neurological or cardiovascular could be even more important. It's just that they haven't been studied.

The reason why it said this is because butadiene is an important derivative or constituent in emissions of motor vehicles. And it's an important constituent in the active smoking, as well as in the passive smoking. So it may be responsible for an important proportion of the cardiopulmonary non-toxicity studies associated with it, in which case the effects may be even larger than the -- that the effects are very one-sided and very well presented for the reproductive toxicity. So I would just change the wording.

And I think that's, you know, this is really the most important point.

CHAIRPERSON FROINES: Beate has a comment.

PANEL MEMBER RITZ: Yeah. I just saw that the FMRs that were referred to actually are reported like those old FMRs from 25 years ago. You have FMRs of 148. I would suggest to turn that into 1.48 because the ratio is always 1 is the null. I know it was used as times 100 to make it easier to write, but that's not clear in the document and what we now use is a 1.

PANEL MEMBER ARAUJO: Yeah. I have to say that personally I should have to go and search for it and see what actually was, because it was not -- so, yeah, I agree Beate.

CHAIRPERSON FROINES: The next person is Alan

Buckpitt.

PANEL MEMBER BUCKPITT: Hi, John. I didn't have a lot to add to that. I sent some minor comments to Andy just this past Friday.

There's a couple of things that I saw that you may want to consider. One is related to the recent work coming out Fred Guengerich's lab, where they're shown adducts with DNA basis based on the glutathione conjugate. And, you know, there was just -- when they originally wrote the report, there was only one publication on this. There's now two of them, and they seem to bind to guanine quite easily.

And I think we -- Doerr tells a disservice if we just ignore that. I know it's very recent data, but if it binds to DNA basis, it's reactive, it likely binds to proteins, unless the essentially hardness of those electrophiles is quite different.

So I think maybe working that in a little bit more to the discussion. And I know it was very recent, but there is another paper in Chem Rez in Tox, and I sent the references to Andy, that you may want to put a couple of sentences into the mechanism on that part of this just to leave it open.

And then that brings us back to the metabolic scheme. And you may want to take arrows and draw them

from the glutathione conjugates back up to the DNA and protein. Certainly, I think there's evidence for that at this point.

And if we look at the metabolic scheme, the mercapturic acids are the N-acetyl-L-cysteine derivatives they're actually drawn as glutathione conjugates. So that's probably just put the sulfur with N-acetyl-L-cysteine that would make that probably a little bit clearer on M1 and M2.

CHAIRPERSON FROINES: Alan, can I ask you a question?

PANEL MEMBER BUCKPITT: Sure.

CHAIRPERSON FROINES: If the -- if they incorporate the Guengerich work which I think they should, are they going to have to explain soft and hard electrophiles.

PANEL MEMBER BUCKPITT: I don't think so at that point, because I don't think, John, there's enough out there at this point. Fred did not look at any protein binding at all. It was only binding to guanine and adenine, and he's shown -- he's provided very good physical evidence for those two adducts.

And, of course, we look back to hexachlorobutadiene, you know, the old work of Simon Lock and his colleagues, that generates a glutathione conjugate

that then becomes again cysteine, and that cysteine conjugate is metabolized by the CFYA in the kidney to a very effective electrophile that produces kidney injury.

So I think we shouldn't ignore that potential pathway. It's just not very well worked out from butadiene at this point.

CHAIRPERSON FROINES: Does that mean that you're finished?

PANEL MEMBER BUCKPITT: That, besides minor comments, John. I mean, I can go through them. I don't think they're worth mentioning. I did send them to Andy.

CHAIRPERSON FROINES: So can we switch to Bill Nazaroff who's published in this area, because he may have relevant comments at this point.

PANEL MEMBER NAZAROFF: I'm happy to. I've only published in one narrow part of the area, which is exposure. And I appreciate the work that's gone into the revisions. I have a set of comments that are all from the occurrence and exposure section, except for one. So I'm going to be giving these comments referencing where I am to the clean version that was distributed by paper. So it's the second one that came to us in February.

So at the beginning on physical and chemical properties section, which is page two Section 2, the statement, "very slightly soluble in water", I guess I

accept qualitatively, but when I was trying to figure out what the 735 milligrams per liter meant, the best I could discern, because butadiene has a vapor pressure above one atmosphere at room temperature, so it doesn't exist as a condensed phase species except in containment.

That 735 milligrams per liter works out to be what you get if you have one atmosphere of gaseous butadiene in equilibrium in contact with liquid water. That's effectively the Henry's Law partitioning under that condition.

It's such a peculiar circumstance. It's not what people normally think, as far as I understand, and Kathy is nodding her head here, with respect to what solubility means. So I would just suggestion striking the number in that line. Just say, "very slightly soluble in water", and leave it at that.

You've given all the other data that one would need anyway, the vapor pressure and the Henry's Law constant. That's enough.

The other comments I have are all in the section Occurrence and Exposure, and they vary in strength. They don't cut to, I think, the core of what this document is about. Overall, this is just really cleaning up some details, but they're important details.

So the second point has to do with the statement

that's made at the top of page three, the primary stationary sources are such and such, primary natural sources are wildfires. That made me wonder about residential wood smoke. And we know that residential wood smoke is an important contributor to PM levels in many communities in California, in the wintertime. And there -- Kathy and I did the quick 10-minute search on Web of Science while we were listening to the other comments.

Now, we found a few papers in the literature that are reporting emission factors of butadiene from residential wood combustion types of activities. And so it might be worth at least expanding the statement to call to people's attention with a reference or two to where these emission factors are measured, that would smoke is a potential source of interest and concern.

At the bottom of page three, there is -- I guess the first sentence, "Despite it's rapid removal....", and so forth, it says, "...with average air concentrations approximately equal to 0.3 parts per billion...". That's a statement that absolutely begs for a reference. And I think -- I think it's too high.

The data that are presented elsewhere wouldn't support that high of a level, so maybe that -- even that statement should be struck and we should just end with -- that it's present in low concentrations in cities and

large suburban areas.

Yeah, that maybe, but some show some higher numbers. That brings me to what is --

DR. SIEGEL: That could have -- I'm sorry to interrupt. This is Dave Siegel. That could have been the average we got from the Bay Area sampling that was an order of magnitude off.

CHAIRPERSON FROINES: Who's speaking?

DR. SIEGEL: This is Dave Siegel.

PANEL MEMBER NAZAROFF: Well, it's talk about -- let me talk about for a minute Tables 1A and 1B, because I have major problems with the evidence that's -- or the way the evidence that is presented is interpreted here.

And the real concern derives from the fact that 90 percent almost -- 85 to 90 percent of the samples, on average, from the two studies are below the method detection limit or minimum detection limit. And so under those conditions, the ability to infer what the average concentration was is -- would take a much higher level of sophisticated analysis and have a very large uncertainty associated with it than what was done here.

