MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ON TOXIC AIR CONTAMINANTS

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

SIERRA HEARING ROOM, 2ND FLOOR

1001 I STREET

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

PANEL MEMBERS:

Michael T. Kleinman, Ph.D., Chairperson

Cort Anastasio, Ph.D.

Jesús A. Araujo, M.D., Ph.D.

Paul D. Blanc, M.D.

Alan R. Buckpitt, Ph.D.

Sarjeet S. Gill, Ph.D.

Stanton A. Glantz, Ph.D.(via teleconference)

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

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Peter Mathews, SRP Support Administration

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. John Budroe, Chief, Air Toxicology Risk Assessment Section

Dr. Daryn Dodge, Air, Community and Environmental Research Branch

Dr. Rona Silva, Air, Community and Environmental Research Branch

Dr. Kathleen Vork

Dr. Jianming Yang, Staff Toxicologist, Air, Community and Environmental Research Branch

I N D E X

I N D E X C O N T I N U E D

P R O C E E D I N G S

CHAIRPERSON KLEINMAN: Okay. I'd like to call this meeting to order. And I want to welcome you to the meeting of the Scientific Review Panel.

Peter, are you going to do a roll call or --

MR. MATHEWS: I can or you can.

CHAIRPERSON KLEINMAN: Why don't we just go around the table starting with Dr. Buckpitt, and just --

PANEL MEMBER BUCKPITT: Alan Buckpitt.

PANEL MEMBER BLANC: Paul Blanc.

PANEL MEMBER ARAUJO: Jesús Araujo.

CHAIRPERSON KLEINMAN: Mike Kleinman.

PANEL MEMBER RITZ: Beate Ritz.

PANEL MEMBER ANASTASIO: Cort Anastasio.

PANEL MEMBER GILL: Sarjeet Gill.

PANEL MEMBER GLANTZ: Stan Glantz.

CHAIRPERSON KLEINMAN: I think -- we don't have anybody on the phone, right?

MR. MATHEWS: Kathy is not here. That's the only one.

CHAIRPERSON KLEINMAN: Right. Okay. In that case, I want to welcome everybody here. We have a couple of goals for this meeting. We have 2 agenda items. And the first item is going to be a second review of the reference exposure levels for ethylene glycol mono-n-butyl

ether or EGBE. These are RELs that were developed using risk assessment methodology for developing RELs under the Air Toxics Hot Spots Program.

This document went -- underwent an initial review at the Panel's meeting in March of 2016. The Panel provided comments to OEHHA, and they made changes to the documents in response to those comments.

And the changes are reflected in the current SRP draft. The lead Panel members for this chemical are Drs. Buckpitt and Hammond. Dr. Hammond is not here today, but Dr. Buckpitt will lead the discussion. So we're going to start out with a presentation from the OEHHA staff on EGBE documents, and include commentary on the response to the SRP comments.

Then we'll discuss and provide feedback on the document. And the materials for the meeting were already provided to the members and are available on the website for the public.

So why don't we start with the staff presentation.

DR. BUDROE: Yes, we will. Good morning. And this is going to be a team presentation. Dr. Jianming Yang will be doing the slide presentation, and then Drs. Daryn Dodge and Rona Silva will be available for answering questions as well as Dr. Yang.

(Thereupon an overhead presentation was presented as follows.)

DR. YANG: Good morning. Hello. Hello.

Good morning, everyone. The following is for the EGBE SRP meeting. I'm going to present a draft document of non-cancer reference exposure level for ethylene glycol mono-n-butyl ether, EGBE.

Next slide, slide 2.

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DR. YANG: This slide shows current proposed RELs for EGBE. The acute REL is 4700 micrograms per cubic meter. It's based on human sensory irritation. The acute REL is the same as the last draft.

For the 8-hour and the chronic RELs, we are based on the nasal olfactory epithelium degeneration in rats. These RELs have a little change increase a little bit because we base it on the data from male and female rats combined.

The 8-hour REL is 164 micrograms per cubic meter, and the chronic REL is 82 micrograms per cubic meter.

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DR. YANG: Slide 3 is another proposed REL for the acute is no change. The last 8-hour REL is 150 micrograms per cubic meter. That is only based on female

rat data only. And the chronic REL is 77 micrograms per cubic meter.

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DR. YANG: Slide 4 is a case study for acute REL that derivation. We use the Carpenter study that include 3 human volunteers inhalation studies. Each study included 2 to 4 human subjects. And they use 3 different exposure levels with the whole body exposures.

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DR. YANG: Slide 5 is continued review of the case studiers. The exposure either 8 hours or 4 hours. And chronic effect is ocular and nasal irritation. We use the LOAEL 98 ppm as the point of departure.

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DR. YANG: Slide 6. The acute REL is a no time adjustment is needed. The LOAEL uncertainty factor equal to 10 by default. Interspecies uncertainty fact equal to 1. Intraspecies toxicokinetic UF equal to 1, and intraspecies toxicodynamic UF equal to 10.

So the cumulative uncertainty factor is 100. We go to the acute REL is 4700 micrograms per cubic meter.

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DR. YANG: Slide 7. This is for 8-hour and chronic REL derivation. We use the NTP 2-years inhalation studies in rodents. The sample size is 50 per sex per group of rat or mice. The exposure is 6 hours per day, 5 days per week for 2 years.

For rat, the exposure concentration is 31, 62.5, and 125 ppm, plus control group. For mice, the exposure is 62.5, and 125, and 250 ppm.

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DR. YANG: Slide 8 is continue REL of the case study for the 8-hour and the chronic REL. We are mainly focused on the non-neoplastic effects in rats. The effect incurred hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation in liver.

In mice, include forestomach ulcers and epithelial hyperplasia, hematopoietic cell proliferation, and hemosiderin pigmentation in the spleen, hepatic Kupffer cell pigmentation, and bone marrow hyperplasia. This is the males only.

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DR. YANG: Slide 9 is for 8-hour REL derivation. The critical effect is rat in nasal hyaline degeneration.

The point of departure is 8.2 ppm. Time-adjusted exposure is equal to the point of departure multiple the 6-hour per day and multiple 5 days per week, pique and was a multiple of 20 divided 10 formula. We got 2.9 ppm.

Human equivalent concentration is time -- equal to time-adjusted exposure multiple regional doses -- regional gas dose ratio equal to 1 ppm. The cumulative uncertainty factor equal to 30. We got the 8-hour REL at 164 micrograms per cubic meter.

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DR. YANG: Slide 10 is for the chronic REL derivation. This actually is the same as the 8-hour REL derivation, except the time-adjusted exposure with other multiples of 10 divided -- multiplied 12 -- 20 divided by 10 formula. So we go to the chronic REL equal to 82 microgram per pubic meter.

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DR. YANG: Slide 10. These are the SRP comments from the last EGBE SRP meeting.

Update old production and usage information with more recent findings; add information regarding measured EGBE concentrations outdoors; include EGBE air concentrations following use of clean products and add

associated paper by Nazaroff; present high EGBE concentrations measured indoors, not just mean values.

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DR. YANG: Next slide is OEHHA response. We checked the ACC and the ACS publications. We updated the most recent annual EGBE production in the U.S., and we also added our favorite in the draft document.

The outdoor concentration of EGBE measured by Daisey and Nazaroff and Weschler, Singer were added. We also include the maximum concentration from the several studies.

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DR. YANG: Slide 13, SRP comments. Clarify hot spots reporting and add California emission trends.

OEHHA response. We added California Toxics Inventory EGBE emission at the tons per year. And we also add a figure for this in the draft document.

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DR. YANG: Slide 14 is the SRP comment about the toxicokinetics part.

General comments. Reorganize the section to increase consistency and clarity; emphasize the importance of inhalation exposure, and discuss the study by Corley

first, then summarize the study limitations of Johanson and Boman that used finger pricks versus venous blood draws; include papers by Hung and Korinth regarding toxicokinetics and occupational dermal exposure to EGBE.

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DR. YANG: Slide 15 is OEHHA response. The section 4 toxicokinetics has been reorganized as requested. We discussed the Corley, and Johanson and Boman studies. We also included Hung and Korinth study in the section 4.1.

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DR. YANG: Slide 16 is OEHHA comments -- is SRP comment. In the metabolism and elimination section provide a table of the different studies and separately discuss differences due to species, age, and metabolic patterns.

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DR. YANG: Slide 17, SRP comment continued.

Include additional table of metabolics -- metabolites, with percentages of each excreted from mice, rats, and humans, and change the structural formulas in the figure 3 to conform ACS journals; evaluate

butoxyacetic acid, BAA, as a biomarker of exposure and clarify the term "urine half-life".

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DR. YANG: Slide 18 is OEHHA response. We added the subsection 4.3 about species differences in metabolism and elimination of EGBE and the subsection 4.4 about age- and sex-related differences in rodents.

We also added table 4 and modified the EGBE metabolism structures as requested remove that in the figure.

Clarified the total urinary BAA as the most appropriate biomarker of the EGBE exposure, and urinary elimination half-life was defined.

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DR. YANG: Slide 19, SRP comment.

Unclear description of metabolism and urine EGBE and BAA conjugation in rats and humans.

OEHHA response. Metabolism discussion revised and clarified in response to comments. I remember our original discussion for the toxicokinetic part. We only have the 5 pages, but in all it's 11 pages.

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DR. YANG: Slide 20, OEHHA response continued.

Description of urinary metabolites of EGBE has been discussed in greater detail. In rats, free BAA is the primary metabolites, but a small amount of EGBE glucuronide, and EGBE-sulfate conjugates are also secreted in urine.

In humans, urinary secretion of BAA is mainly in the form of BAA conjugates with glutamine, a small -- smaller amount is excreted as a free BAA.

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DR. YANG: Slide 21, SRP comment

PANEL MEMBER BLANC: Just what do you mean by smaller? What do you mean by that?

DR. YANG: Smaller, yeah, I think it may be even less than 10 percent or something. But I suppose we will make -- we will arrange these better, this small or larger. Smaller is not a clear term. I'm sorry for that. Yeah, yeah. I guess is less than 10 percent, yeah, yeah, yeah. Yeah, I suppose give a definition of that. Sorry.

PANEL MEMBER BLANC: Yeah, because all of the issue of the hemolysis revolves around whether or not the free acid is present or not present. I think it's why you have to be a bit more meticulous.

DR. YANG: We better, you know, yeah, clarify

that. Yeah, I understand what you mean. Yeah. Thank you. Yeah. Yeah.

Actually, you know, in humans, for that, you know, the variations were bigger. You know, some people conjugation may be in more than 90 percent in some people and maybe less than 10 percent. But yeah, yeah -- but I think we read in the draft document for the slide, yeah, yeah.

Daryn will --

DR. DODGE: Yeah. This is Daryn Dodge.

By smaller amount, generally meant smaller than the conjugate form. It is sort of a general comment there. But in humans, about one-third of 24 BAA conjugates, and then the free form, and about two-thirds of it is conjugate with glutamine.

It's kind of spelled out here in table 4 on page 21. The proportions of the metabolites -- urinary metabolites.

PANEL MEMBER BLANC: Sorry.

DR. DODGE: And you can make comparisons with the percent of BAA released or found in urine in this table with the animal studies as well.

DR. YANG: Yeah, so you can see the variations were bigger, but yeah.

PANEL MEMBER BLANC: I'll be happy to follow up

when we get to that -- to the discussion.

DR. YANG: Okay. So next slide.

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DR. YANG: Slide 21, SRP comments include separate subsection for acute and chronic animal studies; 2, controlled human exposure studies; 3, accidental inhalation, dermal, and acute oral ingestion (poisoning) case studies; 4, add a table of toxics sequelae.

Discuss human exposure study by Bauer, Hung, and Rella.

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DR. YANG: Slide 22, OEHHA response.

We added the subsections 5.1.1 and 5.1.2 in the revised document and summarized human inhalation studies, including occupation and chamber studies, and high-dose oral exposure, respectively.

Table 5 include a summary for clinical responses observed in several human oral poisoning case studies.

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DR. YANG: Slide 23, SRP comment.

Qualitative evaluation is needed of the studies presented, including their strengths and weaknesses.

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DR. YANG: Slide 24, SRP comment continued. Example, the key acute REL study, Carpenter study, is limited by unstated purity of test substance, imprecise performance of inhalation exposures, questionable test substance measurement methods with unknown error and the poor reporting.

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DR. YANG: Slide 25, OEHHA response.

Limitations and advantages of the Carpenter study, and other human chamber studies are now discussed in sub -- in section 8.1. We added a discussion of potential impurities and measurement method; and additional support for basing the acute REL on Carpenter study is presented.

For example:

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DR. YANG: Slide 26, human toxicokinetic studies, such as Johanson study has better methods, but tested a single dose only established a free-standing NOAEL, had small sample size, and mainly focused on the ADME. There is a high risk of miss some adverse effect.

Carpenter study has 3 dose groups, was designed

to examine irritation effects addressed at both subjective and objective symptoms and established the LOAEL.

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DR. YANG: Slide 27 is OEHHA response continued.

For REL derivation, a study with LOAEL is preferred study with only free standing NOAEL. This is based on the OEHHA guidance on the 2008.

A new table, Table 9, added compares NOAEL and LOAEL for the red blood cell hemolysis in rodent EGBE exposure studies.

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DR. YANG: Slide 28, OEHHA response continued.

The NOAEL and LOAEL in rodents from Carpenter study was roughly 2-fold greater compared to the NOAEL and LOAEL in later rodent studies by Tyl, NTP, and Dodd.

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DR. YANG: Slide 29. SRP comment. Given the subpar quality of the Carpenter study using today's standard, it may be helpful to discuss how the draft acute REL would change if the Johanson study was used, and whether the study is more appropriate for setting the a cute REL.

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DR. YANG: Slide 30, OEHHA response. We added a discussion comparing the 2 studies using the Johanson study 20 ppm free-standing NOAEL as a point of departure, an intraspecies uncertainty factor equal to 10 is applied resulting in an acute REL of 2 ppm. This value is twice the REL value of 1 ppm that was derived from the Carpenter study.

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DR. YANG: Slide 31, SRP comment.

How does incidence of nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, forestomach epithelial hyperplasia, and forestomach ulcer in NTP study compare to historical NTP controls.

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DR. YANG: Slide 32 is OEHHA response. Referring to the pathology tables for all routes/vehicles on the NTP historical control database, we cannot find related data. Historical incidence data were available primarily for tumor and cancer endpoints.

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DR. YANG: Slide 33, SRP comment.

Perform a trend test on NTP incidence data to show a monotonic relationship between the dose and the response. Add the sex variable to test whether there is a significant difference between male and female rats. If there is no difference, combine data from male and female rats and model them such that the 31.2 ppm exposure dose is the LOAEL for the nasal hyaline degeneration endpoints.

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DR. YANG: Slide 34, OEHHA response. Cal Cochran-Armitage trend test P-values from the BMDS has been added to the table 8 to show the dose response relationships

Logistic regression was performed to determine the relation between rat sex, EGBE exposure, and incidence of olfactory epithelial hyaline degeneration.

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DR. YANG: Slide 35, OEHHA response. A Wald test indicated that sex was not a significant factor for nasal olfactory epithelial hyaline degeneration in rats. Combining male and female rats for the BMCL estimation is applicable for the nasal endpoint.

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DR. YANG: Slide 36, incidence of nasal olfactory epithelial hyaline degeneration from male and female rats in the NTP 2-year study was combined.

The BMDL from combined male and female rat data serves as a point of departure to develop 8-hour and chronic RELs. The calculated 8-hour and chronic RELs are 164 micrograms per cubic meter and 82 micrograms per cubic meter respectively.

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DR. YANG: Slide 37. Other changes to the document.

Clarified ambiguous terminology, such as significant and reasonably. Some mouse parameter data was excluded in table 10, as trend tests suggested there are no significant dose responses. No significant difference was observed by pairwise comparison for the severity of hyaline degeneration in high-dose exposure between male and female rats.

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DR. YANG: Next slide. Questions part.

PANEL MEMBER BLANC: Wasn't there one more slide you have?

DR. YANG: One more?

DR. BUDROE: No. We had a slide that should have been dropped from the presentation.

PANEL MEMBER BLANC: Okay.

CHAIRPERSON KLEINMAN: Okay. Thank you very much for going through the changes that were in the document. I'd like to open it to Dr. Buckpitt to lead off the discussion.

PANEL MEMBER BUCKPITT: Yes. Good morning. I'm going to make this very brief. I would compliment OEHHA on really revising their report significantly and doing a pretty good job of doing that.

As you might remember, I had a lot of problems with the use of the Carpenter study, the 1956 study. And I think in the revised document, OEHHA does a very good job justifying the use of that study, showing -- essentially discussing all of the limitations of the study, and showing the reasons for its use in setting the acute REL. So I thought that was very well done.

The addition of the information on exposure levels, the updated information on levels out in the atmosphere I think really work quite well. The toxicokinetic and metabolism studies are now in a table. For me, it was much easier to read and to understand. Certainly, I felt in the original document, animal studies were included with the humans. And I had a lot of trouble

following the logic in that. It may be my problem. But the addition of the table, the separation of the animal from human studies I think really worked well.