On Table 1A, it says in footnote that the levels below the method detection or minimum detection limit were recorded at one-half that value. And that's viewed as a very old fashioned not up to modern statistical technique

method. And even when it is used, it wouldn't be recommended to be used with such a high proportion of non-detects.

And then for Table 1B, which has a separate minimum detection limit, that's four times higher than the case for Table 1A, there's still 85 to 90 percent non-detects in that study, and we're not told how the average concentrations are determined or how the non-detects are handled, but we end up with averages that are below the minimum detection limit. So there's -- and they're below half the minimum detection limit, so there's very likely a different means of handling the non-detects in case -- in Table 1B than in Table 1A.

I have, what I would suggest is, at least a moderately strong recommendation for how to deal with this, because you don't really need to support what this document is about. You don't need to be reporting community by community average concentrations. So I would recommend something like this, strike the two tables and replace them with about one sentence each or maybe two sentences each.

The sentence for the Bay Area would say something like N samples were collected over some period of time from M different communities, and the -- with a method detection or minimum detection limit of 0.5 -- sorry, 0.05

parts per billion. Twelve percent on average of the measurements were above the detection limit, the community level maximum values were in the range of 0.05 to 0.26 parts per billion, and do something similar for the South Coast Air Basin.

So, you know, there -- you have a different number of samples collected and a different number of communities, a different detection limit, report what the maximum values were observed by community, and say that only 10 to 15 percent were above the detection limit.

The last few comments I have are minor by comparison, but let's just hit those. At the bottom of page five is a just a weird phrasing. It says, the mean outdoor concentrations of butadiene were whatever they were versus in-home ambient concentrations. And although ambient is a vague term anyway, and it's used in a weird way, usually it's used to mean outdoors. So one wouldn't generally say in-home ambient. I would just strike the word ambient at that point.

On the top of page six in reference to the Marshall et al. paper, I think it's important to note there that the simulation -- this is a simulation study, and it was on modeled concentrations not measured concentrations. Those modeled concentrations I think it's important to attach a date here, because the levels have

tended downward over time. So that study considered modeling results for the period April '98 through March '99.

PANEL MEMBER HAMMOND: Based on sampling from what year?

PANEL MEMBER NAZAROFF: Not that's for the '88 -- it's '98 to '99 --

PANEL MEMBER HAMMOND: Data.

PANEL MEMBER NAZAROFF: -- emissions data.

PANEL MEMBER HAMMOND: Yeah.

PANEL MEMBER NAZAROFF: A simulation of '98 to '99. So the exposure levels would be what we believed to have occurred during that year, not representative of modern -- and then finally, although this is an easy thing to fix, I'm unhappy to see an error like this.

In the middle of page six for two paragraphs, there are a series of concentration levels reported in mass units, micrograms per cubic meter, and then in mole fraction units. And I count six instances where parts per million, or ppm, is given, and it should be parts per billion. That's a bigger error.

That's the end of my comments.

CHAIRPERSON FROINES: Are there comments on Bill's comments?

PANEL MEMBER ARAUJO: My only comment is about

the same point that I mentioned about the solubility. I think that all your points are very well taken, Bill. On the other hand, I have to say that this is how it's shown in the modeling chemistry table. I was searching on various sources, and in all of them -- so they usually -- they'd show the solubility in the water. They do add that it's at 20 degrees, and that's why I mentioned that this would be added.

Your point about a one atmosphere, I think that it's -- they don't usually mention it in the table. Interestingly, they do say it is highly dissoluble in ethanol, ether, acetone, benzene and organic solvents, but they don't mention the solubility. And I was searching for the solubility in any of these organic solvents, and I couldn't find it. I don't know if you know it.

But given maybe the confusion that it could create, maybe the easiest you're saying which is just to strike it, I mean -- and just to delete it, the number.

CHAIRPERSON FROINES: Bill.

PANEL MEMBER NAZAROFF: Well, that was my suggestion anyway, just to strike the number in parentheses, and in -- I guess at this table, I mean I look to Kathy, because she knows more environmental chemistry than I do, but -- I didn't get a clear signal from her, but I think the clear signal I guess to the

point that there is one is that it's not terribly important one way or the other.

PANEL MEMBER HAMMOND: Right, I agree.

CHAIRPERSON FROINES: Kathy, you want to go ahead since your name came up recently.

PANEL MEMBER HAMMOND: I'm sorry. I have no comments. Thanks.

CHAIRPERSON FROINES: Stan, I know you made comments to OEHHA, and so you -- would you want to go next?

PANEL MEMBER GLANTZ: Sure. I gave OEHHA some comments. They revised the report. None of them were major. And, in fact, the version that Andy emailed around had the corrections in them, which were fine.

In just looking at it now, I had one other very trivial suggestion. And that is sometimes like if you look at the acute REL you presented in milligrams per cubic meter, and everything else is micrograms. And I just found that a little confusing. And I think since almost everything in the report is in micrograms, I would just, instead of saying 0.66 milligrams, I'd say 660 micrograms.

Just use consistent units throughout, because it bouncing back and forth was a little bit confusing. But other than that, I think it's -- as you know, I missed the

last meeting, so I kind of read this fresh. And as I was reading through it and thinking of comments, as I kept reading, I found they were answered. So that was reassuring.

CHAIRPERSON FROINES: That's it?

PANEL MEMBER GLANTZ: That's it. I think it's a nice report.

CHAIRPERSON FROINES: So I think I'm missing so far Beate and Paul. Is that -- am I missing somebody else?

PANEL MEMBER BLANC: No.

CHAIRPERSON FROINES: No.

Paul.

PANEL MEMBER BLANC: Well, I also want to echo what people have said about the edits being responsive to the feedback, and it's nice to see such an aggressive approach to updating the references and being more diligent. I want to walk through a question and make sure I understand it correctly. And it's a bit more -- forgive me if it's a bit too basic.

But in the metabolism of this particular product and material, the -- if I understand the text correctly in reference to the key figure on the metabolic pathways, the humans tend to go down the butenediol pathway more, and mice tend to go down a pathway which leads away from the

butenediol, ultimately yielding the M2 instead of the M1 conjugation product, is that correct?

I mean, that is what you meant to understand from the text?

DR. BROWN: Yes.

PANEL MEMBER BLANC: And it is believed biologically that the butenediol metabolite pathway is probably more relevant for ovarian depletion?

DR. BROWN: This is Joe Brown speaking. I'm not sure that that can be said with a lot of confidence. I think the only thing that comes through, in my reading, is that the diepoxy metabolite seems to be a key player in the ovarian atrophy.

PANEL MEMBER BLANC: And which one is the diepoxy?

DR. BROWN: It's the one in the upper left-hand corner.

CHAIRPERSON FROINES: 1,2:3,4-diepoxybutane.

PANEL MEMBER BLANC: Okay.

DR. BROWN: The diepoxybutane.

PANEL MEMBER BLANC: Okay. And does the diepoxybutane, which doesn't go to either one of those two metabolites, what is the intraspecies difference in that pathway?

DR. BROWN: Well, I think in all cases the mouse

has much more -- is a much more active metabolizer than humans or rats.

PANEL MEMBER BLANC: You mean it's excreted unchanged by humans?

DR. BROWN: No, I wouldn't say it's excreted unchained, but more of the diepoxybutane is produced, I believe.

PANEL MEMBER BLANC: Is it said somewhere in the document that that's the case?

DR. BROWN: I think it is, yeah.

"Mice form the initial oxidative metabolite, epoxybutene, approximately 6 to 8 times faster than rats or humans...". That's faster. They're more active the metabolizers, "...and produce a greater proportion of active epoxide metabolites than rats". That's Bond '86.

PANEL MEMBER BLANC: So --

DR. BROWN: That's been used to explain why the mouse seems to be more sensitive to a lot of the effects of butadiene, because it's a faster producer of these epoxide metabolites, particularly the diepoxide, which has the ability to do cross linking and has probably more damaging effects than any of the model oxides. I mean, that's some of the thinking, anyway.

PANEL MEMBER BLANC: And if that's the case, then the pathway that's to the left of the table, the Figure 1,

which is all dependent on the diepoxybutene --

DR. BROWN: I don't think you can read this chart or this scheme to be exclusive of any particular species. I think all of them --

PANEL MEMBER BLANC: No. No, I understand that.

DR. BROWN: They all produce everything. It's just a matter of ratios.

PANEL MEMBER BLANC: Right. But you make the point that the mouse produces more of the final metabolite M2 and the human more of the M1. I mean, you make that point. Is that not a point you wanted to make?

DR. BROWN: It's the point, but I wouldn't say so -- I wouldn't work backwards and say this is the --

PANEL MEMBER BLANC: Well, but this other one, which seems to be the one -- the pathway that's more relevant for toxicity, you don't make any comment about it. So is the implication therefore that if you looked at total metabolites, the 1-glutathione, 2,3,4-trihydroxybutane metabolite would be more -- I'm not talking about the speed of it. I'm just trying to understand.

DR. BROWN: I don't know. I don't know if you can make judgments based on the ratio of metabolites, you know. I keep thinking of arsenic where --

CHAIRPERSON FROINES: It's also true that the

butenediol is an important pathway toxicologically.

DR. BROWN: Yeah.

DR. SALMON: This is Andy Salomon here. I mean, there's a lot of things going on here. And you also have to bear in mind the complexity that just because the rate of metabolism by a particular pathway is some factor X greater in say the mouse than in say by comparison to the rat, it doesn't necessarily mean that other important parameters like the area under the curve or the amount metabolized in 24 hours or something like is necessarily different by the same ratio.

PANEL MEMBER BLANC: What I hear you saying, Andy, is that there's a lot of uncertainty.

DR. SALMON: There's a lot of complexities and uncertainties.

PANEL MEMBER BLANC: And how does that translate into the uncertainty factors that you're using?

DR. SALMON: Well, we include the appropriate methods dealing with uncertainty, including picking the most sensitive endpoints, the most sensitive species, and allowing for uncertainty factors reflecting --

DR. BROWN: We're using toxicokinetic and toxicodynamic uncertainty factors as you look at it.

DR. SALMON: I'm flicking through --

CHAIRPERSON FROINES: We've got too many people

talking.

DR. BROWN: Okay.

PANEL MEMBER BLANC: Well, my question just to repeat it, if it was unclear, is I hear OEHHA people saying there's quite a bit of uncertainty walking from the complex metabolic pathways from mice to humans, and we try to address that with our uncertainty factors. And those include an interspecies uncertainty factor, which is the one that would be relevant from walking from mice to humans. And we're using a toxicokinetic uncertainty factor of one and a toxicodynamic uncertainty factor of the square root of 10, yielding a value of 3, and not -- I'm sorry, of 3 -- yeah, three point something, rather than let's say 10.

And is that consistent with where you see the uncertainties and the degree to which you see the uncertainties walking through from mice to humans? And that's quite a different question than just you using a sensitive endpoint and a sensitive effect.

So I just want to hear you tell me that you've -- or hear you say to me in a way that I can understand it, why, given what you're saying those uncertainty factors are, in your view, sufficiently conservative.

DR. SALMON: Okay. This is Andy Salmon here. I

think -- I mean, we've got a situation here where we have quite a bit of information and several tools which allow us to refine the analysis. But on the other hand, we've got some significant uncertainties, including the uncertainty about the exact, you know, critical metabolite mode of action, and so on.

So to some extent, it's -- on the one hand we've got quite a bit of information. On the other hand, we've got several uncertainties. So our judgment is that these uncertainty factors are appropriate in comparison to what we normally do. You know, these are probably, in most cases, similar to what we've used in other cases, where we have significant amounts of information, like, for instance, including a relatively good toxicokinetic model of many of the things that are going on, but on the other hand we do have residual uncertainties about the negative. So our judgment is that these are appropriate under the circumstances.

CHAIRPERSON FROINES: But, Andy, you sounded like you're making an argument for a more conservative approach.

DR. SALMON: I'm saying that we think this is about right. It's somewhat conservative.

CHAIRPERSON FROINES: Let me finish.

DR. SALMON: Sorry.

CHAIRPERSON FROINES: The issue is that this uncertainty factor turns out to be the square root of 10, which is 3. And the arguments that you've made would -- especially when you consider the fact that there's evidence -- there's enormous data gaps with neurotoxicity and cardiovascular disease. And so when we talk about uncertainty, we need to look at the overall uncertainty and it's not clear to me that 3 is sufficiently conservative.

DR. SALMON: Well, as I say, we considered the range of evidence -- admittedly, there are a number of different endpoints, which may -- you know, which may appear as toxicological endpoints of concern for butadiene. But we do believe that we've picked the most sensitive ones, so that we -- we're dealing -- to some extent, we're dealing with that uncertainty by making that choice.

We're looking at the mice, which are the most sensitive species, which again deals, to some extent, with our uncertainty about the interspecies differences. But, on the other hand, we do have a number of residual uncertainties. And, as I say, we're dealing here with a cumulative uncertainty factor of 100 to cover inter and intraspecies differences. And we -- our judgment was that that was an appropriate level of uncertainty

correction -- or allowance for uncertainty.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: How do you feel this compares with similar chemical determinations that you've faced in terms of uncertainty, where the -- where we actually have perhaps even better understanding of the metabolic differences than it seems that we do in this case, because we don't also understand which metabolites -- we think we believe which metabolites may matter more, at least for the key endpoints that you're using?