And I think overall the revised document is clearly organized. It uses tables to present the summaries. It is more evaluative. It showed that you'd look at the data and said, all right, these are the strong points of the studies, these are some of the limitations of the studies. I think that's really important when you go through and use a study to set your routes.

So I was quite satisfied with the revised document. And that's pretty brief.

CHAIRPERSON KLEINMAN: Thank you.

Okay. I'd like to open it up to the rest of the Panel.

PANEL MEMBER BLANC: Do you not have any comments from the other lead at all? And I understand she's not here, but she should have supplied you with some written comments.

CHAIRPERSON KLEINMAN: I didn't receive any.

PANEL MEMBER BLANC: I think then the minutes should reflect that there were no comments at all received from the second lead.

And I would urge that in the future if a lead can't be present at a meeting, that they be required to

submit some comments.

CHAIRPERSON KLEINMAN: Yeah. I did check back before I came up and I had not seen any commentary from her.

John, you didn't hear anything from Kathy?

DR. BUDROE: No I have not received any comments -- written comments or email from Dr. Hammond.

CHAIRPERSON KLEINMAN: Thank you.

Sarjeet.

PANEL MEMBER GILL: Mike, I was not here for the previous meeting the first time the revision went, but I actually -- one of the things I'm still a bit unclear as to -- this compound has not been regulated right now, is it, or is this the first time the REL study has been made?

DR. BUDROE: No, there is a -- the REL is being revised in response to the new methodology.

PANEL MEMBER GILL: Okay. So one question I have is I do not see actually in item 3 point source emissions. Any particular part that says how much is being emitted as to why that levels are exiting at certain levels in the environment, as to on the basis of why certain regulations is being put to monitor toxic exposure?

In section 3, correct, that's where you wanted production. Major uses and occurrence is fine. And the question is concentrations and emission rates occurs in

table 2. The reason -- my only question is I was a bit still confused as to whether the levels are still in -- are exceeding the REL levels or not? That's the only question I have. It was not clear to me.

DR. BUDROE: Right. Well, for example, the section 3, table 2 and table 3 are actually indoor air emissions rates, and would not -- you wouldn't necessarily -- wouldn't apply a REL to it. They are not regulated under the Hot Spots Program, so they're more for informational purposes.

PANEL MEMBER GILL: So my question is where is the information on the basis of why the hot spots issue comes up, so that you are now developing a REL for that -- a revised REL?

DR. BUDROE: Well, where it would come up would be, for example, if you had -- if an individual facility that was using EGBE say for degreasing, let's say, and emissions from those processes were going out into the surrounding community, the facility would have to model those emissions and would have to apply the RELs to those emissions to get either acute or chronic hazard indices.

PANEL MEMBER GILL: So where in the document is there an example of where that documentation is present that those levels are exceeding certain levels that, therefore, implementation of a REL is needed?

DR. BUDROE: Well, EBGE is a chemical that's required to be quantified under hot spots. But, I mean, hopefully, you would hope that none of the facilities would be -- you know, wind up putting out a concentration in the communities exceed the REL. I mean, this is more for preventing -- hopefully, for preventing that from happening.

But that goes more to the risk management side, which Air Resources Board, more importantly the air districts handle.

PANEL MEMBER ANASTASIO: Can I ask a related question?

So in the studies that looked at occupational concentrations, some of those were well above the REL. And I know that's not an ARB issue, but how can we communicate that to whomever it is an issue? Is this an OSHA issue or --

DR. BUDROE: It would probably be a U.S. OSHA or Cal/OSHA issue.

PANEL MEMBER ANASTASIO: And is there some way that the information that ARB -- or sorry, OEHHA has revised the REL can somehow be communicated to them, so that they might realize it's an issue for occupational exposures?

DR. BUDROE: That's something that OEHHA doesn't

really have statutory authority for. Certainly, if, you know, the concerned public were to see the EGBE REL, and if they knew that occupational exposures were exceeding the REL, that they might comment to Cal/OSHA, and suggest they take that up as an issue, but --

PANEL MEMBER ANASTASIO: But there's no line of communication between OEHHA and Cal/OSHA on this?

DR. BUDROE: No, there is no direct statutory line.

PANEL MEMBER ANASTASIO: Yeah.

CHAIRPERSON KLEINMAN: But the RELs are designed for general population, not for the occupational population, and so the guidelines are totally different. You would -- I doubt very much whether you'd find any occupational, you know, PEL that was as low as an REL, because the RELs take into account, you know, the much broader spectrum of human susceptibility than in the workplace.

PANEL MEMBER ANASTASIO: Yeah. But I would think something like the 8-hour REL would be appropriate for a workplace. I don't know. Paul is shaking his head at me.

PANEL MEMBER BLANC: From your mouth to God's ears.

(Laughter.)

PANEL MEMBER BLANC: It should only be.

PANEL MEMBER ANASTASIO: It only be.

PANEL MEMBER BLANC: But it's never going to be.

PANEL MEMBER ANASTASIO: It's not going to be. Okay. All right. Thank you.

CHAIRPERSON KLEINMAN: I suspect that when PELs are laid out, the REL, if it exists, is looked at, but in general, they -- you know, I think it would be considered, you know, over-conservative for much of the working population to -- you know, because we're trying to set up protections under the RELs for children, for very susceptible people that would not, you know, enter the workplace.

But, you know, it's a good point that, you know, it certainly should be looked at, you know, for something that is considered to have a very low REL. One would need to, you know, see how that fits in with the potential for risk to the healthy worker.

DR. BUDROE: We have been invited to PEL working group meetings from time to time. It's just -- it's not an automatic thing.

CHAIRPERSON KLEINMAN: Okay. Dr. Glantz, did you have any comment?

PANEL MEMBER GLANTZ: No. I did read everything, but I think that the main issues were -- had to do with the toxicological questions not the areas that I have

particular expertise. And from what I can see, as somebody who's read a lot of these, I agree that I think the OEHHA people were quite responsive.

CHAIRPERSON KLEINMAN: Dr. Ritz, do you have any comments?

PANEL MEMBER RITZ: There's very little epidemiology in here, so -- but I did read with interest all of the toxicology, and I thought that was described quite well. So the only note I had was on page 36, 37 where a chronic toxicity study in infants and children was described. And when the indoor air concentrations are mentioned, the text jumps from milligram per cube to micrograms per cube between the cases and controls. And that's kind of hard to -- you have to kind of translate that.

So throughout I would recommend that, you know, those kind of units should be stated in the same way, especially when you are comparing cases and controls. But otherwise, I thought it was very readable.

PANEL MEMBER ANASTASIO: Just one note about that. The same thing happens in sections 3.3 and 3.4, you know, between milligrams per cubic meter, micrograms per cubic meter. It would be helpful I think if all the units throughout the document were expressed as the same units as the REL itself, so you don't have to do the -- I mean,

it's a factor of 1000, which isn't that big a deal, but it -- it makes it a little more complicated than it needs to be.

CHAIRPERSON KLEINMAN: Dr. Blanc, do you have any other --

PANEL MEMBER BLANC: You don't? What are you chopped liver?

CHAIRPERSON KLEINMAN: Well, no --

PANEL MEMBER ARAUJO: I come after you.

PANEL MEMBER BLANC: All right.

CHAIRPERSON KLEINMAN: Just going up the line.

PANEL MEMBER BLANC: Okay. So first, I want to preface this by saying none of my comments should be comments that would require a resolution where the document needs to come back yet again to the Committee, but should be considered in minor revisions that might happen with a resolution accepting the document, pending such revisions. That's the first thing.

So I want to -- and I was lucky in a way that I hadn't been involved in the previous discussion, so the document I read de novo was the revised document to address some of the confusions. And yet, there were certain key topics areas in which I still was not completely clear reading it. So let me walk through what I understand the implications of the toxicology is, in

terms of what the sensitive endpoints were that you used to derive the standard?

And obviously, the big -- the big issue is red blood cell fragility and hemolysis, which is an issue for rats and rice, and much less of an issue for other species. And that's why I asked the question about what does less mean.

DR. YANG: Yeah, yeah.

PANEL MEMBER BLANC: But the actual numbers that you have show pretty wide variation. And this comes to whether there are sensitive subpopulations in humans that for whom the metabolism of this chemical would lead to the free acid that was not conjugated. And are you -- are you putting your 2 cents down on the factor which is the link between the red blood cell fragility in rodents. Greater fragility is greater proportion of the free acid that that is in fact the mechanism?

Because there was a little bit of -- if that's in there, it's kind of buried in there, because that would have implications for the relevance of that endpoint, right? If you believe that the 10 percent of humans have equivalent levels of the acid to a rodent, then any data that suggests there's a subpopulation of humans that would respond like a rodent becomes quite relevant.

You clearly showed that in 1 or 2 of the overdose

cases there was some hemolysis. But then when you discuss these, there was one interesting study which did show some red blood cell effects. And then you said, well, we're discounting that because the fall in hematocrit was still within normal range, which I found not a reasonable reason to reject the study.

There's a small matter, and this you really do need to correct. The other -- this is more nebulous, and you can explain it to me maybe, and go back yourselves and decide what -- how you might handle it. But there was one point where you said there was a 3 percent fall in hematocrit, and that was not clinically meaningful. It was statistically significant.

Well, hematocrit is usually reported as percent. So I don't know if you mean 3 percent of the percent hematocrit or you mean a 3 percent fall? A 3 percent fall in hematocrit would be a transfusion of 1 unit of blood. So that's not trivial at all. In fact, that's clinically when you say somebody actually really is losing blood somewhere.

Now -- so I don't know what you meant, because I didn't go back and pull the study and read it. But you should either clarify that it was a percent of a percent that you're talking about, and what the actual percent hematocrit fall was, or you should delete the comment that

that's not clinically meaningful.

DR. BUDROE: Okay. So we need to clarify whether that's an absolute or a relative decrease.

PANEL MEMBER BLANC: Right. And then -- and I don't think that the argument that whatever fall there was, they still weren't outside the range of normal is the point, right? Because you're talking about whether it's real or not, not did they become clinically anemic. You know, is Group A of workers clinically -- this is, I think, the decal workers in Taiwan, wasn't it, if I recall correctly?

DR. DODGE: Yeah, that was one of the studies where they did see a reduction, or a -- in red blood cells. But that study, the exposed group also had a lot of dermal exposure. So that was probably the main reason they were seeing some slight reductions.

PANEL MEMBER BLANC: Well, I don't think you were going to try to use it. You were mixing apples and oranges.

DR. DODGE: No, we couldn't use it.

PANEL MEMBER BLANC: I'm not saying you should use that to get a REL. You couldn't anyway. But if the argument is hemolysis is not a relevant endpoint in humans, therefore we shouldn't use any rodent study with hemolysis, and then you have a human occupational study

that shows that there's some effect on red blood cells, it undermines that argument.

And similarly, if the argument is the reason why it matters in rodents and it doesn't matter in humans is because we conjugate and they don't, and then you say, but, you know, about half the people don't conjugate, that's also, you know, not reassuring, shall I say, or has to be dealt with in a more head-on way.

If you -- you can say it's a limitation or we realize this, but even so. So I'm not saying go back change your REL, but I think that the logic of some -- at some points in the document, the logic is not convincing, or my disbelief is not suspended, or whatever, you know, euphemism you want to use.

DR. DODGE: Right. We include a sentence, I believe, in the chronic REL section where we look at these occupational studies and decided that there just wasn't enough evidence there to really base a REL on hemolysis.

PANEL MEMBER BLANC: And I'm not --

DR. DODGE: But we could -- what you're saying is we really need to go into that a little more instead of just stating that we didn't think --

PANEL MEMBER BLANC: Well, and the rationale for stating it was partly, you put in parentheses, an per the EPA this is still with -- the fall was still within the

normal range. And I don't -- that's not a legitimate argument whatsoever, in my view. That's not a public health protective argument, you know, that the workers weren't frankly anemic, and therefore, it wasn't a real effect, or it wasn't a substantive effect.

Does that make sense?

DR. DODGE: Yes.

PANEL MEMBER BLANC: I'm not arguing go back and redo the REL. I'm -- these are things that I think you can deal with, but you -- I think could be dealt with better. And in a similar vein, the key, you know, table, figure that -- that's in the current document, which is the metabolism. And I guess you -- what you did was you put in structures there or something in response to the previous -- I didn't -- it's on page 14, and it's adapted from two different sources, right?

So, I mean, that's a pretty key figure for anybody reading this document, right, that's trying again to get at this question of the free acid, right? I mean, you would agree with that?

DR. BUDROE: We would.

PANEL MEMBER BLANC: Yeah. So the glutamine conjugate, which is the dominant one in humans, first of all, you can't tell from that figure that the glycine conjugate is a trivial human metabolic pathway, right? I

mean, you say that elsewhere, but the figure could put in that same parentheses -- first of all, you don't mean -- do you mean human only? You don't know that other primates don't. You just mean that non-rats or something, right?

DR. BUDROE: Correct.

PANEL MEMBER BLANC: So you might -- I mean --

DR. BUDROE: Well, it's -- I mean, we could -- it would be kind of difficult to put all of the qualifiers in the actual graphic.

PANEL MEMBER BLANC: I would just put humans only, not -- not present in rats and mice, or something. I mean, that would be my own choice. I don't live or die by that, but it's a little misleading. But in any event, I think you could say minor and major, you know, in the same thing. And without -- without only -- if you'd said minor human metabolic pathway, major human metabolic pathway.

But the other question is do you really think there's an equilibrium that once it goes from the conjugate to the acid, some of it goes back to the conjugate? I mean, that seems really unlikely to me. Isn't it a one-way thing? Is that really what you adapted from indicated, or did you just pro forma use the bidirectional arrow?

DR. YANG: Yeah, I think it's one way, because we adopted this figure. In that case, ATD, ATDS and others suggest one-way is not --

PANEL MEMBER BLANC: So shouldn't you change that?

DR. YANG: Change one-way. We can change it one-way.

PANEL MEMBER BLANC: I mean, that would be clearer, because that just kind of like really confused me when I saw that.

DR. BUDROE: Okay. We can clarify the structure there.

PANEL MEMBER BLANC: And then, as I said, I would put your 2 cents down if you're making the argument that the reason why humans are generally resistant is because, generally speaking, much less of it becomes the acid or not. You should -- you could say that more clearly somewhere.

PANEL MEMBER GLANTZ: You know, one, way just as a reader, to deal with, I think what Paul is suggesting, might not be to make big changes to the figure, because I can see how you'd want to make that so complicated. You could simply add it to the caption to explain what these different things mean.

PANEL MEMBER BLANC: Except for arrow. That's

simple to change.

PANEL MEMBER GLANTZ: Yeah. Well, then the arrow is a different question. But I think in terms of the relative importance and human only.

PANEL MEMBER BUCKPITT: While we're on that figure, can I make one more comment?

Your sulfate could use a couple of oxygens, I think.

DR. BUDROE: Excuse me?

PANEL MEMBER BUCKPITT: Your sulfate could use a couple of oxygens.

PANEL MEMBER BLANC: Those were deleted there in the second line. They fell out at some point.

So anyway, that was, you know, the -- you know, one thought I had.

So the -- and then coming back, again not asking you to redo your stance, but this more sort of for my own clarity. You had this old Carpenter study that you were forced to use, because that's -- because you want -- would rather use the one with the low effect level than a single test with a no effect level.

But, you know, the no effect level study, it's actually a pretty close exposure level, right, for the acute? One is 98, and one is --

DR. YANG: 106.

PANEL MEMBER BLANC: -- 86 or something. I mean, it's really pretty close, right? It's not even half the Johnson[sic], or whatever his name is, is that correct? Do I understand that correctly?

DR. DODGE: Yeah. In the metabolism studies, they were looking at one concentration. One was 20 parts per million --

PANEL MEMBER BLANC: Per million.

DR. DODGE: -- the other was around 49 parts per million. And the Carpenter study LOAEL was 98 parts per million.

PANEL MEMBER BLANC: Oh, it was that much lower. Okay. I got confused again, because the milligrams per meter -- I thought the Carpenter was all in milligrams per meter. Are you sure about what you're --

DR. YANG: It is 98 ppm.

DR. DODGE: Ninety-eight parts per million was the Carpenter.

DR. YANG: Yeah, yeah. 98 ppm, Carpenter.

PANEL MEMBER BLANC: And 20 part per million for the other.

DR. DODGE: Yeah, 20 and 49 were NOAELs.

PANEL MEMBER BLANC: Okay. And the -- you know, I know that you go through this thing where you say if we use the 20 parts per million as a NOAEL, you would come

out with a level that was twice as high as the level that you'd come out with with the Carpenter study. But that's partly explained by the uncertainty factor of 10 for the small study size, isn't it? I mean, if you used an uncertainty factor of 5, you'd get exactly the same number.

DR. YANG: That's right. Yeah, that's right. Yeah.

PANEL MEMBER BLANC: Right?

DR. YANG: Yeah, yeah, yeah.

PANEL MEMBER BLANC: So in a way, it's a -- it's somewhat artificial in a sense. I mean, I'm just pointing that out. You know, you're never going to get a fight with me about being public health protective. But I just want to point that out that, you know, even a sentence that said that would -- you sort of -- it underscores that it's not crazy to use Carpenter, if that's -- you know, if you feel like you need to defend it more.