By the way, I am completely supportive of using the ovarian outcomes. I think people recognize that that's an important area of toxicity generally, and that, in some ways, butadiene is a paradigm environmental toxicant that has reproductive effects based on these ovarian studies in mice, so -- and also, there's this dimer of butadiene, which apparently doesn't occur in nature, is that correct? It's only an industrial byproduct, is that correct?

DR. SALMON: I don't know.

PANEL MEMBER BLANC: Should we even be -- shouldn't be mentioned perhaps in a sentence that -- John, are you familiar with that chemical?

CHAIRPERSON FROINES: The dimer?

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: No.

PANEL MEMBER BLANC: It's -- first of all, there is an interesting -- the reason I say the comments about the appropriateness of the endpoint is there's a good review on xenobiotic effects on ovarian preantral follicles that's fairly current from 2011. And butadiene is one of the chemicals that they discuss at some length. And they do cite all of the studies that this review cites, which is also reassuring.

But when they come to butadiene -- and they do emphasize the butadiene diepoxide. The related chemical that they discuss is 4-vinylcyclohexene, and it's diepoxide metabolite diepoxide. And they state that the dimerization of butadiene forms 4-vinylcyclohexene. And they cite some papers on that.

What I don't know is if that's only an industrial process that would do that or if there are other situations in which it might dimerize.

And it's probably worth alluding to it, just so that it's clear that we're aware that --

DR. SALMON: We should follow that up.

PANEL MEMBER BLANC: Right. Yes. But I guess I am not entirely convinced, but I guess if you want to convince me that your approach to the interspecies

uncertainty, because I think that's where we're really -- what we're really talking about is appropriate, then I think there needs to be some text that more explicitly justifies it rather than simply us having a discussion around the table.

DR. BROWN: This is Joe Brown. There is some text I think on page 38 comparing our work with other agencies.

PANEL MEMBER BLANC: Yes. And you say the EPA is --

DR. BROWN: So there's some -- there's a universe there --

PANEL MEMBER BLANC: -- the EPA was more --

DR. BROWN: Was more, but over --

PANEL MEMBER BLANC: -- conservative. That's the only time in my --

DR. BROWN: Well, it's an older analysis.

PANEL MEMBER BLANC: Well, I know, but it's the only time in my memory that the EPA has actually been more conservative in an uncertainty factor. That's one of the sort of things that makes me slightly uneasy. And when you say it's because that we have more data, it's not necessarily because we have more data of the sort that let's you reduce the uncertainty in some of these key areas, is it? I mean that's --

DR. BROWN: The only difference is we're using a pharmacokinetic model and we're using, you know --

PANEL MEMBER BLANC: But how does that help with the interspecies uncertainty?

DR. BROWN: Well, it doesn't. It doesn't.

DR. SALMON: It allows you to replace the -- you know, the -- to some degree, it allows you to replace extrapolation based purely on uncertainty. The extrapolation based on modeling and model comparisons between species, which is what we are doing here. And, I mean, I think one of the complacencies about butadiene is that we actually have a lot more information about butadiene than we do for most chemicals. You know, this is, in fact, particularly in the area of metabolism, an extremely information-rich chemical. The problem is it's also a very complicated chemical.

So we've got a bit of a trade-off between actually, by general standards, knowing a heck of a lot about what goes on with butadiene, but on the other hand having a lot of residual complexities.

But, I mean, in many chemicals, we've used, or attempted to use, toxicokinetic models to refine the interspecies extrapolation, but we haven't necessarily had anymore clarity about exactly what the -- you know, the effect of metabolites are and than we do with butadiene.

In many cases, we've had to use things like total amount of metabolism or some such parameter.

So I think, in this case, clearly it's very complicated. Clearly, we've, by no means, know everything. We do actually also have, by comparison with many other chemicals actually, have quite a bit of information here.

PANEL MEMBER BLANC: But isn't most of that relevant to intraspecies uncertainty?

DR. SALMON: It's relevant to both. We do use the fact that we know a little bit about rats versus mice, and rats versus humans, and those sorts of comparisons. We factor in the extent to which we understand those comparisons in our estimation of what the likely uncertainty in the overall safety proposal is.

PANEL MEMBER BLANC: You know, I don't want to badger people here, so, Mr. Chairman, since we're not around the table, and I can't see other people, I have no idea whether I'm way out in left field on this or not.

PANEL MEMBER RITZ: This is Beate. I might have mentioned that before. But since the main outcome is ovarian atrophy, or better the shortening of the reproductive lifecycle in females, I think that's a very large uncertainty. When we're talking about mice, we're talking about months of cycle, and months of exposures.

In women, we have, on average, a 36-year cycling. And whether a woman loses her fertility at 40 or 50 is a big difference.

So thinking about cumulative effects, they could be much stronger in animals that live longer and have a much longer reproductive life span. And I don't see how any of that comes out here or is taken into account.

Maybe, it's impossible, but at least that's another uncertainty factor, right?

PANEL MEMBER NAZAROFF: This is Bill. And I think Kathy and I are enjoying the conversation, so you needn't feel that you're troubling us, Paul, for raising the point. I think it's an important one.

PANEL MEMBER HAMMOND: Yeah, and I agree. I think that both the other points, and Paul's points, are important in terms of the very specific -- rather than the general sense of going from animals to humans, but very specific ways in which there's some differences, which we may not be able to capture, but maybe we can at least acknowledge that we don't know how to capture it.

PANEL MEMBER GLANTZ: Well, this is Stan. I mean, just having been listening, I mean, are you saying that the uncertainty factor should be put back to 10 from the square root of 10? The one dealing with the ovarian atrophy. I guess you used that in two of them.

I mean, when I read this -- and, I mean, I have to say that I, you know, I had to take some of the toxicology at face value. I was looking at this more from, you know, the point of view of my area of expertise, which is statistics.

But it looked to -- it seemed to me that just reading it that the correction -- the uncertainty numbers they used seemed consistent with sort of the general practice in other documents.

Now, if it turns out that the -- you know, that we should go beyond that because of the issues you're talking about, I mean, I'm willing to go along with that, but because I don't really -- it's not an area I feel technically competent to speak to. But when I read this, you know, sitting there myself, I thought what they did seemed pretty typical of the way these things have been handled in other documents we've reviewed.

I mean, I think the question coming down -- you know, from listening to the discussion, I think the question for the Panel is, given the issues that Paul has raised and what the other people have been saying, are we saying that the square root of 3 -- or pardon me, the square root of 10 toxicodynamic correction -- I guess that's the one we're talking about -- is too small and you should take away the square root sign. I mean that's what

it comes down to.

I mean -- and so -- I mean, what do you guys think? I mean, I don't have an opinion about that, but it seems that's the question.

CHAIRPERSON FROINES: I think that you're right on target, Stan. And I would go back to Beate and ask her if she thought -- and we are talking about the toxicodynamic factor. And so is the implication of what she said sufficient to argue for taking away the square root sign?

PANEL MEMBER RITZ: Maybe the only other thing I have to add is that the ovaries are cells that we're born with. They do not reproduce. So every insult is really cumulative and, in essence, this happens when not enough ovarian cells are there any more. So it's relevant in that sense as well.

PANEL MEMBER BLANC: I guess I have a question for Melanie if she's on the line still.

DR. MARTY: I'm still here.

PANEL MEMBER BLANC: So Melanie, taking a step back and taking the long view. As you look over the life span of these discussions and the evolution of our uncertainty -- approaches to uncertainty, do you see that there is a precedence here -- either a precedence that we're making in the wrong direction were we to be more

conservative in the interspecies toxicodynamic uncertainty factor here or is there precedence from some earlier example that you can think of where we were dealing with endpoints that are a bit more tricky like this?

So this -- to me, this isn't the same as talking about nasal atrophy in rats or some of the other endpoints that we end up using. This is starting to get more like the developmental neurotoxic outcomes that are so troubling, for example, in terms of interspecies uncertainty or data uncertainty.

DR. MARTY: Well, I'm not really sure how to answer the question. I mean, a couple of thoughts are that humans, yes, live longer than rodents, and there are other tissues that we've looked at as toxicological endpoints, where we haven't said, oh, but we live longer and therefore we should have an additional uncertainty factor, because, you know, frankly, I don't think that's that relevant. We live longer, but the rodents also age faster. So it's -- you have to kind of look at the life times as equivalent. I think we --

PANEL MEMBER RITZ: Actually -- this is Beate -- I disagree coming from the neurodegeneration field. The mice live two years. And all of my friends who do mouse models of Parkinson's know that the cells in the brain of the mice never will die.

However, they will show atrophy or they will show dysfunction, if you hit them hard enough. And only if you, you know, use a very high load of neurotoxins, they will really die, but the brain of the mouse can never be compared to the brain of the human, because the cells just don't age enough.

And the dopamine cells are actually the only other cell type in the body that's just like the ovaries, meaning we're born with a number of cells and those cells do not divide. They just keep dying. So it's really a cumulative effect for these two cell types. And I think it has to be treated different from other tissues.

DR. MARTY: Okay. Well, we have not done that in the past. That was my point. Then in terms of the kinetics -- in fact, we started out the discussion with the kinetics, talking about differences in metabolism and the reason that we had initially chosen a UFA sub K of one is because it appears from data in a number of studies that the mice metabolize to the diepoxide considerably faster than primates in humans and rats as well.

So we thought with the kinetic, the PBPK model and the information that mice metabolize faster that we would be okay with the toxicokinetic adjustment of one for the interspecies factor.

PANEL MEMBER BLANC: But we just heard earlier

that we don't know what that means about the area under the curve. Are you saying that the area under the curve would -- or my interpretation to that comment was therefore the area under the curve might be more relevant to the toxicodynamics of it, rather than the toxicokinetics. Is that, strictly speaking, not true? And how, if we don't know the area under the curve, did the toxicokinetic --

DR. SALMON: Well, actually we do know the area under the curve, because that's what we're modeling in the PBPK model. I'm just pointing out that just because you've got a certain ratio for the rates, doesn't mean that it's the same ratio as to the area of the curve, but we, in fact, do have those parameters as estimated by the model in this case.

This is one of the areas where, you know, it is a lot more complicated than the average case, but we have more information as well, so -- but this is, I think -- the question about, you know, how -- do we need to make some additional allowance for the unique toxicodynamic properties of this endpoint? That's a --

PANEL MEMBER BLANC: Right, I understand.

DR. MARTY: Yeah, so I don't -- you know, I think, Paul, you asked if I thought we would be going in a wrong or funny direction if we increased the toxicodynamic

uncertainty factor. And I can't say that we would be going in a wrong direction.

PANEL MEMBER BLANC: Okay.

DR. SALMON: On the other hand, some people, including I think that review -- that meta-analysis that you cited in your update, didn't they say that they -- they were arguing in the opposite direction.

DR. BROWN: Yes. This is Joe Brown. Yes, they argued in the opposite direction coming up with values that were very much higher than what we're talking about here.

CHAIRPERSON FROINES: I'm not clear on who you're referring to.

DR. BROWN: The Kirman and Grant paper that I discuss and that's discussed toward the end of the document.

PANEL MEMBER BLANC: Right.

DR. BROWN: This was the paper that was brought to us right before the last meeting in the fall.

PANEL MEMBER BLANC: The meta-analysis of the pool rodent data.

DR. BROWN: The meta-analysis, yeah. And their conclusions are that you could tolerate much higher butadiene exposures based on their analysis, than what we're talked about here.

DR. SALMON: We don't agree.
DR. BROWN: We don't agree with that --
DR. SALMON. I'm just pointing out --
DR. BROWN: -- for another reason.
DR. SALMON: -- the arguments in both directions.
DR. BROWN: Another argument. And we could not use their -- we don't buy their assumption, and we could not use their assessment as it is. What we did say was they had an interesting methodology --
PANEL MEMBER BLANC: Which you then --
DR. BROWN: -- which we then apply to our data set to see what the difference was.
PANEL MEMBER BLANC: As the sort of mind experiment.
DR. BROWN: In the mind experiment.
PANEL MEMBER BLANC: Right, which I thought was fine and, you know, was helpful to see.
DR. BROWN: But we could not tolerate their assumptions. I mean, they assume that all species behave the same way, and clearly, rats don't.
PANEL MEMBER BLANC: Well, you know, I mean, I apologize for bringing this up in this way, because it does a bit throw a monkey wrench in, depending -- I mean, this -- it's a kind of a major thing, and it's not easy to say, well, you know, we're going to accept the document,

but the final number on the chronic exposure may change by a factor of, you know, three, depending on what you guys decide. So I don't know --

DR. BROWN: Yeah. If we make it one part per million instead of three parts per million.

PANEL MEMBER BLANC: Right. Yeah. So I don't know -- I don't know what to say.

PANEL MEMBER GLANTZ: Well, I think -- and this is Stan. I think -- again, I can't speak to the toxicology here, but I mean we've had a very detailed discussion. I mean, if people think that we should adjust the uncertainty factor, something I will abstain on, but I think that's the question.

And there's been a pretty robust discussion, and I mean maybe we should ask the people who know the toxicology do you think -- and, I mean, no one has said that taking away the square root sign would be like a really undefensible, horrible thing to do.

DR. BROWN: We'd have to support it. I mean, we can write something, but we have to support it.

PANEL MEMBER GLANTZ: Well, I understand, but I mean, we've had a pretty robust discussion up to this point. And I think the issues about, you know, the biology of ovaries and, you know, the things that have been discussed -- I mean, again, if I was just reading

this as a reader, I think that would be good -- I thought those were compelling arguments for saying we should take away the square root.