So those were some of the areas in which, you know, just reading it as a naive reader, not having been involved in the last discussion, you know, struck me as areas that the argument could be better presented.

And then the only other substantive thing, and again I'm not asking you to bring it back to the Committee, but in your -- oh, one really tiny thing.

Where you say you had a personal communication from somebody, and it was from 2005 --

DR. DODGE: Yes.

PANEL MEMBER BLANC: -- I guess that was a personal communication at the time that you had a previous document. Obviously, you haven't been working on this documented for 10 years.

DR. DODGE: Well, EGBE was -- we were asked to look at that from the Integrated Waste Management Board, because they had some indoor levels of EGBE that was kind of high. So we did some preliminary work way back when, and developed a unofficial indoor REL value for them.

PANEL MEMBER BLANC: So all I would say is I would add 3 words there or something, "At the time of a previous agency review", or something, because it really sort of strikes one as odd, right, just...

And the other thing is if you know -- I know you said these other -- the Johanson and the other paper didn't -- were studying metabolism, so they weren't structured to look at sensory complaints. That wasn't an endpoint that they studied.

So they don't say anything about sensory irritation. So you take that as a no, right? I mean, that was what you meant basically, right?

DR. DODGE: In their written report, yes, that's

correct.

PANEL MEMBER BLANC: They don't talk about it one way or the other, right?

DR. DODGE: No, they don't.

PANEL MEMBER BLANC: Do -- and these are papers or reports? Reports? These are papers?

DR. DODGE: Published reports.

PANEL MEMBER BLANC: Published papers, right?

DR. DODGE: Yeah.

PANEL MEMBER BLANC: Do they report that any subjects had to terminate the exposure protocol or did everyone who started it, complete it?

DR. DODGE: I believe everyone that started it did complete it.

PANEL MEMBER BLANC: Because that might be worth saying literally, right? Because if somebody had a whole lot of eye irritation, they've unlikely to continue for 4 hours.

DR. DODGE: Right. We would definitely have included that, if we had known that happened. And I don't think it happened in those studies.

PANEL MEMBER BLANC: Well, I would report the negative. I mean, it supports your argument. I'm just trying to find out ways of, you know -- and they did not report that anyone terminated the study, right?

DR. DODGE: Right.

PANEL MEMBER BLANC: So the only other thing I want to ask you about is in your review of the literature, did you ever deal with or encounter the issue of immune modulation from this chemical?

DR. YANG: No, not at all.

PANEL MEMBER BLANC: So it's been an issue with glycol ethers. And there is one relevant study of this chemical as an immune modulator, in terms of blunting the T-cell response. And the same authors did a previous paper.

And I think it -- for completeness sake, you may want to say something about it. It's been an issue with this, in terms of the asthma argument. Because if something were an adjuvant or, in some way -- you know, in some cases, it could promote, in other ways suppress immune response.

So I'd -- I'm happy to give you the one reference, but it may lead you to a few others, and might cause you to write 3 sentences, and add a couple of references. But I think if somebody reading the document who's concerned about that with this class of chemicals, in general, and the specific chemicals might want to know that you -- it's not that you didn't know anything about it, it's just that you -- it wasn't -- in the end, there

wasn't enough there to drive you towards...

DR. BUDROE: We can do that.

PANEL MEMBER BLANC: That's it.

CHAIRPERSON KLEINMAN: Okay. Jesús.

PANEL MEMBER ARAUJO: That's why I have to come after you. So I don't have really anymore comments to say.

(Laughter.)

PANEL MEMBER ARAUJO: That was a very -- I would agree, you know, that it's important to be precise in the changes on the hematocrit. I also think that it's -- but aside from that, I don't really see -- I think that it was a clear document. It was an improvement from the previous version. And I will have to say that I didn't really pick up so many of the findings that Dr. Blanc mentioned, but I think that those are -- seem to be all appropriate.

PANEL MEMBER BLANC: You know this use in window cleaners, which is sort of on the fourth page there's one line about it's used big in that. I mean, that's -- you know, that's the elephant in the room with this chemical, right? This is where tons and tons and tons of it are used.

So the fact that that appears kind of one place in one line is -- it's your editorial judgment, but -- isn't it also used in foams for fire control? One of the

studies is of, you know, firefighter's doing a controlled airplane disaster simulation thing?

DR. YANG: I cannot recall that. If -- if we, you know, the -- let's --

DR. BUDROE: No, it doesn't pop up as --

PANEL MEMBER BLANC: Could you double check that though, and may be that might be something you'd throw into that paragraph --

DR. BUDROE: Okay.

PANEL MEMBER BLANC: -- where you talk about uses, if that's really true. Because I think one of the papers that is you know -- thanks.

CHAIRPERSON KLEINMAN: Sarjeet.

PANEL MEMBER GILL: Just for completeness sake, on page 15, line 310 to 311, just delete the last phrase after "shift", because that's an opinion, and that's not validative for the opinion. On line 310. Line 310, page 15. Just delete the last phrase, "Indicating slight accumulation of relatively slower elimination". There's no basis for the judgment in that. Just delete that phrase.

DR. YANG: Okay. Okay.

PANEL MEMBER GILL: It doesn't make any difference actually. As one reference, at least I found, which is not listed is Boatman, 2014. Regulatory

Toxicology's review by Boatman, you may want to just for completeness sake.

So I just have one other question is because one of the concerns I had was exposure levels indoors are very high. But I know the REL is far outside. So the question is on how does REL levels really affect people who are working, and at the same time have high exposures indoors, like window cleaners, for example, in a point source?

I know that's not your -- that's beyond your judgment, beyond your authority. But just as a curiosity, how would he affect it?

Because exposure levels of individuals are actually relatively high, because of the source in which it is being used.

PANEL MEMBER BLANC: Just to clarify, I think what he's asking is, you know, if we thought this was also a contaminant of water, there's been cases where we've taken into account total exposure from different routes and how the air level could contribute to that. I can't think of -- I think we've -- we've dealt with this in the past. So I think the question is, okay, now we're not talking about people get it in their drinking water, plus they're inhaling it, although they could, but we're talking about people get it outdoors in a sort of a low level, and indoors in a sort of high level. I mean,

wasn't that part of the issue with the secondhand smoke exposure issues? Stan, do you remember that?

PANEL MEMBER GLANTZ: Yeah. I mean, the ARB doesn't have any regulatory authority over indoor air, but you are free to talk about indoor air in the report for purposes of informing the public. I mean, that's happened in lots of these reports. So it might be worth adding, you know, this point, just so it's there.

DR. BUDROE: Multiple source exposure?

PANEL MEMBER GLANTZ: Huh?

DR. BUDROE: Multiple source exposure?

PANEL MEMBER GLANTZ: Yeah. And the fact that indoors you can have quite high levels, because of the use of some of these products, just so it's on the record.

PANEL MEMBER BLANC: They do cite the relevant papers, so it wouldn't be extra references. It would just be a sort of connecting sentence maybe or...

DR. BUDROE: Okay. We do have -- on page 9, table 3, we do have some of the daily average exposures from this. So we do provide some information on it in the document. I mean, I guess it's a question of how far do we want -- are we going to editorialize with it.

PANEL MEMBER BLANC: Well, I wouldn't editorialize, I would just recognize that your REL does not take into account multiple sources of exposure, right?

It doesn't take into account water --

PANEL MEMBER GLANTZ: I don't think -- I wouldn't put that it way, because -- what I would just say -- just put a comment about you can have high levels of indoor exposure, and just, you know, a sentence or 2 to point that out.

I think that's a different point than the multiple levels of exposure question, because you know, I mean, there's the sort of scientific -- there's the risk assessment question which is what we deal with, which is, you know, if people get exposed to enough of this stuff, what will -- you know, how much do you need to get worried about? And then there's the risk -- there's the regulatory question of what kind of regulations get put in place based on the information in this document, which is a separate question.

And so the ARB can't set a rule for indoor exposure. But, you know in terms of providing a more complete discussion, you know, I think that's a good idea to add that. Again, it's not something that's going to affect the REL or that I think should hold up the report, but it's worth mentioning, especially, you know, just to make the document more useful, because there are people out there who are trying to look at integrated exposures.

You know, it may not be in an ARB rule, but these

documents are valuable for other -- you know, other organizations and other people. So that would be worth -- I mean, again, it's just an editorial change, not a substantive change.

DR. BUDROE: Okay. We could add a couple sentences on that.

PANEL MEMBER BLANC: So, Dr. Kleinman, are you looking for a motion at this point?

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER BLANC: So I would move that the document be accepted presuming that certain minor textual changes are made, reflective of the discussion we've just had.

PANEL MEMBER GLANTZ: If I could suggest an amendment, in that we delegate the authority to approve those changes to the Chair.

PANEL MEMBER BLANC: And that we delegate those -- friendly amendment accepted.

CHAIRPERSON KLEINMAN: Can I have a second?

PANEL MEMBER BUCKPITT: I'd like to second that.

CHAIRPERSON KLEINMAN: Good. Thank you.

All in favor?

(Ayes.)

(Hands raised.)

CHAIRPERSON KLEINMAN: Showing unanimous

approval. All right. The motion passes.

We have discharged our duties with this particular document. And I -- you know, as you get the final version, I will be happy to review it, and make the comments back to the group and to the Panel.

DR. BUDROE: Okay. Thank you, Dr. Kleinman.

PANEL MEMBER BLANC: Bathroom break?

CHAIRPERSON KLEINMAN: Yes. I'd like to take a 10 minute break and we'll get back at 11:30.

(Off record: 11:18 a.m.)

(Thereupon a recess was taken.)

(On record: 11:31 a.m.)

CHAIRPERSON KLEINMAN: Okay. I'd like to reconvene the meeting. The second item on the agenda is a review of the cancer unit risk factor for tertiary-butyl acetate, TBAc.

The unit risk factor was developed using risk assessment methodologies under the Hot Spots -- the Air Toxics Hot Spots Program. The document was made available for public review. And the agency did receive a set of comments on the document. The lead commentators on this will be Dr. Araujo and myself. And just as a reminder, when you are making a comment, turn your microphones on.

(Thereupon an overhead presentation was presented as follows.)

CHAIRPERSON KLEINMAN: And we're going to start off with a staff presentation, and then we'll move on to the comments from the leads, and then comments from the other members of the Panel.

John, are you going to do this?

DR. BUDROE: I will, in fact, as soon as I can figure out how to get this into full screen.

F5. Okay.

PANEL MEMBER GLANTZ: We are very accomplished experts at going into full screen mode.

(Laughter.)

PANEL MEMBER GLANTZ: And that's on the record.

No regulatory impact whatsoever.

DR. BUDROE: Well, I'd like to make -- use the excuse I'm a Mac user, but I'm really not, so I just -- you know, I'm out of luck with that one.

(Laughter.)

DR. BUDROE: Once more, good morning. And thank you for your attention on the second document of the day.

I'd like to start off with some background information on tert-butyl acetate, or TBAc.

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DR. BUDROE: TBAc is a solvent that's used in several applications. It's used in industrial coatings, cleaners, and adhesives. The vapor pressure is 47

millimeters of mercury at 25 degrees C. That means it's considerably less volatile than, for example, acetone, but which has got a vapor pressure of about 250 millimeters of mercury, but it's in the ballpark with say ethanol, which has got a vapor pressure of about 50.

And there are no carcinogenicity studies for TBAc. However, exposure to tertiary-butanol, or TBA, which is a primary metabolite of TBAc, has been shown to cause tumors in rats and mice.

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DR. BUDROE: And TBAc is fairly quickly metabolized to TBA. Groth and Freundt reported that rats inhaling 440 parts per of TBAc for 5 hours had increasing blood concentrations of both TBAc and TBA during exposure. And TBA blood concentrations that were slightly higher than that of TBAc, 300 versus 300 micromoles per liter of blood respectively after exposure

Similar exposures at 900 ppm TBAc for four and a quarter hours yielded similar results in blood. And TBAc blood concentrations were halved by 45 minutes post-exposure, but TBA levels were unchanged.

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DR. BUDROE: Now, to discuss TBAc toxicokinetics. Absorption, Cruzan and Kirkpatrick rat data suggested TBA is absorbed rapidly upon inhalation, but saturation

absorption may occur at high exposure concentrations. These same studies also suggested inhaled TBAc is rapidly distributed to tissues or exhaled. And the metabolism is through hydroxylation, oxidation, and/or glucuronidation.

Two major metabolic pathways have been proposed in rats.

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DR. BUDROE: And this is a adapted from Cruzan and Kirkpatrick. This is just the graphic metabolic scheme.

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DR. BUDROE: And the major pathways are hydroxylation of TBAc to 2-hydroxymethyl-isopropyl acetate. U1 on the metabolism graphic. And then oxidation to 2-hydroxyisobutyric acid, U2, which is the major urinary metabolite, or conjugation to 2-hydroxymethyl-isopropyl acetate glucuronide, which is U6 on the graphic.

The other major pathway is cleavage at the ester linkage in TBAc to form the TBA intermediate. And then oxidation to U2, or it's conjugated to -- you have a glucuronide conjugate, which would be U4 in the metabolism graphic. And there's also a minor pathway that involves hydroxylation and then glucuronide conjugation to U8.

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DR. BUDROE: So which would be this pathway. So this is the first major pathway. This is the second major pathway, and then this is the minor pathway.

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DR. BUDROE: Now, TBAc elimination. Most of the inhaled doses eliminate it within the first 24 hours post-exposure. The primary route of excretion is through the urine. Sixty-nine to 89 percent of the inhaled dose is eliminated that way. The secondary excretion routes are feces. Essentially, 1 to 2.7 percent and exhaled air roughly 5 to 27 percent. And exhaled air has a larger role as a route at higher exposure concentrations.

A low level of tissue retention, less than 3 percent, was reported. And as stated earlier, the half-life elimination in rats is 45 minutes.

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DR. BUDROE: The TBAc cancer risk assessment is based on a 2-year TBA drinking water study in rats and mice, which was done by an NTP, National Toxicology Program, in 1995. And the studies used either Fischer 344 rats or B6C3F1 mice, 60 animals per sex per treatment group. And one thing of note there is that for the rat study, 10 rats were sacrificed at 15 months for histopathological examination.

The exposure method and duration. Drinking water

ingestion for up to 103 weeks of concentrations used for male rats were 0, 1.25, 2.5, or 5 milligrams per ml.

For female rats, the concentrations were slightly higher 2.5, 5, or 10 milligrams per ml. And both male and female mice were exposed to 0, 5, 10, or 20 milligrams per ml.

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DR. BUDROE: Now this table shows the increased tumor incidences in the male rats and male and female mice exposed to TBA in drinking water. And there was no significant increase in male rats in renal tubule adenomas and carcinomas when single sections were done.

However, there was a -- the 2.5 milligram per ml dose group did show a significant increase in tumor incidence compared to controls. And the difference between step sections and single sections, single sections are what they sound like. There's a single section taken from each animal in the kidney. Step sections, 5 to 6 sections are taken per kidney, and that includes the -- that includes the control group.

So you can actually see, for example, the tumor numbers per animal go up in the step section group, and including in controls where they went from 1 to 8.

And basically, NTP considers step section evaluation to be a more complete evaluation. However,

they do not do it for every study that they turn out because it's that much more labor intensive.

And in female mice, there was a significant increase in thyroid follicular cell adenomas at the high dose. And this group also showed a significant trend test for dose response using a Cochran-Armitage trend test.

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DR. BUDROE: So the critical effects were renal tubule adenomas and carcinomas in male rats, and thyroid follicular cell tumors in female mice. And the tumor incidence data was then a poly-3 survival-adjusted lifetime tumor incidence correction was then applied to the those 2 data sets to compensate for non-tumor related mortality.

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DR. BUDROE: This table shows the poly-3 corrected tumor incidence data for both the step section male rat renal tubule tumors and the female mice thyroid tumors. And there is one unfortunate difference between this table and the document, the document for the female mouse thyroid tumors actually shows the uncorrected data. This table in the slide here shows the correct data, so that will be -- the document will be corrected to reflect that.

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DR. BUDROE: TBA cancer slope factors, or CSFs, were calculated from the poly-3 corrected data using the multi-stage cancer model function of the U.S. EPA benchmark dose software. We used version 2.6, the most recent version. A CSF animal of 4.3 times 10 to the minus 3 per milligram/kilogram day was calculated using BMDS from the corrected male rat kidney tumor data set with the high dose, 420 milligrams per kilogram day, and that's an exposed dose actually.

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DR. BUDROE: Go back there. That's the administered dose. NTP actually calculated an exposed dose for all the dose groups.

PANEL MEMBER GLANTZ: What's the difference between an administered and exposed dose?

DR. BUDROE: An administered dose is the actual concentration of TBA in the drinking water. For an exposed dose, NTP calculated it from -- actually monitored their water consumption and body weight, and calculated an actual exposed dose from -- in milligrams per kilogram day.

So the high dose tumor incidence data was dropped from the model to allow model convergence, and a first degree polynomial was used to model the data for goodness-of-fit purposes.