But on the other hand, you know, you could argue that, well, that's all true, but it's not over the line. So I guess what I would do to just sort of call the question, and ask the people who know the biology what they think we ought to do.

CHAIRPERSON FROINES: Well, I think, Stan -- I think we're in a place where everybody recognizes. We're in a place where, one, we want to move ahead, and I think everybody shares that view.

PANEL MEMBER ARAUJO: Can I -- this is Araujo. This is clearly not my area of expertise, but one question that I would like to pose to the people that are more familiar is -- and I think I understand the different perspectives and arguments, is based on the literature this is published and based on everything that's been reported, what is really the number that are -- have been used in other cases where there is an ovarian atrophy?

And I'm just doing some searches on the Internet. And there is one document that I found on the 4-vinylcyclohexene published in development support documents 2011 from the CCEQ, I found that when they're talking about an acute and -- so they use a intraspecies

uncertainty factor of 10 and an interspecies uncertainty factor of 3. When they talk about the chronic, so they use like an intraspecies uncertainty factor of 10 and interspecies of 3, but for lethargy, tremor, and mortality and intraspecies UA of one for ovarian atrophy.

So, again, I don't know if that decision -- the issues are looking at the same tables that I'm trying to interpret in this rush for a few seconds of review.

Yes, you're right, Beate. So in the subchronic to chronic uncertainty factors, they used a factor of 10 for ovarian atrophy, which is what we're talking about here, right --

PANEL MEMBER RITZ: Um-hmm.

PANEL MEMBER ARAUJO: -- whether to use 3 or 10. So do people know about for all the compounds and --

PANEL MEMBER BLANC: Well, the compound you're speaking about is the dimer of butadiene, just so you know.

PANEL MEMBER ARAUJO: Oh, okay.

PANEL MEMBER BLANC: So that would be certainly an analogous chemical in which to invoke that degree of uncertainty. Although, I'm -- there likely to be less data there, but it seems what I've heard mostly is that the data -- the richness of the data set is most applicable to the toxicokinetic piece of it. And where

we're starting to get on thinner ice is with the toxicodynamic interspecies part.

I guess I would say if -- to be consistent with how I've approached these things in our previous discussions or in previous comparable situations, not through this Committee, I would have to say that I would favor using a value of 10 and not a value of the square root of 10. That's my own personal sense. I would love to hear the opinion of our Chair, however, on this matter.

CHAIRPERSON FROINES: Paul, are you suggesting that -- you're discussing using the square root of 10 in terms of the toxicodynamic factor across interspecies?

PANEL MEMBER BLANC: I'm saying that where we currently use the square root of 10 that it should be 10 instead.

CHAIRPERSON FROINES: For intraspecies.

PANEL MEMBER BLANC: Interspecies.

CHAIRPERSON FROINES: That's what I meant to say. I meant to say inter.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON FROINES: Well, I think, at this point, it seems to me that one of the key issues is what Beate has told us about ovarian cells versus -- in terms of their relationship to neurologic cells, for example. And that if I take what she said to imply what that should

mean, I would tend to reinforce what you just said. And I think Beate would as well, but I'm not sure.

PANEL MEMBER RITZ: No, I do. I do.

PANEL MEMBER GLANTZ: Well, I guess -- this is Stan. So is there anybody who would disagree with changing it to 10 from the square root of 10?

PANEL MEMBER NAZAROFF: I don't that I -- this is Bill. I don't know if I want to reach the point of saying that I disagree, but I do have a -- I feel a reluctance for the Committee -- I mean, I only have the three years of experience serving, and I don't know what the longer history looks like.

It feels kind of abrupt to have the Committee making a conclusion on a point like this, rather than referring the matter back to OEHHA. I guess the Committee could ultimately -- you know, we have the power to do it, but it doesn't feel like it's a sufficiently well thought out or well reasoned or well researched basis to come to such a conclusion on the basis of something that was just brought up in the same meeting in which we're making that decision.

CHAIRPERSON FROINES: Well, Bill. This is John. I agree with you a thousand percent. What I'm concerned about is that we're talking about a fairly significant change, when we're sitting here in different rooms across

the State of California, and the sound isn't great, and the whole dynamic is very difficult. And so the deliberative process is, I think, very thoughtful on the one hand, but I also think it's very difficult on the other. And so we need an approach that can address the fact that the circumstances are not best for a significant decision.

PANEL MEMBER GLANTZ: Well, this is Stan. I don't agree with that. This has been a sensible a discussion as I've ever sat through. It is kind of a drag to be on the phone, but I think that the discussion has been quite substantive. Andy wanted to say something.

DR. SALMON: Well, I was just going to say not entirely true to say that this is a discussion which is sort of just suddenly come up here. I wanted to -- you know, I wanted to emphasize that OEHHA has been thinking about these sorts of issues for some considerable amount of time, and we have, in fact, you know, been following literature, including, you know, developing our thoughts in terms of our response to the current meta-analysis.

So, you know, this isn't a debate with which we are altogether unfamiliar. On the contrary, it's one that we've actually been, you know, dealing with internally for some extended period of time ourselves.

PANEL MEMBER GLANTZ: Well, then let me ask this

question. In light of this discussion that we've had, I mean, do you think it's acting precipitously to make this change?

DR. SALMON: No, I don't. I think it's something which we -- you know, we could, and in fact have, considered, you know, during our discussions in developing the report. And, you know, with the support of the Panel and their expertise behind a recommendation, I don't think we would have the problem taking that recommendation at all. Quite the contrary, you know, we have on numerous occasions assembled the argument that would be made to support that.

PANEL MEMBER BLANC: Well, I think what we're -- you know, also I think we're very lucky in that, Beate, you're one of the primary reviewers, correct?

PANEL MEMBER RITZ: Am I? Maybe.

CHAIRPERSON FROINES: No. No.

CHAIRPERSON FROINES: Alan and --

PANEL MEMBER BLANC: That's right. That's right. I'm sorry.

So what I would suggest is that as a sort of hybrid approach to this, that we tentatively accept the document presuming that the -- not only will the uncertainty factor be 10 instead of the square root of 10 for interspecies toxicodynamics, but that also there will

be text -- new text in the document that will explicitly discuss and underpin that factor. And that Beate can serve, in a focused way, as the primary reviewer for that new text, and work with OEHHA in that regard. And that we'll -- that our approval is contingent on those two things happening along with the minor textual changes that have already been discussed in the record.

CHAIRPERSON FROINES: Well, I think that's a very good suggestion. Let's get people's -- let's get the views of the Panel on Paul's suggestion before we sort of make it a vote.