We also calculated the CSF animal with 7 times 10 to the minus 5 per milligram/kilogram day from the corrected female mouse thyroid tumor data set using a third degree polynomial multi-stage cancer model.

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DR. BUDROE: And this slide shows the BMDS output data where the BMDL, which is the lower 95 percent confidence level on BMD of 11 -- essentially roughly 12 milligrams per kilogram day the female mouse thyroid tumor BMDL was considerably higher, roughly 650. So you're looking at roughly the rat CSF being about 60-fold greater than the mouse CSF.

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DR. BUDROE: And that's a -- the graphic of the plot of the data.

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DR. BUDROE: So the male rat kidney tumor data yielded the lowest CSF animal value. And this animal cancer potency estimate was converted to a human potency equivalent. This was done using body weight to three-quarter power scaling.

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DR. BUDROE: So a CSF human was derived from the CSF animal data -- from the 4.3 times 10 to the minus 3. After body weight scaling, the value is 1.5 times 10 to

the minus 2 milligram per kilogram day.

And we then derived a TBAc CSF oral from the TBA CSF human oral value above, assuming 2 factors, a TBAc to TBA metabolic conversion factor of 0.71 and a molar conversion factor of 0.64 which is the ratio of a TBA molecular weight to the TBAc molecular weight.

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DR. BUDROE: So the TBAc CSF oral is equal to the TBA CSF human oral times the molecular conversion factor times the molar conversion factor. And the oral factor for TBAc is 7 times 10 to the minus 3 per milligram/kilogram day.

We then derived a TBAc inhalation slope factor from the oral slope factor using the following relationship, where fractional absorption was 95 percent. And that resulted in an inhalation slope factor of 6.7 times 10 to the minus 3 per milligram/kilogram day.

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DR. BUDROE: So having derived a inhalation slope factor, we then use that to derive a TBAc unit risk factor from the inhalation slope factor for TBAc. And the inhalation -- the unit risk factor is the risk per -- extra risk of cancer per exposure to 1 microgram per cubic meter of a given chemical.

And we used the human breathing, default

breathing rate of 20 meters per day -- 20 cubic meters per day. Average human body weight is 70 kilograms, and the milligram kilogram -- milligram to microgram conversion factor of 1000. And the result is a unit risk factor of is 1.9 times 10 to the minus 6 per microgram per cubic meter.

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DR. BUDROE: So to summarize the proposed TBAc risk factors: The oral slope factors is 7 times 10 to the minus 3 per milligram/kilogram day. The inhalation slope factor is 6.7 times 10 to the minus 3. And the unit risk is 1.9 times 10 to the minus 6 per microgram per cubic meter.

And the previous TBAc risk factors that were informally developed for Air Resources Board were a inhalation slope factor of 2 times 10 to the minus 3 per milligram/kilogram day, and a unit risk of 4 times 10 to the minus 7 per milligram per cubic meter.

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DR. BUDROE: And I want to go back. One thing that if you were looking at the slide presentation might have missed is somewhere there a 0.25 power next to the -- that parentheses got dropped from the presentation. I think it got squeezed off the slide, but that would be 70 kilograms per 0.431 kilograms to the 0.25 power.

So that concludes the presentation on the document. Dr. Kleinman, if you'd like questions now or held until the response to comments presentation.

CHAIRPERSON KLEINMAN: I think it would be better to go through the responses to the other -- yeah, the outside comments, and that way we have the whole package, and then we can comment on those, unless somebody has a burning question?

PANEL MEMBER GILL: I just have one clarification for slide 5, the metabolism figure. I just want to say -- just to make sure that I got it correctly, you say the major pathway is on the left-hand side?

DR. BUDROE: Yes. That and that would be the major pathways, and that's the minor pathway.

PANEL MEMBER GILL: But based on metabolism study, then the major pathway should be the butanol pathway. The other one is -- should still be very minor, correct, if you look at the blood data?

DR. BUDROE: Correct.

PANEL MEMBER GILL: Okay.

DR. BUDROE: Yeah. It's a question of you decide which one is major and which one is minor. Like that one is, you know, very low rates of metabolism. These 2 are greater, but you're correct.

PANEL MEMBER GILL: The reason my question is

because if you're going to base your data subsequently on TBA, it cannot be based on the left-hand pathway. It has to be based on the major pathway of butanol.

DR. BUDROE: Correct. And that is what you were seeing with the -- with the Groth and Freundt data.

PANEL MEMBER ARAUJO: May I ask something, since we are already talking about the -- so the metabolic pathways. If you put the diagram again. I guess at -- the question would be is the hydroxylation and the formation of the 2-hydroxyisobutyric acid corresponds to the pathway that is on the left or the pathway that is on the middle, and all it comes equally from both. And that can help to asserting whether one pathway is more than the other. Because at the end, if a lot of it really comes from the left side, so the left side would still be a major pathway.

If it is coming more like from the butanol, as you're saying, so it could be the one on the middle. And I'm saying this just based on the fact that about 40 percent of the -- of the -- or this metabolite consists of like 40 percent of all the metabolites and -- that generate from the TBAc. Do we know about that?

So whether that -- and you call this like a U2, right? Yeah, the U2, the 2-hydroxyisobutyric acid. So that is like -- you mentioned that it's roughly like about

40 percent, depending on whether it is a low dose or high dose and exposures to the TBA.

And when you're exposing to the TBAc, is that really coming primarily from the butanol or is it coming from the 2 hydroxymethyl-isopropyl acetate?

DR. BUDROE: It's not completely easy to tell from the Cruzan data. Can I get of one my colleagues up here to -- okay. Yeah, Dr. Kathleen Vork is one of the co-authors on the document.

So in the Cruzan and Kirkpatrick metabolism data that the percentage of the pathway that's being hydroxylated to the U1 then U6 increases with -- that pathway decreases with dose. Hydrolysis of the TBA results in U4 increases with dose. And metabolism to U2, which would involve either pathway essentially is constant with dose.

PANEL MEMBER BUCKPITT: Do you know anything about the metabolism of butanol, and would that tell you what the contribution butanol versus the other pathway is?

DR. BUDROE: There probably is. We didn't evaluate it for this pathway, but that might be worth look.

PANEL MEMBER BUCKPITT: But it would be worth it, if you want to answer that question.

DR. BUDROE: Right.

Any other questions before we move on to the response to comments?

CHAIRPERSON KLEINMAN: Why don't we move on and then we can return.

DR. BUDROE: Okay. OEHHA received comments on TBAc from the Lyondell Chemical Company and from Dr. James Felton on behalf of Lyondell Chemical Company.

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DR. BUDROE: The public comment topics in general were addressed. Male rat kidney tumors, the mode of action. And topics and subtopics in this were non-genotoxicity, male rat specificity of renal effects, sustained and elevated self-proliferation, does-response similarities between the mode of action and tumors, and then TBA-induced female mouse thyroid tumors, and the inhalation unit risk derivation.

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DR. BUDROE: In comments on the mode of action, Lyondell felt that -- Lyondell felt that the use of TBA-induced male rat kidney tumors as a primary basis for the derivation of the TBAc unit risk fact, or URF, was not justified given that this tumor response is likely mediated through the non-human relevant alpha-2u globulin MoA.

They further stated that the weight of evidence

examination of the data supports the conclusion that TBA is causing tumors by the alpha-2u globulin MoA, and that all 7 criteria for this MoA, as outlined by IARC, have been fulfilled. And this was included in their table 1.

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DR. BUDROE: And to discuss this table, this -- essentially, IARC back in 1999 put together a criteria of for determining if a chemical that caused male rat kidney tumors was doing it slowly through an alpha-2u globulin mode of action, and therefore should not be considered to be relevant to human cancer risk assessment.

Lyondell laid this out as essential criteria and additional supporting evidence. And this is what is, as described in a paper by Swenberg and Lehman-McKeeman, who were part of that -- the working group. However, the consensus report listed all 7 criteria as all being essential. They did not delineate between essential criteria and additional supporting evidence.

And OEHHA feels that the use of the consensus report criteria list, as laid out by IARC, is more appropriate for use in determining if chemicals do, in fact, induce male rat kidney tumors as a result of an alpha-2u globulin MoA.

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DR. BUDROE: Now, our general response to the MoA

comments are that the weight of evidence supports our position that male rat kidney tumors observed in the NTP TBA drinking water study are relevant to human cancer risk assessments, and we'll give our responses to specific comments in the following slides.

And as I stated earlier that the use of complete IARC criteria for male rat kidney tumors an alpha-2u globulin MoA is listed in the consensus report and described in the document is appropriate.

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DR. BUDROE: Now, Lyondell comments on genotoxicity of TBAc. They stated that TBAc and TBA were negative in high quality studies examining bacterial reverse mutations, in vitro human lymphocyte and mammalian cell Chinese hamster ovary cell chromosomal aberrations for TBAc and TBA respectively.

Mammalian cell mutations in the mouse lymphoma assay for TBA, and in vivo rat bone marrow and mouse micronucleus assays for TBAc and TBA respectively.

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DR. BUDROE: And that weight of evidence evaluation of the genetox data in the document should result in the clear conclusion that both TBAc, and its metabolic surrogate, TBA are nongenotoxic.

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DR. BUDROE: An our response to this is that the genetox data for TBAc is generally negative, but it's limited. And TBA has not been shown to cause chromosomal damage, but has produced mixed results for bacterial gene mutation. TBA has also been observed to cause DNA damage in a variety of assays that causes -- been shown to cause primary DNA damage, adduct formation, and oxidative DNA damage.

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DR. BUDROE: And these assays were performed in vitro and in vivo using several different assay endpoints and they were uniformly positive. It's also notable, given the positive DNA damage data for TBA, that the positive bacterial gene mutation assay data was generated in a salmonella strain, which is sensitive to oxidative DNA damage.

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DR. BUDROE: Negative results from different types of chromosomal assays may increase the weight of evidence regarding chromosomal damage, but does not necessarily pre-dominate in an overall assessment of genotoxicity.

Positive data should not be dismissed lightly, and it's -- you know, there is no such thing as a perfect positive study. There are always things that can be

nitpicked in it. But, in general, the default for genotoxicity assay is it comes out negative.

So overall, we believe that the genetox data do not prove that TBA is nongenotoxic, and therefore TBA does not fit IARC Criterion 1.

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DR. BUDROE: Additional Lyondell comments on genotoxicity is that methyl tert-butyl ether, or MTBE, and ethyl tert-butyl ether, or ETBE, are extensively metabolized to TBA, and therefore represent metabolic surrogates of TBAc through their common metabolism, the TBA, and that these negative genetox profiles of MTBE and ETBE should be included in the overall weight of evidence evaluation.

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DR. BUDROE: Our response to these comments is that a comprehensive evaluation of MTBE and ETBE is beyond the scope of this document. However, the document does discuss TBA genetox studies that also present positive genetox data for MTBE. And those studies include reports of DNA damage, bacterial gene mutation, and DNA adduct formation.

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DR. BUDROE: Lyondell further commented that there are problems with the studies by Tang, Sgambato,

Williams-Hill, and Yuan. With respect to the Tang study that it assessed DNA breakage in the Comet assay using a non-standard subjective and qualitative method, reporting only the appearance or lack of appearance of a Comet tail in an HL-60 cell line not known to be metabolically competent.

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DR. BUDROE: And our response to this is that Tang visually quantified the percentage of DNA present in the tail. Although this potentially adds some variability, because you can be using different data squares due to the subjectivity of visual scoring. It's still an acceptable laboratory method.

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DR. BUDROE: Lyondell's comments on the Sgambato study were there it only used a single IC50 concentration, which is a concentration that will produce a 50 percent inhibition of growth and only one indication of cytotoxicity the MTT test in their Comet assay.

And than an IC30 is recommended -- is generally recommended to avoid cytotoxicity confounding as is the use of multiple cytotoxicity tests.

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DR. BUDROE: And our response is is that Sgambato did not observe a significant difference in the amount of

dead cells in treated verse control cultures. And we acknowledge that cytotoxicity is a potential confounder in the interpretation of the Comet assay results contained in the Sgambato study and we added that information to the document.

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DR. BUDROE: Lyondell's comments on the Yuan study were that it used an accelerated -- accelerator mass spectroscopy method that is prone to false positive results of DNA adduct formation. It did not use synthetic standards of adducted DNA bases to avoid misinterpretation of the results.

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DR. BUDROE: Our response is that regarding the Yuan study, OEHHA has not found a scientific consensus that accelerator mass spectrometry is prone to false positive results. However, use of synthetic standards to confirm the identity of the DNA adducts would have been helpful, and we've added the discussion of this information to the document.

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DR. BUDROE: Lyondell's comments on Williams-Hill. The Williams-Hill study is that -- were that Williams-Hill observed the mutagenic response of the non-GLP, good laboratory practices, study using salmonella

strain TA102, which they claim has a high and variable background rate of revertants.

And TBA only induced a very weak response, barely meeting a requirement for a positive response a 2-fold increase mutation incidence.

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DR. BUDROE: Additionally, those findings were not replicated in 2 independent and GLP-compliant assays using TA102, which confirmed that the DMSO vehicle, which is an oxidative stress inhibitor, did not influence their negative findings in the TA102 strain, which is sensitive to oxidative stress.

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DR. BUDROE: Our response to these comments is that GLP standards are designed to be applied to data submitted to the U.S. Food and Drug Administration, FDA, for regulatory approval. And these are primarily record-keeping requirements, that a study be able to track the results in the study all the way through. But it -- what it essentially does is mandate record keeping.

Research data submitted to peer-reviewed scientific journals, such as the Williams-Hill study, are not required to meet those GLP standards, and GLP studies should not be construed as being more scientifically valid than non-GLP studies.

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DR. BUDROE: Additionally, the control revertant rate reported by Williams-Hill is consistent with the laboratory, quality control standards they described. And their mutation data show a dose response relationship with the mid-dose exposure group showing a mutation response of about 2-fold greater than control.

Therefore, the positive -- the positive TBA bacterial gene mutation data reported is valid and should be considered in any discussion of TBA genotoxicity.

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DR. BUDROE: Switching to next topic, male rat specificity. Lyondell commented that TBA is at most a very weak kidney tumorigen. A positive finding of tumorigenicity was not identified in the NTP study using standard kidney histopath sectioning. Statistical significance of the response was only achieved in the mid-dose when subsequent step sectioning of the kidney was conducted. And NTP declared the TBA kidney finding only as some evidence of carcinogenicity in male rats.

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DR. BUDROE: Our response to those comments is that standard pathology sectioning and step sectioning were described as analogous to a partial evaluation and a definitive evaluation respectively.

So the step section procedure is essentially a more sensitive procedure for detecting tumors in the tissue under examination.

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DR. BUDROE: Additionally, the explanation of levels of evidence of carcinogenic activity section of the NTP report states that the 2 categories of positive results of carcinogenic activity are clear evidence and some evidence. NTP therefore, clearly considers the TBA male rat kidney tumor results to be positive results.

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DR. BUDROE: Additional comments by Lyondell and male rate specificity. In the TBAc document, the lack of fulfillment of IARC Criterion 2 is largely based on kidney changes described in the female rat, namely exacerbation of chronic progressive nephropathy, or CPN, increases in renal inflammation, and renal pelvis transitional cell hyperplasia.

And in the 2-year study, females were affected with a dose-related exacerbation of CPN not an alpha-2u globulin MoA.

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DR. BUDROE: Although an adverse effect, CPN is not a nephrotoxic effect. It's an enhancement of the development of the spontaneous disease process that is

common in the F344 rat but not relevant to humans.

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DR. BUDROE: Our response to these comments is that the document has been revised to include an expanded description of the NTP findings regarding CPN, suppurative inflammation, and transitional epithelial hyperplasia, or TEH, that was observed in TBA-exposed rats. It also included a discussion of the differing male and female rat dose responses for CPN, suppurative inflammation, and TEH. And that these data indicate it's unlikely that either suppurative inflammation or TEH are directly linked to CPN.

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DR. BUDROE: The document has also been specifically revised to indicate that the exacerbation of CPN in female rats indicates an adverse renal effect, and that the induction of suppurative inflammation and TEH are definitively nephrotoxic effects. And the data listed in the revised document and described above in this slide indicate that TBA does not completely fit IARC Criterion number 2.

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DR. BUDROE: Now, Lyondell's comments on sustained and increased cell proliferation, which is Criterion 6. The TBAc document used 3 studies to assess

whether Criterion 6 was supported, Borghoff, Takahashi and Faber. Borghoff reported a dose-independent increase in renal tubule cell proliferation, or CP, at 10 days post-TBA exposure.

Takahashi applied proliferating cell nuclear antigen, or PCNA, staining to recuts of kidney tissue from the NTP 13-week TBA drinking water study. And this is NTP did a 13-week study prior to doing the fall 2-year study, to essentially evaluate toxicity before going into a lifetime study --

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DR. BUDROE: -- and reported an increase in the median cell proliferation only in the mid-dose exposure group of 20 milligrams per ml, a dose much higher than the high dose, 5 milligrams per ml, used in the NTP cancer study. Faber reported a negative cell proliferation in the 13-week study of TBAc. And Lyondell felt this comparison was not strictly appropriate, as the tumor finding applied in the document was to TBA and not TBAc.

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DR. BUDROE: And finally, Lyondell felt that the document did not refer to the work of Lindamood who demonstrated via PCNA in the 13 -- the NTP 13-week drinking water study a statistically significant increase in renal tubule S-phase nuclei indicating cell

proliferation at doses of 1 percent and 2 percent of TBA in male rats matching the occurrence of the hyaline droplet response in their study.

And one thing that should be noted is that 1 and 2 percent are the equivalent of 10 and 20 milligrams per milliliter drinking water concentration. Tumors in the lifetime study were observed in the 2.5 milligrams per ml dose.

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DR. BUDROE: To continue Lyondell's comment. At the 4 -- high dose of 4 percent in male rats. There were no hyaline droplets or any cell proliferation responses noted by Lindamood. None the -- nevertheless, the male rat data of Lindamood and Takahashi at 13 weeks are consistent and coupled with the results of Borghoff at 10 days provides some evidence that IARC Criterion 6 is fulfilled.

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DR. BUDROE: Our response to those comments is that we revised the document to include a description of the Lindamood male rat renal tubule epithelial cell proliferation data from the 90-day -- NTP 90-day TBA drinking water study.

However, the Takahashi study appears to report virtually the same data as that in Lindamood, with the

primary difference that the graph -- the data are presented in graphic rather than numeric for -- format.

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DR. BUDROE: The NTP report did not report the PCNA proliferation data, included in Lindamood and Takahashi. And, you know, they didn't specify why HO is not included, but they didn't. And these data, based upon the 90-day, but not the 2-year NTP study, are insufficient to change the conclusion in the TSD that the TBA does not completely fit IARC Criterion 6.

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DR. BUDROE: Lyondell comments on the dose response similarities between the MoA and the proposed MoA in tumors. The TBAc document, TSD uses immunohistochemical staining of rat kidney for alpha-2u globulin as evidence of an absence of dose response. And they believe that this technique should only be used for qualitatively localizing accumulating hyaline droplets that stain positively for the alpha-2u-globulin protein, and should not be relied upon to support regulatory decision making.

They also state that ELISA is a more sensitive and quantitative measure of changes in the kidney's accumulation of this protein.

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DR. BUDROE: Our response is that OEHHA agree that an enzyme-linked immunosorbent assay, or ELISA, for renal alpha-2u globulin is more sensitive and easier to quantify than renal alpha-2u globulin immunohistochemical staining. However, we're not aware of any published evidence that indicating that staining is unreliable, and therefore it would not be reasonable to throw out data that was generated using that staining technique.

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DR. BUDROE: Lyondell also comments that other evidence of the dose response correlation is seen in the presence of precursors of granular casts, mature granular casts, and linear papillary mineralization observed in male rats at doses of 2.5 and 5 milligrams per ml correlating with renal tubule induction -- excuse me renal tumor induction.

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DR. BUDROE: They also state that CPN compromised survival of the rats in the 5 milligram per ml groups, and that allowances should be made in the document to account for confounding factors of CPN exacerbation and survival.

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DR. BUDROE: Our response to this is that NTP reported that incidence of linear mineralization, which is associated with alpha-2u-globulin induction did increase

with dose in the NTP 2-year study, but the corresponding severity scores did not exhibit a dose response. And we have added this information to the discussion of Criterion 7 in the document.

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DR. BUDROE: NTP also observed that there was no morphological evidence of extensive cell necrosis evidenced by granular cast formation resulting from TBA exposure. And this information has also been added to the document.

However, NTP did not state that nephropathy was a cause of mortality in male and female rats, or that survival affected tumor response, or that either nephropathy or mortality were confounding factors regarding renal tumor response in male rats.

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DR. BUDROE: Further, Lyondell comments on dose response Similarities. They felt that the TBAc document has given no consideration to a more likely alternative MoA. A feature of the TBA studies was exacerbation of spontaneous CPN, which was probably the cause of lower survival in the high dose male rats, and that advanced end-stage CPN has been shown to be responsible for a low incidence of renal tumor -- renal tubule tumors in control rats, and is therefore a risk factor for renal cancer

development, especially in male rats.

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DR. BUDROE: Our response to this is that F344 rats have a relatively high incidence of CPN, but the male rat renal tubule tumor incidence in the NTP historical control database is low. It's less than 1 percent. And there are several chemicals that exacerbate CPN without increasing male rat renal tumor incidence.

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DR. BUDROE: Also, I'd like to note that Melnick evaluated 58 NTP carcinogenicity studies using male F344 rats and 11 studies using female F344 rats for relationships between exacerbated CPN and induction of rat renal tumors.

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DR. BUDROE: Melnick found widespread inconsistencies in the hypothesis -- hypothesized relationship between CPN and rat renal tumors.

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DR. BUDROE: Melnick also stated that CPN is not an established MoA or mechanism of renal carcinogenicity and that neither the etiology of this kidney disease in aging control rats nor the mechanism of chemically exacerbated CPN in rats is known.

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DR. BUDROE: And there is no basis for -- they -- Melnick also stated that there is no basis for establishing an MoA for enhancement of CPN in rats or for defining critical biological processes that could occur in rats and presumably could not likewise occur in humans.

This indicates to us that it's unlikely that nephropathy is the cause of the male rate kidney tumors in the NTP study. And one piece that I'd also like to add with regard to the alpha-2u globulin MoA that's not on the slide, is that the Doi in 2007 published an evaluation of alpha-2u globulin responses in male rats and corresponding tumors. And they found that -- found no or at best weak associations of tumor responses with renal alpha-2u globulin concentrations, indices of cell turnover, or Microscopic evidence of alpha-2u associated nephropathy.

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DR. BUDROE: The next topic -- comment topic area was TBA induced mouse thyroid tumors. And Lyondell commented that use of TBA-induced male thyroid tumors would not be justified based on MoA information suggesting a quantitative and/or qualitative lack of human relevance.

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DR. BUDROE: They felt the data suggested the high dose specific thyroid tumorigenicity of TBA results from a non-mutagenic MoA associated with intense --

enhanced catabolism of thyroid hormone mediated by TBA. And this MoA is common to multiple rodent thyroid carcinogens such as phenobarbital, or PB.

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DR. BUDROE: Our response to this comment is that the TBA-induced female mouse thyroid tumors observed in the NTP study are relevant to human cancer risk assessment, and that data indicated it's unlikely that those tumors are results of compensatory thyroid hyperplasia secondary to thyroid hormone insufficiency.

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DR. BUDROE: The corresponding section to the document notes that TBA causes little or no increases in absolute or relative liver weights; does not induce cytochrome P450 activity to the same degree as seen with phenobarbital; does not cause large decreases in T3 or T4 levels;

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DR. BUDROE: Does not increase thyroid stimulating hormone, TSH levels; and, does not cause acute abnormal mouse thyroid histopathological changes.

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DR. BUDROE: Additionally, TBAc has not been shown to cause significant changes in the thyroid gland histopathology or thyroid and parathyroid gland weights in

mice; does not induce decreases in T4 levels at relatively high dose exposures in female mice or increases in TSH levels or decreases in T3 levels in male or female mice.

So essentially what we're saying is the data that you need to see to say that the TBA or TBAc are causing liver metabolism of thyroid hormone, and as a result you get increases in THS levels, thyroid hyperplasia, and this results in tumors is the data does not support that hypothesis.

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DR. BUDROE: Additional comments on the mouse thyroid tumors by Lyondell. They felt that TBAc toxicity limits the achieving of TBA tumorigenic doses in mice. And they cited Bus 2015, that in their review of the data found inhalation of 3000 ppm of TBAc for 6 hours caused mice essentially to be exposed at that level be prostrate.

And TBA-induced tumors in only female mice given roughly 2000 milligrams per kilogram day in drinking water, which they felt was equivalent to 3300 ppm TBAc by inhalation, assuming 100 percent TBAc to TBA metabolism.

So real -- as they put it, realistically assuming 50 percent metabolism, 2110 milligram per kilogram day equates to almost 7000 ppm TBAc, which would exceed the maximum tolerated dose in mice.

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DR. BUDROE: Our response to this that according to the model by Bus to producer the TBA dose that caused thyroid tumors in female mice, TBAc exposures would have to exceed 3000 ppm, the level that produced adverse CNS effects in the Cruzan and Kirkpatrick acute study.

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DR. BUDROE: In the NTP study, female mice were not exposed to TBA levels greater than the MTD. There's no reason to discount female mouse thyroid tumor data on the basis of mortality. And use of the BMDS model assumes that there's cancer risk at all carcinogen doses greater than 0.

So even if the model proposed by Bus was correct, TBA -- TBAc exposure is still expected to pose a cancer risk at concentrations below 3000 ppm.

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DR. BUDROE: The Bus model overestimates TBAc air concentrations required to produce an oral TBAc dose of 2115 milligrams per kilogram day. In their algorithm, body weight minute volume are sensitive parameters, and work by Salazar acknowledges changes in the metabolism with repeated exposure.

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DR. BUDROE: We recalculated the TBAc inhalation concentration at the high oral dose for the female mice in

the NTP study to be 2393 ppm using the average body weights for male and female mice in the NTP study, and minute volumes calculated from U.S. EPA guidance that considers specific mouse body weights. Bus used a default reference mouse minute volume.

And the 2393 ppm that we calculated is less than the 3000 ppm observed to cause acute CNS effects, and is roughly 4-fold greater than the TBA BMDL05, which is the point of departure of 647 milligrams per kilogram day.

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DR. BUDROE: Additional comments on -- by Lyondell on the risk assessment were that an alternative approach to TBAc chronic risk assessment has been proposed, based on noncancer neurotoxicity findings by Bus. This alternative approach yielded acute and chronic TBAc reference concentrations of 1.5 and 0.3 ppm respectively.

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DR. BUDROE: Our response to this is that the TBAc cancer unit risk factor decried -- described in the document is both adequate and justified by the available data, and that the derivation of the TBAc noncancer reference exposure level is outside the scope of this document.

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DR. BUDROE: Further, Lyondell comments. There are several issues with the TBAc inhalation unit risk estimates. These include unspecified rationales for the use of a 5 percent BMR response versus a 10 percent standard, and the elimination of the top dose in derivation of the BMR, which resulted in the 2 point dose response.

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DR. BUDROE: Our response to those comments is that the 2009 technical support -- cancer technical support document the statement made in there that -- that document states that a benchmark tumor incidence rate of 10 percent is often used. However, it's not -- that's a general recognition of what really U.S. EPA was doing at the time, and we intended to use the 5 percent BMR more recently.

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DR. BUDROE: Additionally, the animal cancer slope factor was calculated from the NTP male rat kidney data with the high dose eliminated due to lack of model convergence. And an explanation of this was added to the document. And the U.S. EPA benchmark dose technical guidance considers this approach appropriate when none of the available models provide an adequate fit. So U.S. EPA suggests this in circumstances as we saw with the male rat

kidney tumor data.

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DR. BUDROE: Lyondell also commented there are several issues with the TBAc inhalation unit risk estimates. These include unexplained assumptions of the 95 percent TBAc absorption and 71 percent TBAc to TBA metabolism.

And the 95 percent estimate wrongly assumes that the total amount of TBAc radioactivity equivalents in rats after a 6-hour exposure, 50.7 per milligram per kilogram was equal to the total amount of TBAc inhaled over the course of that entire exposure period.

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DR. BUDROE: Assuming an EPA default minute volume in rats, and a body weight -- rat body weight of 0.21 kilograms, they essentially run through a series of calculations and suggest that the absorbed dose may actually be about 35 percent.

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DR. BUDROE: And our response to that is the calculations and the comment use the U.S. EPA default rat body weight to generate an estimated rat respiration rate, and overestimate the minute volute and inhaled milligram of TBAc by a factor of about 10 percent.

The body weight -- rat body weight is available

from Cruzan and Kirkpatrick metabolism study to calculate an estimated respiration rate for those rats. And using the low-end body weight in that study of 210 grams, we calculated the 6-hour TBAc dose of 50.7 mill milligrams per kilogram. This does indicate that the absorbed dose could be as low as 40 percent. However, there are some caveats with that estimate.

Bun one, Cruzan and Kirkpatrick reported that 4.8 percent of the inhaled mass was exhaled up to 7 days post-exposure. And they didn't measure the excreted in first 6 hours. And this could explain much of the difference between the calculated and absorbed radioactivity.

Additionally, they use nose-only exposure, and this can depress animal ventilation rates.

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DR. BUDROE: And human studies estimate VOC, volatile organic chemical, lung retention at greater than or equal to 80 percent, depending on the water soluble -- solubility of those chemicals.

So respirator rate is adjusted downward by using the U.S. EPA regression equation, and an adjustment for depressed respiration, suggested by Mauderly, would bring the predicted and observed inhaled dose into closer alignment.

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DR. BUDROE: Thus, the chamber concentration and inhaled dose is not expected to reflect the depressed respirations observed in nose-only administration methods. And the comment on the metabolism. OEHHA concluded from the radioactivity study that metabolism to TBA could be as much as 71 percent at the lower of the 2 single dose levels, and as much as 82 percent at the higher dose level based on the U2 and U4 pathways reported in table 5 of that paper.

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DR. BUDROE: And thank you for listening to all 90 slides. And I'd be happy to entertain questions.

CHAIRPERSON KLEINMAN: Thank you for a very extensive response to the questions.

All right. Let's see, it's 12:30. I think we probably ought to hold off on our -- you know, the Panel comments till after lunch. And if nobody objects, I think we can adjourn for an hour, and have some lunch, and then reconvene at 1:30.

PANEL MEMBER BLANC: How about 45 minutes for lunch?

CHAIRPERSON KLEINMAN: Works for me. All right. 1:15. We're adjourned temporarily.

(Off record: 12:35 p.m.)

(Thereupon a lunch break was taken.)

A F T E R N O O N S E S S I O N

(On record: 1:21 p.m.)

CHAIRPERSON KLEINMAN: Okay. I'd like to reconvene and call the Panel back to order, or as close to it as we can.

We left off after the discussion of the Lyondell and Fenton comments, and the responses to those comments. Now, I'd like to start with the Panel discussion. And the panelists are -- the leads are Dr. Araujo and myself. And I'd like Dr. Araujo to start out.

PANEL MEMBER ARAUJO: Okay. So this is really a revised document, you know, from a previous document that it had really been written and approved about a decade ago, as I understand.

I think that it's -- overall the -- so the document is well written, and it is clear. I do have some comments, and I have also some questions. And so some of the comments have to do with -- I believe that they -- what they -- the document goes about the calculations of the cancer potency values. And I think that it does give most of the data that is relevant for that.

There are some general concepts and some background that I think will be good to have, and that -- and I think that it's missing. For example, so there is one first section where it describes the physical and

chemical properties, and a second small section on the health assessment values. And then it goes into the carcinogenicity and, et cetera.

But something that is left out is -- aside like maybe like from one or two sentences, where it says what is what the TBAc is, it doesn't really describe much. You know, I mean what is -- what it is, and what is its importance on where it is used and what are the sources, and what is the relevance, and what are the exposures, and how are the exposures, and -- so you gather like from the document that the exposures may be by inhalation or may be oral. In some places, it's a skin. But you have like a spread. I mean, I think that it would be helpful to have some section in the beginning where that is described.

And there is one toxicological review that I don't believe that is cited at the moment, and it would be -- it can be quite helpful to report that in an introductory section. And it is authored by Bus B-u-s. And it was published in the Critical Reviews in Toxicology last year, 2015.

And it's really -- it's a very nice and thorough review on this. And it also reviews like a risk assessment quite well, which is another thing that is missing. This is not a risk assessment document, I know. But having some concepts like about the relevance and the

importance of this, and what is what people or subjects who get exposed, and get exposed to, you know, in what concentrations, and -- so in other words -- and so we -- so the reader will have an idea on is -- of how relevant this is really for humans and what kind of subjects and who will be exposed to that.

And these unit risk factors, and these inhalation and oral slope factors will cover or will get some importance in -- within the context of, okay, so you have a factor of 1.9 times 10 to the minus 6. But what does that mean? I mean, that means something dependent on the concentrations of the TBAc, and that will be present in the specific scenario, or context where the subjects that are exposed will be exposed to. So that's one thing.

PANEL MEMBER BLANC: Do you want them to respond to that, because it may be a simple answer.

PANEL MEMBER ARAUJO: Oh, sure. Yeah.

PANEL MEMBER BLANC: It doesn't have to do with what this is an appendix to. This appendix B. Is there -- was there some doc -- other document to which this is an appendix of that has some of the stuff that we were just referring to?

DR. BUDROE: Yes. Technically, this is -- it will go into appendix B of the 2009 cancer potency factor technical support document, so -- and that does have a

discussion of what a unit risk factor is, for example, how it's used to calculate cancer risk in the population.

PANEL MEMBER ARAUJO: What about everything about the importance, relevance, exposure, and risk assessment. Is there another document where all that is described in details? And if there is, so what about having a section or a paragraph where the most significant facts are listed or mentioned, and then reference it to the main document?

I do know, for example, that in this review that I mentioned from Bus, they talk about study from the ARB, and they show a lot of data and tables. So maybe those studies that are in that other -- in those other documents. But I haven't seen them, so I don't know.