PANEL MEMBER GLANTZ: Okay. Well, this is Stan. I just wanted to say that as Paul was talking the two OEHHA people in the room were nodding their head in agreement. So I'm compensating for the fact that we're not all in the same room. I'm being the verbal television. But they were smiling and nodding their heads.

CHAIRPERSON FROINES: I think that they should speak for themselves, Stan.

PANEL MEMBER GLANTZ: Well, do you want to speak?

CHAIRPERSON FROINES: No disrespect intended.

DR. SALMON: Yeah. This is Andy Salmon here. I'm certainly very willing and keen to proceed according to those methods according to your instructions

definitely.

CHAIRPERSON FROINES: Bill, how do you feel, because you're the person who raised the negative?

PANEL MEMBER NAZAROFF: Yeah. I'm okay with where we are. I mean, I can go along with the proposal as Paul outlined.

CHAIRPERSON FROINES: Jesús.

PANEL MEMBER ARAUJO: I was actually going to go with you, Bill, before you changed. No. No. Bill's original point, which is that to have a directly important change in the document and with not enough data or supported on what has been done or reported before, may look like a little bit dangerous.

On the other hand, I also agree with him. We have only been on the Committee for three years and the people have been a lot longer have more experience in how to handle these things.

One additional suggestion would be how about approving the document as Paul is suggesting with a uncertainty factor of 10 having the comments or the statement that he also mentioned, but what about also having OEHHA do a search into all the compounds that induce an ovary atrophy, and how is that this uncertainty factor has been handled, and so we could make a final decision based on what has been done also before in a

conscientious manner.

CHAIRPERSON FROINES: Well, I think --

PANEL MEMBER GLANTZ: This is just --

CHAIRPERSON FROINES: Can I just take the prerogative of the Chair. I disagree strongly with Jesús. And I disagree, because I think that one of the concerns that we have as a Panel, over 30 years of the Panel meeting, is that we want to not drag chemicals on forever and a day, and that we try and move to closure. And doing what Jesús is suggesting, while very good, is going to slow this process down precipitously.

And I think that we would be better -- the time would be better spent -- or not saying it would be better spent. I'm sorry. I think that Paul's suggestion is a reasonable one, and I would argue that we should not defer for a lengthy investigation that is really a question of a factor of three.

PANEL MEMBER GLANTZ: You know, the other thing. This is Stan. I mean having been on the Panel longer than three years, forever -- almost. Not quite as long as John. I mean, these are the kind of discussions that we do have, and we're here to deliberate, and make decisions.

And, I mean, I think that the discussion here has been as substantive as I've ever heard. And, you know, I -- again, I would defer to people who know the biology

better. But the fact -- I mean it sounds, from what the OEHHA people say, that this was something in their discussions, in terms of preparing the document that could have gone either way.

And I think that good arguments have been raised for being more conservative. And so I think we should just move forward. And if -- in the future, I mean, there is a process, just for the people who haven't been on the Committee forever, where, if somebody, industry or someone, things there's an error in one of these documents or that there's new information, there is a process for, you know, bringing it back and getting it reconsidered.

PANEL MEMBER BLANC: Paul Blanc here. Jesús, also I want to say that my intention in the process I'm outlining, which is that we approve the document contingent on the change in the uncertainty factor and supporting text, leaves open the possibility for OEHHA, as they develop that supporting text, if they feel that they can't draft such text that is satisfying to them scientifically, then they would have to come back to us and say we can't meet the contingency of your approval.

And I think that leaves them the out that is appropriate, and also means that -- and I'm sure that in developing that text, they are going to look specifically, I think, at what's out there, which isn't going to be very

much. But to the extent that there has been some work on the dimer of butadiene, I think that's very relevant, which you were able to find easily.

Jesús, does that answer your qualms?

PANEL MEMBER ARAUJO: Sure. Yes.

CHAIRPERSON FROINES: Paul, at this point, what I'd like to do is to move us to a motion, and there can be discussion after the motion, but let's have a motion on the floor, so we can move forward.

PANEL MEMBER BLANC: I move that we accept the document contingent -- that we accept the document contingent on the major change of the use of an interspecies toxicodynamic uncertainty factor of 10 instead of the square root of 10, that there be supporting text explicating that decision, and the other minor textual changes that this record reflect. That's my motion.

PANEL MEMBER GLANTZ: I'll second it.

PANEL MEMBER HAMMOND: This is Kathy. May I speak to the motion?

CHAIRPERSON FROINES: Please.

PANEL MEMBER HAMMOND: Having been on the Committee an intermediate time, I have an intermediate position on this, I guess.

I am strongly moved by Paul and Beate's points.

I think that they're compelling points. And, to me, it brings me back to one of the moments that we think about under what conditions do we use the factor of 10 and under which one is the square root of 10. And I know OEHHA has prepared documents on that very point, that that's in those documents that they've given us.

And I guess I would like to -- I do think that there -- I think one needs to be able to justify going to the square root of 10. And in the absence of really strong data, I think one should use 10. The square root of 10 should be used when you can say there's less uncertainty than normal. I think that's the way that stands. So, I guess, I would like to, if anyone at OEHHA feels they can talk to the circumstances underwhich 10 or the square root of 10 should be used, that would be helpful to me, because I do think that this is a major change that hasn't been announced to the public or been on the website and all of that. So to make that change at this point, I would like to know that this fits within the realm of what's in the parameters OEHHA has laid out.

DR. SALMON: This is Andy Salmon here. The technical support document in question recommends the square root of 10 is the default value for this uncertainty factor. However, it very clearly lays out a number of specific instances where that would be regarded

as insufficient, and that a larger value should be used.

And it also, in several places, makes the point, that it's a matter for the individual expert judgment given the -- you know, given the evidence for the chemical being considered. And the use of the default is something which is not automatic, and, you know, always done whether it's justified or not.

On the contrary, it's pointed out that where more chemical-specific information is available, that needs to be considered in evaluating whether the default is -- the recommended default is sufficient or whether or not a value should be chosen.

That's how it's laid out in technical support.

PANEL MEMBER HAMMOND: So following along that lines, what I think I'm hearing then is that although the default is a square root of 10, and correct me if I'm hearing you wrong Andy --

DR. SALMON: No, that's right.

DR. BROWN: That's right.

PANEL MEMBER HAMMOND: -- but that some strong default, that it doesn't take a huge amount of evidence to move it back to 10.

DR. SALMON: It takes evidence, but --

PANEL MEMBER HAMMOND: Some evidence. And I think that I'm hearing -- you know, the comments I'm

hearing are that we have a sense that the different metabolic metabolisms of the compound leading to more potent chemicals give us a pretty strong reason to have an a priori species difference, not just saying there might be something we don't know, we can identify something.

DR. SALMON: No, we're not talking about metabolism here. We're talking about the toxicodynamics.

PANEL MEMBER HAMMOND: Oh, I thought there was some of it related to more of the dimer was formed.