DR. BUDROE: Sure. We'll -- I mean, we can add chemical-specific information on the sources of TBAc, what the exposures are that would be expected, the routes of exposure, et cetera. We can do that.

PANEL MEMBER ARAUJO: Right. And if it's -- if it's present in the other documents, and so it doesn't need to be long or extensive. It can be quite concise, but it will give the relevance and then you can reference it properly.

I have small comments in various sections, but maybe I will mention the 2 most important points that I'd like to go over and discuss.

So one has to do with the calculations. And I don't know if you have the ability of actually showing some of the slides that you show in the beginning, or the oral CSF, ventilation CSF, and the unit risk factors.

DR. BUDROE: Okay.

PANEL MEMBER ARAUJO: You even have the formulas and -- okay. Do you have the oral or the -- right. Okay.

So one of the things that you very well present throughout the document is that there is not much data or no carcinogenic data in humans and specifically from TBAc. And most of the data has to be like from studies that have been done with a tert-butanol, the TBA.

And I am -- here is a question. I am not sure. I've just been thinking through this, and even done my own calculations and -- but you have -- the data that you have has been calculated and you describe how it was generated. It comes from the TBAc, right?

I'm sorry from the tert-butanol, the TBA. And then you use a metabolic conversion that you're calling there the MC, right, and which is 0.7. And then you're also using a molar conversion factor that you're calling there the MCF, and you're given a value of 0.64.

And the reason why you are doing that is because you're calculating the ratio of the molecular weight of the TBAc -- oh, the TBA divided by the TBAc, and that's

how you generate the 0.64, and how you generate the 0.71 is based on how much of the TBAc is converted into TBA, I think, if I understood it.

DR. BUDROE: Correct.

PANEL MEMBER ARAUJO: But one general concept that I will have is, so the TBAc is bigger in molecular weight than the TBA, right?

So if you are to generate -- if you go for the TBA -- from TBAc to the TBA, shouldn't you just be going like from a larger number into a smaller number? In which case, and my question is that should you really be multiplying by the 0.71 and the 0.64 or should you actually be dividing, because you're not calculating the TBA based on the TBAc, you're calculating -- you're going backwards. You're going from the TBA going back to the TBAc. And what you're multiplying with this smaller conversion factor, and this metabolic conversion factors is like a -- if you were going like from the TBAc to the TBA.

Unless I'm having some fundamental concept, and there is not well -- am I expressing -- or do you or others follow what I'm saying? Am I expressing myself well?

To convert from the TBAc to the TBA, so you would divide the TBAc by the TBA, right, so you will have a

positive ratio?

DR. BUDROE: Well, you wind up with a fraction there.

PANEL MEMBER ARAUJO: You end up going to the fraction, but what you're trying to convert is the data from the TBA back to the TBAc. So shouldn't -- if you multiply it by these factors which are fractions, you're actually getting smaller numbers, which doesn't make sense.

PANEL MEMBER ANASTASIO: Can I make a comment here?

PANEL MEMBER ARAUJO: Yeah.

PANEL MEMBER ANASTASIO: So I went through the calculation because I had the same question. And if you actually go through the unit analysis, where you put milligrams of TBA or TBAc, it all works out. So the calculation is correct.

PANEL MEMBER ARAUJO: It does?

PANEL MEMBER BUCKPITT: Yeah.

PANEL MEMBER ANASTASIO: Yeah. And it's weird because the units are inverse milligrams per kilogram day, which is the confusing part of it. But the units are correct.

CHAIRPERSON KLEINMAN: One other thing that could help in thinking about this --

PANEL MEMBER ARAUJO: But -- oh sorry. Yeah.

CHAIRPERSON KLEINMAN: -- is there's some data in there from an inhalation study that showed that the TBA levels and the TBAc levels rose slightly during the exposure. And then the TBAc dropped off to about 50 percent after about 4 hours, but the TBA stayed constant.

So at -- depending on where, you know, the amount of time we're talking about, the TBAc could be -- you know, it would be expected to be somewhat lower, than the TBA at least in serum. Now, whether -- and, you know, maybe it would be helpful to have, you know, some of that data graphed. It's mentioned in a paragraph, I think, but maybe put in -- you know, if it's possible to graph the data, it might make it a little clearer that, you know, the relationship between the TBA and the TBAc, at least in a limited experiment.

PANEL MEMBER BUCKPITT: Were there complete pharmacokinetic studies done on that or toxicokinetic, so that you actually have AUC values for those two, TBAc and TBA?

DR. BUDROE: No, they were not.

PANEL MEMBER ARAUJO: What --

PANEL MEMBER GLANTZ: Just to -- and I -- and when I was reading it, I got confused by this same point too. And I think if in the report, you actually put the

units in, basically do what Cort did, it would make it clearer, because I had kind of the same reaction. It seemed like it was backwards.

But I think if you -- instead of putting the 0.71, actually put the units of what divided by what. So when you see the thing worked out, you can -- I think it would make it a lot clearer, basically to do what he did, because I didn't think to try that.

DR. BUDROE: Okay. We can add that.

PANEL MEMBER ARAUJO: Well, two things. So, yeah, what Dr. Kleinman mentioned is actually on page 2 of the document. And it does relate to the pharmacokinetics. I went to the original reference, which is a study from Groth in Human and Experimental Toxicology in 1994, because it just appeared strange to me that statement, and that there was a decrease in one of the compounds from the TBA, but the other compound it stayed the same.

Well, that can be sure, but it depends on the time frame when this has happened. Eventually, the TBA has to drop, and that is not mentioned in the paragraph. And that what is could be misleading.

So what I did find in the study is exactly what you're saying, but they did a follow up of -- and the whole kinetics is for 300 minutes. At the moment, when the TBAc starts dropping, it's like in the 250 minutes of

their experiment, and they just follow up like for 50 minutes more.

So if they had continued seeing these like, let's say, for 100, 500, or 10000 minutes. And eventually, they're going to see that the TBA will drop. So I think that this will need to be edited, and that information will need to be added.

And if -- and if -- if the figure were to be inserted, so that would certainly make it very clear, because that would not be -- it would leave any ambiguity out. But going back to the risk factor -- to the conversion factors. I know that the units make sense and everything. It's -- and I don't want to spend a lot of time, because I could be mistaken, and so maybe the way to do this is that after -- or what if we just invite to review these calculations, and I can actually get together maybe one-on-one, you know, and look at the calculations and per se, and either I understand them and it makes sense for me, or actually we see where the problem could be.

But again, it has to do is with the directionality, and I'm thinking of the ratio. It's not the units. I don't have any problems with the units. I think that the molecular weight is correct, that the conversion factors are correct, and the ratios are

correct. I think it is in the way how the factors are used. That's what I'm having a problem. I have the feeling that it could be instead of multiplying, that it could be dividing.

PANEL MEMBER ANASTASIO: Well, and another way to think about it is, you know, so this is a risk per dose, right? So TBAc weighs more than TBA.

PANEL MEMBER ARAUJO: Right.

PANEL MEMBER ANASTASIO: Therefore, the risk per dose of TBAc is lower than the risk of TBA per dose of mass. So the directionality is correct.

PANEL MEMBER ARAUJO: Oh, I see. I see what you're saying. Okay. All right. We'll talk.

What was the other point then that I wanted to -- okay. So the other point then, which you spend like about, you know, 80 percent of the response is focused on that. It focus is on a fundamental question is that it is being asked by the company, is the TBAc carcinogenic, yes or no?

And they are arguing that it's not. And then you're showing the evidence, and the agency is showing the evidence, and that supports, and that it should be considered a carcinogenic. And the section does list and pretty much all the relevance that it is, and all the relevant information.

It's a bit confusing though in the way how it's presented, and it is organized. It is actually very well presented in here in the slides. And when you're reading it, it's a little bit of back and forth. And at the end, you don't even have a clear feeling of what is -- really, what case are you making?

So I think that I do have some suggestions. The discussion comes into whether the compound feels or meets like the 7 criteria for these to be considered or the tumors that are developed are due to these alpha-2 globulin as a suggested response or are due to genotoxic and -- or some other mechanism effect.

And basically, what you're saying is that it doesn't fulfill all the criteria, right?

And because it doesn't fulfill all the criteria, so you cannot -- and they're arguing it does fulfill at least some -- the 4 essential criteria. It doesn't need to fulfill all the 7 criteria.

So you start like by -- I could suggest that once in page 21 where you put like the 7 criteria, that you have some sort of like a summary statement or introductory statement, even from the dinning, saying, you know, that the TBA fits completely some of the criteria, and put criteria -- right -- partially some of the criteria and put criteria 3, 4 and 5, and does not fit any criteria,

and put the criteria.

So, you know, even from the beginning, you know, what is -- what is -- what to look after. And then you can start a discussion of each one of the criteria and then -- but -- yeah, and after you do the whole discussion, I would say that you have sort of like a summary or a concluding paragraph at the end where you put the position. So based on this data and that it doesn't -- it meets some of the criteria, but it doesn't meet some of the criteria, so we cannot conclude that this carcin -- tumorigenic effects are due to this alpha-2 globulin associated effect. So there will be all the data, but it would be like a clear message, and at the end.

And I think that having a table like the one that you showed to -- in response to the company, and that you show in the slides today, you put a table where you compare your analysis with -- and the -- and other analysis. You don't need to put the other analysis, but you can have a table like that, where you summarize actually Criteria 1, 2, 3, 4, 5, and then have like the different studies or things and support, and that -- whether it fits or it doesn't fit the criteria.

So I think that that would make it really helpful. And it's important. It's really the hope -- you

make the whole case on whether this is carcinogenic or not is actually based on these 10 points, right? So having this quite clear, I think that it would be beneficial.

And then was -- so these are the 2 more fundamental points. And some others will be -- on page 3, where you are discussing the metabolism and the pharmacokinetics in paragraph number 4 of page 3, you talk about, "Two major radioactive components, A1 and A2, were detected in expired air from high-dose animals 6 hours post-exposure", but you never define what A1 and/or A2, or at least, I couldn't find them.

They are not even -- they are not shown either in the figure 1 where you have the proposed metabolic pathways. I have the feeling that they actually come from the study indirectly. And maybe, they -- and I was going to look at the study, but I couldn't really find it.

So if you could define those, what are A1 and A2, and would even mention the specific compounds that you're referring to. Otherwise, it is just not very clear.

In page 3 also, at the end of the last paragraph. And so you're saying the -- and this is -- also talks about the metabolic and pharmacokinetics, you talk about like the free TBA was not detected in the blood, and after the whole -- so my question to you is like it is not detected, there is no free TBA period, and it is -- is it

bound to have all other components and proteins, lipids, lipoproteins and -- or it is that the whole TBA is metabolized, and to the -- metabolize to the other compounds that you mentioned. Do you know?

DR. BUDROE: Well, not everything is -- not all the TBAc is metabolized to TBA.

PANEL MEMBER ARAUJO: Right, but you do mention is that free TBA -- but once the TBAc is metabolized to TBA, so there will be -- you should be able to detect it, and actually you detected it -- you detect TBA in the blood, whether that is free or coupled with other things, that I don't know. I don't know what is the form, how TBA is found in the blood.

DR. BUDROE: Well, you'd wind up -- what you're going to wind up finding is either 2-hydroxyisobutyric acid, which is the U2 in the metabolic scheme, or the T-butanol glucuronide conjugate, so --

PANEL MEMBER ARAUJO: But those are the metabolites.

DR. BUDROE: Right.

PANEL MEMBER ARAUJO: What about the TBA? The TBA is measured in the blood, not the metabolites, the TBA.

DR. BUDROE: Well Groth and Freundt found that in the blood in their study -- what Cruzan and Kirkpatrick

were looking at were -- was a metabolism study. And after that single dose, you know, when they actually did the measurements, they didn't find free TBA at that point, so they were looking at it downstream time-wise far enough.

PANEL MEMBER BLANC: How far down? Maybe the confusion is you how downstream it is, how far after the dosing. And I have to say that in the other study, you're not explicit that they -- about the implications that they never achieved steady state. So when you talk about the half-life of the parent compound, the animals never achieved steady state. They were still increasing their levels. And that -- doesn't that have some implications for how you interpret what you're calling a half-life, in a way?

DR. BUDROE: That does. And we can go back and look at that and clarify that.

PANEL MEMBER BLANC: And do you have a sense as to why they never achieved steady state? They were obviously exceeding the metabolic capability of the animals.

DR. BUDROE: Could be saturation.

PANEL MEMBER BLANC: I mean it has to be, doesn't it?

DR. BUDROE: Um-hmm.

PANEL MEMBER BLANC: So does that have some

implications about the proportions that go different ways. I mean, your -- your inference by the level of the metabolite you care about being 350, and the level of the parent compound was 300, or whatever it was, something like that, I don't remember exactly, is that, you know, that's the major way it's going. But that's the major way it's going when you've saturated the metabolism.

So I don't know what it means, if you weren't saturating metabolism.

DR. BUDROE: If you were using very low doses.

PANEL MEMBER BLANC: Well, yes, lower than what these animals were exposed to.

PANEL MEMBER BLANC: And then related to that, just while I'm here, did you -- was there any data -- I know there's no human cancer data or no human epidemiologic data, but is there no human metabolic data even in vitro?

DR. BUDROE: None.

PANEL MEMBER BLANC: So you have no idea actually if this metabolite is a metabolite in humans exposed?

DR. BUDROE: No, we're making the assumption that rats parallel humans.

PANEL MEMBER BLANC: Do you -- do you have other enzymatic reasons to make that assumption, in terms of what you think -- I mean, is there some basis for making

that assumption, or is it just a public health protection assumption?

DR. VORK: This is Dr. Kathleen Vork. We have looked at other chemicals that metabolize to TBA, and those chemicals do have some human data, so we can look at that further to answer your question.

PANEL MEMBER BLANC: And I would say something about it in the text maybe, because it's kind of an obvious, you know, question one would ask oneself about -- about this.

DR. VORK: Thank you.

DR. BUDROE: To get back to Dr. Araujo's question earlier. The radioactive components, A1 and A2, that were detected in the expired air, we actually have in the document that A2 was chromatographically identical to TBAc. And the author's couldn't identify component A1.

PANEL MEMBER ARAUJO: They don't say what it is.

DR. BUDROE: No, they couldn't identify what A1 was, but A2 was TBAc.

PANEL MEMBER ARAUJO: So in that case, so you could say it instead of just saying A1 or A2, because A1 or A2 is just a label that they make.

DR. BUDROE: Right. Now, we actually state that A2 is TBAc.

PANEL MEMBER ARAUJO: Oh, oh, that you're saying

it after. The author has stated -- I see.

How do you say, so it doesn't --

PANEL MEMBER BLANC: Confused.

PANEL MEMBER ARAUJO: Yeah. So maybe you can make 2 major reactive components of which the authors label or name as A1 and A2 were detected, blah, blah, blah. But the thing is when you're putting 2 major recommendations A1 and A2 and you're coming from a whole description where you talk about you -- you, 1, U2, 4, 6, et cetera, and you have a good correlation with the figure in figure 1. When it just comes with A1 and A2, it just throws you off. Where is that?

I actually went to the figure and tried to see which one is A1 or A2 and I didn't see it. So just maybe mention it, you know, the -- clarify that way, and --

DR. BUDROE: Right, we can clarify that.

PANEL MEMBER ARAUJO: Okay. In that same page, it is awkward that you were able -- or they were able to detect the TBA in various tissues after the administration, tissues such as the larynx, trachea, lungs fact with the lows -- animals that were exposed to low concentrations.

But when they were exposed to high concentrations, so they could not detect productivity in none of these tissues. And you do mention that maybe that

was probably due to the low specific activity of the Carbon 14 TBAc that it was used.

My question is, is this your speculation, is this the author's interpretation, was there any data in that paper that show that that could be the reason, or that -- are there any other alternative explanations of why is that happening?

DR. BUDROE: That was the author's conclusion that we're citing in the document.

PANEL MEMBER ARAUJO: Did it show any data? Because this is -- this is freely like a very hand waving, you know, like -- they will have to actually show some compounds or they do the measurements of the current 14, and then they see like the radioactive counts, and per tissue, or maybe -- weight, and with lower in the high concentrations versus the other, if they use the same. Carbon 14 as very long half-life, right?

And it is likely that they probably had like the same path. Why to explain that they will have in one -- same -- probably same experiment one would hide a specific activity that allows you to detect all these, and then another one with a very low specific activity that doesn't allow you to detect it?

PANEL MEMBER BUCKPITT: Well, the specific activity is the amount of radioactivity per milligram of

compound, or nanomole of compound.

PANEL MEMBER ARAUJO: Right.

PANEL MEMBER BUCKPITT: So when they went to the high doses, they probably used the same material, but had to dilute it with cold material to use it.

So that necessarily decreases your ability to detect. You can take their data and actually put limits of detection. Assume twice background, you can work backwards based on their specific activity and determine what the limits of detection would be. And if you want to, put that into your report and say, all right, they could have detected at this level or above, and that might solve your problem.

PANEL MEMBER ARAUJO: Might solve -- exactly, yeah.

DR. BUDROE: Yeah, and that -- your description of what's going on is correct. And we can go ahead and work up a limit of detection for that and --

PANEL MEMBER ARAUJO: And this has to do with pharmacokinetic data. Although it's not mentioned in this first section. It's mentioned elsewhere, like, for example in page 34, but you talk about fractional absorption for the TBAc of 95 percent and you're using it like for the derivation of your CSF values, but I never saw a reference for that.

And this number is different to the number that was used in the previous document, and by other authors where today the number has been as lower as 70 percent or something like that.

So if you have it, so I think that you should just reference it, because you're making a change in the document based on a value that is not being substantiated.

Actually, you even put it in the first page, right, in the second -- in the first paragraph -- at the end of the first paragraph you put the unit risk factor and inhalation slope factor assumes that 95 percent of an inhaled dose of TBAc is absorbed systemically, but other authors have used like different doses -- different fractions, I'm sorry.

DR. VORK: Okay. The value of 95 percent -- this is Kathleen Vork -- is coming from table 3 of Cruzan and Kirkpatrick for the low dose, table 3, where the amount of exhaled from air is radio -- amount of radioactivity exhaled from air is 4.8 percent of the inhaled dose.

PANEL MEMBER ARAUJO: Okay. So you can just say it and reference it --

DR. VORK: Thank you.

PANEL MEMBER ARAUJO: -- and then you will know.

The document is about the cancer potency values. And this is where you need to focus, but I -- again, I

don't know if this is -- what I'm going to say is present in one of the other documents about this compound from the -- for the Agency. But mention or having a brief mention of some of the other effects and the TBA costs -- causes will be helpful also to have that overall perspective on the toxicity of the compound. So mention something about the reproductive toxicity, something about the developmental toxicity, something about the neurodevelopmental toxicity.

In some documents, those are like a very long paragraph, and long sections. It doesn't need to be a long section, but at least, you know, that it gives -- it allows to have that perspective that a TBA does something else in addition to have a risk of for cancer, and also mention about side effects, you know, when you get exposed to it, and what are the symptoms, and that you have. And I don't know if you mentioned it somewhere in the document and I missed it, but --

DR. BUDROE: Okay. So you'd like a short TBA noncancer toxicity summary.

PANEL MEMBER ARAUJO: Yeah. Okay. Now, going back to the point of the different studies and that are used to document on the toxicity of the TBAc. And so you have like in vitro studies and you have in vivo studies. And the in vivo studies don't really show it, and it's

mostly like the in vitro studies and the Comet assay, and you responded to the company well.

Why is that -- and you also mentioned that in the in vitro studies that toxicity was excluded as a cause for or to explain like the -- a false positive result and with Comet assay.

However, with the animals, something curious happened. So you do have some -- a statistical significant difference that they meet those, but you don't have a significant difference with the highest dose. And the explanation that you give, and probably the authors give, and that is in table 1, page 7, is that the animals -- it's because of decreased survival at the higher dose. So it is like the lower number of animals, so probably the animals don't really make it all the -- don't -- to exhibit the carcinogenic effect. What do they -- do you know what was the reason for lethality on why did they die off? Did the author say it in the paper?

DR. BUDROE: No. NTP didn't specify what the --

PANEL MEMBER ARAUJO: But that presumably tells you that TBAc is doing other things that are actually quite important, it even decreases survival, and at the higher dose that are not cancer related. So even -- so that's in the NTP, right, because that was the National Toxicology Program study?

DR. BUDROE: Correct.

PANEL MEMBER BLANC: Can I ask a question?

PANEL MEMBER ARAUJO: Sure.

PANEL MEMBER BLANC: Did I understand though the numbers, right, where you said only 1 survived to the end of the 2-year period? Whereas, the -- no, and then you said only 10 in the once that didn't have the high mortality? Did I -- was I misreading what you were saying about how many survived and didn't survive to the end of the study period? That's right in the same section.

PANEL MEMBER BUCKPITT: Line 133, I think. 133 through 139.

PANEL MEMBER ARAUJO: 133?

PANEL MEMBER BLANC: Which page?

PANEL MEMBER BUCKPITT: Page 5.

PANEL MEMBER BLANC: Yeah. Survivals were 10 of 50, 6 of 50, 4 of 50, and 1 of 50. That survival to the end of the study period.

DR. BUDROE: Right, 1 of 50 animals survived to the end of the study.

PANEL MEMBER BLANC: Well, so I guess what we care about is, you mean, they died 1 week early? Because if only -- you know, if 49 of them died at 1 year, that's a lot different than if 49 of them died at 1 year 11 months and 12 days.

DR. BUDROE: Right. And that's one reason we did the poly-3 incidence correction.

PANEL MEMBER BLANC: But the poly-3 incidence correction didn't change much. It really didn't have a big effect. So it doesn't seem to me that they died all that early, if that's true.

DR. BUDROE: They -- yeah, the survival curves -- I don't have the NTP document with me, but most of the mortality was fairly late in the study.

PANEL MEMBER BLANC: So could you please, rather than simply say that other sentence, which is kind of shocking, give some sense of the median survival or something.

DR. BUDROE: Right, when the mortality occurred in the study.

PANEL MEMBER BLANC: Right. Otherwise, it doesn't make any sense. Your -- the impact of your survival adjusted-risk factors should be -- it should change dramatically. It should become much more potent, if that was really the case, I would have thought, but it doesn't seem -- you have these adjusted numbers, which is, you know, 7 out of 33. Somehow, the adjustment adjusts down the number of animals studied is what it seems to do, if I understood it.

DR. BUDROE: Correct. It reduces the effective

incidence, but you're --

PANEL MEMBER BLANC: But not -- but by reducing -- it just -- it should increase the incidence, which it does actually, because it's not 7 out of 50, it's 7 out of 33.

DR. BUDROE: I misspoke. It reduces the denominator.

PANEL MEMBER BLANC: Right, but if you notice the denominator numbers are actually really close to each other, right? It's like 33, 36, 34. So the statement about the decreased survival time affecting what you saw doesn't -- isn't consistent with what you then report? So therefore, I wouldn't say that decreased survival time is the explanation for why, in the highest exposure group, you see less -- a less absolute incidence of disease.

DR. BUDROE: We can reevaluate that statement.

PANEL MEMBER BLANC: Then also, if I might, in light of what you said, and maybe Stan wants to comment on it, but I actually don't know that, at least if you're going to use a 0.05 level of significance, I don't know how you're allowed to just pick and choose which group you say is statistically significant from the baseline at 0.05.

Obviously, you did 3 separate tests, the second -- the first dose versus no dose, the second dose

versus no dose, and the third dose versus no dose. And you say the middle dose is statistically significant at the 0.05 level, but those are not 3 independent tests, in that sense.

DR. BUDROE: Well, we did pairwise comparisons between the dose levels and the controls, and that gets commonly done. NTP does the same thing.

PANEL MEMBER GLANTZ: Did you adjust for the multiple comparisons?

DR. BUDROE: No.

PANEL MEMBER GLANTZ: Okay. Well, that's the point Paul is raising, so you should, unless -- I mean, unless there's an established protocol not to be. But if you're doing a family of comparison like that, that's going to inflate the number of significant findings that you get beyond the nominal 0.05 P-value.

DR. BUDROE: Well, NTP commonly doesn't when they present their results. They do pairwise comparisons and they do a trend test for dose response, and that's it.

PANEL MEMBER BLANC: Well, the trend test is allowable. You did that.

PANEL MEMBER GLANTZ: Yeah.

PANEL MEMBER BLANC: And that was significant, if I looked at the footnotes correctly, right?

PANEL MEMBER GLANTZ: Yeah. I mean, the trend

test avoids this problem. But if you're going to do a bunch of pairwise comparisons, they should be corrected for multiple comparisons.

DR. BUDROE: Okay. We can take look at that issue.

PANEL MEMBER BLANC: Sorry, I interrupted.

PANEL MEMBER GLANTZ: I mean, I think that -- I mean, I think the trend test actually makes more sense, because you're presuming there's a dose response, right?

DR. BUDROE: Correct. And although the high dose probably causes problems with that is probably why there wasn't a positive trend test for the male rat kidney tumors.

PANEL MEMBER GLANTZ: Well, so what's wrong with the high dose data? I mean, I noticed that too when I was reading it. I mean, is that just random fluctuations, or when you get to the very high doses, does something change in the way the drug is being handled or the chemical is being handled?

DR. BUDROE: No. Beyond the mortality being slightly higher for the high dose, we probably don't really have an answer for that.

PANEL MEMBER GLANTZ: Yeah, because if you're presuming that the -- that the -- that there's not some fundamental change in what's going on biologically that

would account for a non-linear effect, then it is a problem. But just doing the pairwise comparisons -- I mean, if you do enough comparisons, something will be significant.

PANEL MEMBER BLANC: If they -- if you do a Bonferroni adjustment on your P-value of 0.01 -- 0.012 is still significant, if you divide 0.05 by 3. So you're -- so maybe that is the way they handle that problem.

PANEL MEMBER GLANTZ: Yeah, or you could use the Holm-Šídák, which is going to be less conservative.

But I do think -- I do think this question of why did the curve bend down at the high doses, I mean, is that just random, because it -- I mean, because you don't have thousands of rats, so -- or is there something going on there? I mean, that's what I wondered in looking at it. I mean, this is not my area of specialization, but just looking at the statistics, I did find that a little odd.

CHAIRPERSON KLEINMAN: But even at -- you know, in the control group, you had 90 percent mortality at 2 years. Two years is really, you know, pushing the age on these guys on the mice.

PANEL MEMBER GLANTZ: Well, then it may be that you should back -- you should just make that case and look at the effect that a shorter time period than 2 years, because if you're -- if the background death rate is going

up because you waited 2 years, then that is going to obscure the -- detecting the effect of the drug -- or I keep saying drug, the chemical.

DR. BUDROE: Okay. And there's also -- it's been pointed out to me that the metabolic pathway has somewhat shifted as dose increased in the Cruzan and Kirkpatrick study. And there's the possibility of what your seeing is a shift in -- a shift in metabolism as the dose increases. I mean, hypothetically, that's one possibility.

PANEL MEMBER GLANTZ: Well, I mean, if you think that's what's going on, then maybe you should make the case not to look at the highest dose group, because what you're interested in looking at is the effective low levels of exposure.

DR. BUDROE: Okay. We actually do drop the high dose group from the BMDS model.

PANEL MEMBER GLANTZ: Well, that's true, yeah. Well, then maybe you should be consistent through the report, if you have a good reason to do it from a biological point of view.

DR. BUDROE: Okay. Well, we can correlate the biology with the curve fitting.

PANEL MEMBER GLANTZ: Yes. That's a good idea.

I actually had something to say, which surprised me.

PANEL MEMBER BUCKPITT: As long as we're on this topic, I have a problem reading this. It says the 24-month termination you had 13 out of 15 animals had their adenomas and carcinomas of the renal tubules. And yet, 2 sentences later, you say the 2-year survivals were 1 out of 50 in that low -- in that high dose.

How can you get 13 out of 50 animals having carcinoma at 2 years, when only 1 out of 50 survived?

DR. BUDROE: That's the cumulative incidence by the end of the study. So if you have animals that died on round --

PANEL MEMBER BUCKPITT: Got it. Thank you.

PANEL MEMBER BLANC: I don't suppose the NTP gives you the actual survival time by rat, do they?

DR. BUDROE: They didn't, but we got that data, I believe. Dr. Rona Silva, the -- that was included in the data that was used to generate the poly-3 correction?

DR. SILVA: Hi. This is Dr. Silva. Yes.

PANEL MEMBER BLANC: So you have -- each rat how many days they survived, and that's what you used for the adjusted analysis?

DR. SILVA: Yes.

PANEL MEMBER BLANC: So is there a way to do a proportional hazards analysis where you look at cancer free survival time and you censor the ones that died

cancer free adjusted for the exposure level?

DR. SILVA: Oh, they will look into it. There is a way to do it.

PANEL MEMBER GLANTZ: Yeah. I mean, that is a good suggestion, because --

PANEL MEMBER BLANC: And I hope you noticed the way he said that's a good suggestion. In other words, anything else I said wasn't so good.

(Laughter.)

PANEL MEMBER GLANTZ: No, that -- that was one of your many excellent suggestions.

(Laughter.)

PANEL MEMBER GLANTZ: No, but that -- that would -- that would get at the -- at the issue I was trying to raise. If you -- you know, if the rats died of other things would be to censor them when they died of something else, yeah. That might fix this problem. And that will probably give you a more sensitive measure, too.

PANEL MEMBER ARAUJO: Okay. So I -- following up just a small point. So on page 2, it's just changes in how to say things, and -- or how to show them. Like, usually in animal studies, those -- don't use animals that were killed, you know, instead say "sacrificed" or "euthanized". So second paragraph, page 2, instead of saying 2 animals per group were killed immediately after

exposure, I would change that to again "sacrificed" or "euthanized".

On page 5, the numbers in the last paragraph, when you talk about the incidence of the adenoma and -- or renal tubule adenoma in the various studies don't really match the numbers that I -- that you're showing in table 1. So the numbers like, for example, control male rat renal tubule adenoma incidence was 2 out of 327. And you are actually -- and you go to table 1, and you don't really see where the 2 are coming from. You actually have -- in one group you have 1, in another you have like an 8. And even if you add like all the different groups. So I don't know if I am creating too much and -- but I'm not really making much sense in the --

DR. BUDROE: Well, those incidence numbers and like line 144, 145, that's actually the historical control incidence for that tumor type. So that's not the incidence -- the study incidence, that's just a relative comparison --

PANEL MEMBER ARAUJO: Oh, I see. I see.

DR. BUDROE: -- of what the control incidence would be.

PANEL MEMBER ARAUJO: Oh, okay. Got it.

Do they say it? I don't know. But you did say, "Comprising the recent NTP historical control database

from drinking water studies". So you say it at the end.

Okay. So never mind.

And page 7, just a misspell on the heading "Biochemical Effects and Cell Proliferation". Make sure that you fix the cell.

And page 10, in the legend of the table, it is confusing how you're showing like the different probabilities. And so it seems that the other supply of Kruskal-Wallis test in looking at significance, and then you put little A for all the P-values in the control group, and mention something like, "Probabilities associated with the vehicle control group represent the Kruskal-Wallis test. For all other probabilities, P-values are from comparison of the respective group versus the vehicle control using a Mann-Whitney U test with the Z-scores corrected for ties".

I'm not at a decision -- Stan, please correct me I am wrong, but I assume that they did --

PANEL MEMBER GLANTZ: What page are you on?

PANEL MEMBER ARAUJO: -- that they did -- this is table 2 on page 10. So I assume you're having like different doses and 4 different groups. And they're doing a non-parametric study. So I think that they did a Kruskal-Wallis to see if there was any significant difference. And once the Kruskal-Wallis was positive, it

showed that there was a difference, they did a Mann-Whitney test to localize the differences, I imagine, because that's usually how it is done.

But you show -- like, it is always, like I say, like you're doing, like, 2 different statistical tests, and have like it for different groups and different concentrations, and that like put in a little A for all the P-values and the control group. That doesn't

DR. BUDROE: So you want a footnote -- one footnote for a vehicle control group and a different footnote for the other comparison.

PANEL MEMBER ARAUJO: I don't understand that. What are these P-values in the control group? What do they represent? The ones that you're putting with the little A, what is what they --

DR. BUDROE: I'd have to go back. To be honest, I'd have to go back and look at the study, because this is -- what we've got in here is how the author has cited these results.

PANEL MEMBER ARAUJO: Oh, I see. I see.

DR. BUDROE: So we didn't do that statistical analysis. The authors did.

PANEL MEMBER ARAUJO: Again, I'll -- you know, my -- I guess, my guess is that at the Kruskal-Wallis in each one of these categories hyaline droplet, hyaline

crystals, nephropathy, and PCNA, because the date have all these different groups. They saw that there was a significant difference and then they asked whether are they differences? And they did pairwise comparisons with the Mann-Whitney in between each concentrations and the vehicle control and they are showing the Mann-Whitney P-values for each one of those, but this is not what it's saying in the legend.

And what it's saying in the legend doesn't make any sense to me. So if it is not what I'm thinking it is, it should be something else different, but I don't believe that it's really --

DR. BUDROE: All right. So you're suggesting we have a better, a clearer definition of what the statistics were -- what the -- what the statistics that the authors did mean, just clarify their work a little bit.

PANEL MEMBER ARAUJO: Right. And if you're showing these P-values or what is what these P-values are. So what I think that you're saying is the P-values are for comparison with their respective group versus the vehicle control. So they P-values for the concentrations are all -- are clear. I think that all those are Mann-Whitney values. I think that it is more the question about the little A -- the P values and the little A, what it's -- really what that means.

Page 12, figure 3, you're showing the figure 6 from the paper. Your legend doesn't really reflect what the figure is showing. I think that you should have your -- sort of like a subtitle or title for the legend and then you can leave the whole explanation, if you want,

Because what you're putting as the legend is sort of like your interpretation of the figure, but it's not really a title or subtitle for a legend.

PANEL MEMBER GLANTZ: Could I just -- so one -- just one thing that I was confused by in this figure is where did they get the R^2 from, because what they have -- they have error bars around the points. And so did they -- were they using the raw data or were they just taking the mean values that is where the dots are, and if they -- without worrying about the variability, or did they somehow allow for the variability in the calculations?