DR. SALMON: The proposal, which Paul has made, relates to the toxicodynamics, and it relates to the point which Beate was making, in particular, about reasons of thinking why impacts on fertility, in general, would be more severe in the case that you made.

PANEL MEMBER BLANC: It has to do, Kathy, with the biology of reproduction in humans.

PANEL MEMBER HAMMOND: I do understand -- I had thought that your point and Beate's were distinctly different points. I didn't know that there was --

PANEL MEMBER BLANC: No, I got my question answered more about the toxicokinetics to my satisfaction. Otherwise, I might be saying we should be doing worse.

PANEL MEMBER HAMMOND: I was thinking of both sides.

PANEL MEMBER BLANC: Right. Right.

PANEL MEMBER HAMMOND: So in that case, given what Andy has said, and then, you know, what Paul just said, I think I would be in favor of this motion. It doesn't sound like it's as out of line as I was concerned it might seem to be.

CHAIRPERSON FROINES: Others?

Comments from other people?

Does somebody want to call the question?

PANEL MEMBER GLANTZ: I'll call the question. This is Stan.

CHAIRPERSON FROINES: I guess we have to do a voice vote.

PANEL MEMBER HAMMOND: Roll call.

PANEL MEMBER BLANC: Roll call is what you mean, John.

You want to call the names, John.

CHAIRPERSON FROINES: Peter, should call the names.

PANEL MEMBER BLANC: Peter, you want to call the names?

MR. MATHEWS: Sure.

UCLA. Jesús Araujo?

PANEL MEMBER ARAUJO: Yes.

CHAIRPERSON FROINES: He said yes.

MR. MATHEWS: Yes.

Beate Ritz, UCLA?

PANEL MEMBER RITZ: Yes.

MR. MATHEWS: Chairman Froines, UCLA?

CHAIRPERSON FROINES: Yes.

MR. MATHEWS: UC Berkeley, Kathryn Hammond?

PANEL MEMBER HAMMOND: Yes.

MR. MATHEWS: William Nazaroff?

PANEL MEMBER NAZAROFF: Yes.

MR. MATHEWS: UC Davis, Alan Buckpitt?

PANEL MEMBER BUCKPITT: Yes.

MR. MATHEWS: UCSF, Stanton Glantz?

PANEL MEMBER GLANTZ: Well, based on the discussion, I'm voting yes.

MR. MATHEWS: And lastly, Paul Blanc?

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: So it's unanimous.

PANEL MEMBER BLANC: John, is there anything else on the agenda or can one of us make a motion to adjourn?

CHAIRPERSON FROINES: I think somebody can make a motion to adjourn, with one exception, is that I'd like people to stay on the phone after we break -- after we make the vote, because I think that there's one other item that I would rather prefer not to have on the record.

CAL/EPA DEPUTY SECRETARY SOLOMON: Yes. Hi, John. This is Gina Solomon. I was hoping to raise

something that may be related to your issue or -- well, actually, I think it could be on the record. It should be the record.

CHAIRPERSON FROINES: So what is it?

CAL/EPA DEPUTY SECRETARY SOLOMON: I just wanted to update the Committee on the status of various appointments. As you know, the terms of the Committee members are staggered and three people -- three members of the Panel's terms expired on January 1st of this year, which is not a problem, because people continue to serve until reappointed or replaced.

So I'm happy to say that both Jesús Araujo and Alan Buckpitt have agreed to serve another term and should be getting their reappointment letters very shortly.

Unfortunately, Dr. Bill Nazaroff declined to serve another term. I'm hoping after today's discussion that maybe we could convince him to change his mind. I certainly tried, but he has a lot of other commitments and I totally understand.

So we were forced to seek another atmospheric scientist. And that appointment should be announced in the very near future. But I also would like to thank, on behalf of the Secretary, Dr. Nazaroff for his very, very important service on the Panel.

CHAIRPERSON FROINES: Okay. I think given that

Gina's comments we can proceed to move to close the meeting.

PANEL MEMBER GLANTZ: Motion.

PANEL MEMBER BLANC: Okay. I'd second Stan's motion to adjourn.

CHAIRPERSON FROINES: Any discussion?

So, Peter, take the roll.

MR. MATHEWS: UCLA, Jesús Araujo?

UCLA, Beate Ritz?

UCLA, Chairman Froines?

CHAIRPERSON FROINES: Wait. We have to get votes from everybody.

PANEL MEMBER GLANTZ: Well, why don't you just ask if there's any objection?

CHAIRPERSON FROINES: Why don't we just go around and finish this.

You're voting to close the meeting.

PANEL MEMBER ARAUJO: Oh, yes.

PANEL MEMBER RITZ: Same here, Beate.

CHAIRPERSON FROINES: Me, yes.

MR. MATHEWS: Okay.

PANEL MEMBER BLANC: Peter keep going.

MR. MATHEWS: UC Berkeley, Kathleen Hammond.

PANEL MEMBER HAMMOND: Kathryn Hammond votes yes.

MR. MATHEWS: William Nazaroff?

PANEL MEMBER NAZAROFF: Yes.
MR. MATHEWS: UC Davis, Alan Buckpitt?
PANEL MEMBER BUCKPITT: Yes.
MR. MATHEWS: UCSF, Stanton Glantz?
PANEL MEMBER GLANTZ: Yes.
MR. MATHEWS: Paul Blanc?
PANEL MEMBER BLANC: Yes.
MR. MATHEWS: That's it.
PANEL MEMBER BLANC: Meeting is adjourned.
CHAIRPERSON FROINES: Okay. I just wanted to give Bill a chance, if we wanted to to say something about his appointment.
PANEL MEMBER NAZAROFF: Or my non-appointment. So thank you, John. I do want to express my gratitude for the collegiality that I've experienced with the rest of you on the Committee during these three years of service. I've found it rewarding and it's just a matter of coming to a realization that I can accept working hard. I've done that through my whole career, but I reached the point where I can't do everything that's worthwhile at the quality that I want to give to it, and I have to cut back on some things.
And so this is just an area that I felt I couldn't continue to contribute to without it cutting into other things that I'm getting involved in now.

CHAIRPERSON FROINES: So we will miss you. You've been a great addition to the Committee.

PANEL MEMBER NAZAROFF: Thank you.

CHAIRPERSON FROINES: So speaking for the Committee, I would say thank you very much for your efforts.

PANEL MEMBER NAZAROFF: Thanks, John.

CHAIRPERSON FROINES: We're finished.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 5:11 p.m.)

C E R T I F I C A T E O F R E P O R T E R

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California;

That the said proceedings was taken before me, in shorthand writing, and was thereafter transcribed, under my direction, by computer-assisted transcription.

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

IN WITNESS WHEREOF, I have hereunto set my hand this 8th day of April, 2013.

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

4/9/2013
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