So I had a hard time interpreting that picture. And, you know, if you'd just look at the graph, they -- the line extends beyond the data down -- the data ends at about 140, and they extend it all the way down to 75. I don't know quite where they got that line from. And you're going to get -- if you have -- because if you have -- if you're just looking at the center points, that's probably going to overestimate the R^2, because it's

leaving out the variability around -- in the little clouds around each one of the points.

DR. BUDROE: I will not dispute that whatsoever. The -- and for an exact explanation of what the authors did in there, I'd have to go back in, so we could --

PANEL MEMBER GLANTZ: Yeah, I mean, when I looked at that, I mean, I worried a little bit that it's making it look like there's a stronger relationship than there is.

DR. BUDROE: Yeah, well, that was -- that was the point that we were trying to make is that it didn't look like there was -- with increasing dose, there wasn't that much of an increase in cell proliferation until you got to a really high dose.

PANEL MEMBER GLANTZ: Okay. Well, just applying the eyeball test looking at that, I think that's a reasonable interpretation. But I had kind of a hard time understanding it. And I think, you know, it may be that the thing you need to do is to redraw the graph. And, you know, the other thing is it wasn't clear what the error bars are. Are they standard errors, are they standard deviations, are they confidence intervals?

And so that could have a big effect on what -- you know, what that picture looks like or how you would interpret what's in the picture.

CHAIRPERSON KLEINMAN: The other problem with this graph is the alpha-2 microglobulin data, you know, later on we're using the fact that you don't have a difference between the 250 and the 400 alpha-microglobulin statistically, but there's an increase in the labeling index, which indicates that, at least at those lower levels, you know, the toxicity is not related to the alpha-2 microglobulin. And then at the higher dose, it goes up.

DR. BUDROE: Right. There's a -- there's a disconnect between the labeling index alpha-2U production.

CHAIRPERSON KLEINMAN: So this -- yeah, it's almost like there's a threshold kind of thing. I think the graph itself is very misleading in terms of the way you're going to use the data. In here, they're showing that there's some sort of a relationship which is, you know, looking at those first 3 data points spurious.

DR. BUDROE: Right. Well, what we were -- we put that graph in there, but we're essentially disagreeing with the author's interpretation of the data. We may not have made our description in the document clear enough on that point, so we can try to go ahead and clarify that.

PANEL MEMBER GLANTZ: Well, you know, as I said, to a couple other people, I'm not a toxicologist. And I found this -- a lot of asterisks in this report kind of

hard going because it was talking about things I don't know a lot about. But, you know, when I -- see I'm glad -- I had totally missed the interpretation that you're putting on this.

No, I don't blame you for that. That maybe is reflecting my lack of knowledge, but I looked at it in exactly the same way Mike did, is that they drew that line on there, but it really looked to me like there was a threshold effect.

CHAIRPERSON KLEINMAN: Right.

PANEL MEMBER GLANTZ: You know, so I think you would do better to, you know, maybe if you want to include this and say here's what he said, and then have a side-by-side version with what you think of -- think it actually shows, that would be a lot -- I would have been less confused. And, you know, the best thing would be if you could somehow manage to get the raw data.

DR. BUDROE: I would not be -- yeah, that might --

PANEL MEMBER GLANTZ: That's not easy, I know.

DR. BUDROE: Yeah.

PANEL MEMBER GLANTZ: But you could even -- you know, depending on what those errors bars are, which isn't specified. You could if -- you knew what the N's are, you can almost simulate a set of data. And then that would

let you look and see does this support a threshold, if that's an important point you want to address.

CHAIRPERSON KLEINMAN: But I think the point is that the self -- cell proliferation is a function of the dose of the TBA, and that it's not a function, a real function, of the alpha-2 microglobulin. So if you wanted to show a linear relationship or some sort of relationship, I would change the X axis to be the concentration of the chemical, and then show that you've got these spots -- you know, this is the level of the alpha-2 microglobulin. And it's, you know, just scattered up there.

And then, you know, I think you could do that. But, you know, there are really 3 parameters that you're dealing with. And the 2 that are important are the labeling index and the dose. And it looks like the alpha-2 microglobulin is not an intrinsic factor to the response.

DR. BUDROE: I agree. And that was the point we were trying to make. And I think part of the problem we've had with this also is that all the data was graphically represented, but we don't have numeric data to go back and re-analyze.

CHAIRPERSON KLEINMAN: What I did to, you know, sort of clarify it for myself was I drew a circle around

the first 3 points, so you could see that those -- or you could put a bar across it showing that these are all essentially the same level of alpha-2 microglobulin. And yet, there is an increased response to the chemical, you know, if you wanted to use that graph, you know, without changing the -- you know, the thing and redrawing it.

DR. BUDROE: Right. I mean, and the whole point with that graph was that if the alhpa-2u globulin mode of action is actually operative, then as you see an increase -- an increase in alpha-2u globulin should correlate with an increase in labeling index, because it's -- the increased protein causes toxicity, causes the compensatory cell proliferation.

So if you see one, you should -- it should match up with the other. And that's not occurring here. You're seeing an increase in labeling index at the different doses. It's not matched by an increase in alpha-2u protein accumulation.

PANEL MEMBER ARAUJO: They don't mention any P-value for that correlation in the study?

DR. BUDROE: They mention an R^2, but I don't think a P-value. I'd have to go back and check.

PANEL MEMBER GLANTZ: But if they computed the P-value based on just the 4 points, that's going to be wrong.

PANEL MEMBER ARAUJO: It should be more.

PANEL MEMBER GLANTZ: I mean, I think -- I think if the point you're trying to make here, now that I understand what you were trying to say, which I think is a reasonable argument based on this graph, I would actually redraw the -- I would say here's -- you got the data from this guy, but redraw the graph to make the point you're trying to make. I think Mike suggesting of flipping the axis would probably be a good idea too. And then you could just make the point in the text that the author drew a different conclusion.

So rather than presenting their conclusion and arguing against it, you should present your conclusion and then make a comment that this is different than what the original authors said and why, or maybe a stick a footnote in there.

So I was very confused by this. I'm glad that I wasn't alone.

PANEL MEMBER ARAUJO: Okay. So let's just -- a couple of other points and -- page 23, table 5. So you have all the data, and in between parentheses, you're having some other data that for one of the numbers is shown as little C, right, the 1.7 and the concentration of 0. And you go to C, it says, "Average severity of lesions in affected animals", 1, 2, 3 and 4.

So I would imagine that all these values at the different concentrations that are between parentheses are in C, but they don't -- but you're not showing it, so just put the little C.

But then I ask you, you also have values in between parentheses for the female rats, and not all those values relate to severity of lesions. So one of them talks about inflammation, suppurative, mineralization, and nephropathy. So do they also correspond -- so are these semi-quantitative ranking of 1 to 4 or those are like a -- different other values?

DR. BUDROE: Yeah. The severity ranking is the same. We can footnote those additional data types. So like inflammation --

PANEL MEMBER ARAUJO: So from 1 to 4 mile moderate --

DR. BUDROE: Right.

PANEL MEMBER ARAUJO: So I would suggest, in that case, eliminating C. Take the C out of the column, and then just say something in the legend. "Numbers in between parentheses represent semi-quantitative, blah, blah, blah, blah for that parameter, and 1, 2, 3 and 4 as minimum, mile, moderate, and marked.

And page 28, last paragraph, you talk about for line 875, "TBA significantly increased BROD activity".

Line 876, "Content and PROD activity", so just define them before, which I think that you -- yeah, you defined them in the list of acronyms, just have it in the text, because this is the only time when you mention them in the text.

And the same goes on with the unit risk in page 32. So the first time that you mention it, that is in line 994, so that CSF and UR, so justifying find UR also prior today, which you also have it defined in the list of acronyms, but it is always helpful to do it in the text as well.

I think that that's it as far the document.

I only have one comment on your response letter. And I think that it is very well written. And overall, you really address other points as well, and make really good cases and good explanations of your points. Very minor thing is on page 43, in the response to Dr. Felton comment 7, so you are saying that the samples are purified in the samples is an indication that the sample is sufficiently pure when they are talking about a ratio of the DNA or the 260/280 ratio of 1.8, right?

And then you put it between parentheses, free RNA and protein. So they ratio doesn't distinguish in between DNA and RNA. So you can -- actually, you have RNA and the ratio could be 1.8 or higher. And all what you can say is that it is low in protein purity or some other things. So

just remove the RNA and it's a...

PANEL MEMBER GILL: Mike, I took your comment on figure 3, if you replot the data from a log dose versus labeling index, you nearly get a straight line. So there is a difference. So you may want to replug the data. I just took approximate values and you -- from the graph itself. So it is not -- the base has been plotted with microgram protein gives you erroneous -- plot it again. Of course, you cannot plot Log 0.

So that's a difficult thing to plot. But the other 3 are nearly a straight line, which indicates therefor -- it makes your point even clearer.

CHAIRPERSON KLEINMAN: Okay. I have a few comments in addition to what we've talked about. First, I want to correct a misstatement I made earlier about the removal rate from the serum. I had said something like a 4-hour removal rate. And that's really the length of time that the animals were exposed. The removal rate was 45 minutes for the half -- for 50 percent to go away. That's the number that was used in the calculations.

On figure 1, we had talked earlier, there was some confusion about what's a major metabolic route and what isn't. And I think since, you know, this is from the Cruzan and Kirkpatrick data anyway, would it help to put the percentages on the metabolites?

So U1 would 9 percent, U2 would be 45 percent, you know, or you could put it in at 2 different times. But I think it gives you a picture of where the major metabolites are actually showing up in the sera, and it just makes the -- that table a little bit more, you know, visual, you know, and brings the point across.

DR. BUDROE: Yeah, I see where you're getting at, and yeah, we could do that.

CHAIRPERSON KLEINMAN: Great. On page 5 is the first time you mentioned step sections, and I appreciate the -- you know, in your commentary you actually defined it, but I think it would be worthwhile, because a lot of people reading this might not be in tune with it as I wasn't, what specifically a step section was. So just, you know, the definition would be helpful.

There were a few minor typos, and I'll just catalogue those and give them to you.

On figure 2, the axis -- and I'm guessing this is also something you've, you know, basically copied from the document Faber et al., but they talk about an alpha-2 microglobulin score as opposed to a concentration. And are those the same thing, is the score actually the nanograms per milligram of total protein or is that something different?

DR. BUDROE: I believe it's essentially

impossible for me to give you an exact answer without having the paper in front of me.

(Laughter.)

CHAIRPERSON KLEINMAN: Okay. I think, you know, it's just something to --

DR. BUDROE: Oh, I can go -- I can go back, and we can add a description of what the authors meant by alpha-globulin score to the text.

CHAIRPERSON KLEINMAN: And then on page 11, on line 316, it says there's a statistically significant increase in cell proliferation, which I think parenthetically you could put in expressed as a labeling index, because you don't mention it earlier, and just for clarity.

PANEL MEMBER GLANTZ: Well, but isn't that talking about the figure that we were just talking about? The text you're talking about there is talking about figure 3?

CHAIRPERSON KLEINMAN: Yeah, it's talking about figure 3.

PANEL MEMBER GLANTZ: Yeah, so you're probably going to want to rewrite that whole thing, because that may be that done properly the statement is wrong.

DR. BUDROE: Okay. We'll look at that and the -- It will be considerably -- there's considerable

remodeling done on that section, so.

CHAIRPERSON KLEINMAN: Okay. I was a little -- I may have been misreading something, but on page 14, table 3, the leading paragraphs talk about an experiment with ends of 15 per group, and then table 3 only -- you know, the number of animals is shown, which, you know, 6, 5, 5, 6. So I wasn't sure whether that was from a different experiment or the one that you were talking about earlier with the -- yeah, where they were talking about the liver enlargement?

DR. BUDROE: Okay. I believe that they did a subset, but I'll have to go back and check against that, but I could see, either way, that that could use some clarification as to how they got from 15 nanomoles in looking at some of the gross pathology to, you know, 5 or 6 nanomoles in the -- in looking at the hypertrophy. So we'll clarify that.

CHAIRPERSON KLEINMAN: Okay. Great.

Oh, page 18, there's -- on line 500, I'm not sure I -- whether you were -- well, it says P greater than 0.01. I presume you meant P less than.

DR. BUDROE: (Nods head.)

CHAIRPERSON KLEINMAN: Okay. It changes the way I read it. Okay.

PANEL MEMBER ARAUJO: But he actually said, "No

significant increases in the frequency of micronucleated immature erythrocytes an no substantial decrease in the proportion", so I guess that he's --

CHAIRPERSON KLEINMAN: So it -- maybe it's P greater than 0.1 or some other number.

PANEL MEMBER ARAUJO: Yeah.

CHAIRPERSON KLEINMAN: That's what I had written down P greater than 0.1 is a --

DR. BUDROE: Right. Something went sideways there. We'll go ahead and fix that.

CHAIRPERSON KLEINMAN: Okay. On the section about cytotoxicity on the Sgambato Comet assay data.

PANEL MEMBER GLANTZ: Where are you at?

CHAIRPERSON KLEINMAN: This is on page 19, line 542 to 546. And the last sentence is that the test concentration exceeded the upper limit concentration recommended for the tests. So given that, did you -- was that a rationale for not considering those data in the genotoxicity assessment? Did you --

DR. BUDROE: Well, that influences whether it goes into the consideration of whether you should consider that assay or not. But the number of dead cells were not appreciable greater between controls and in treated groups. So we could add a discussion of that in there. We essentially answered the comment, but we could have

provided the additional information that we actually have in response to comments and didn't get into the document.

So we can transfer that. We can add what -- what we put in response to comments into the document itself.

CHAIRPERSON KLEINMAN: Yeah, I think -- you know, that was a -- yeah, that was an area that was helpful to cover. The other -- yeah, so as I said, I had some minor other changes, but those really covered -- you know, and I think we've had quite a bit of discussion, but I'd like to go around the table and give people a chance to comment, because I want to try to be conservative about our time. So, Stan, do you have any further commentary?

PANEL MEMBER GLANTZ: Well, I just had one other point and this is on the -- we got a letter dated November 28th from LyondellBasell. And at the -- you know, kind of just responding to the response. And there was just one point in there that I just thought would be worth asking about, if there's any of the ARB lawyers here.

But in the very last substantive paragraph, you know, they -- basically, they're arguing that TBAc is a better alternative to some other chemicals, which are used. And, you know, they're expressing some concern that if we accept this unit risk fact -- or the carcinogenic unit risk that that would, you know, be bad in terms of regulatory impact.

And my understanding is that's really not on the table for us. That's really a risk management decision to be made by the Air Boards. And so I just -- if that's -- I just -- if that's not correct -- if that's correct, I think -- I just wanted to have that understanding in the record. And if it's not correct, then somebody needs to tell us about it.

But that kind of tradeoff decision is not something I've ever seen come before this Panel before. So and that -- you know, it was a fairly strongly worded letter. So I just wanted to mention that. Otherwise -- well, and I have one other point, but you wanted to say something?

PANEL MEMBER ARAUJO: Yeah. No, I agree with you. I -- and I think that the response was very good in how you're responding to them.

I wonder whether there should be a mention in our document, or in this document, even though this is not a document about this compound, but where it is closest that even other compounds that convert into TBA, such as the two compounds that you mentioned, and have a conflicting -- or have -- didn't say conflict in -- and you can mention even the positives and negative studies, you know, that you are enumerating in the response to the company.

And that way, it would be addressed, and that way it will not be -- it will not seem as if this was just left out or not considered. At least it will give the impression that, you know, that you will -- you've considered, you've thought about it.

DR. BUDROE: You're talking about MTBE and ETBE?

PANEL MEMBER ARAUJO: Right.

DR. BUDROE: That would make this a vastly more complex document because there is a large amount of data out there for both those 2 compounds. And to try to boil that down into a summary to put in this document would be challenging.

PANEL MEMBER GLANTZ: Yeah, I don't think that's good idea --

PANEL MEMBER ARAUJO: I see.

PANEL MEMBER GLANTZ: -- because that's why they've separated the risk assessment from the risk management part. I mean, there is an MTBE document that went through this Committee a long time ago. I actually worked on that one too. So I don't think we want to get into comparative statements.

The only reason I brought this up was to try to, you know, show that we are paying attention to what these public comments are. And to make sure that my interpretation that those kind of issues about trade-offs

between chemicals is not our job here. Our job here is to assess whether the unit risk in this document is reasonably set an defended, and not to look at -- you know, given this, are -- even with this, are you still better off using this chemical instead of some other chemical in some industrial process. I don't -- that's not our job.

PANEL MEMBER ARAUJO: Yeah.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER ARAUJO: But I don't know if there will be another way of addressing this, because I think the point is very good. There's -- we are making a case that this TBAc is carcinogenic --

PANEL MEMBER GLANTZ: Yeah.

PANEL MEMBER ARAUJO: -- not based on TBAc data, but based on TBA data, right?

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER ARAUJO: And there are other compounds that generate TBA that are not considered carcinogenic on that -- with that same basis. So it's sort of like a lack of consistency, right, in how we analyze. I don't know if something very brief could be -- and I think that you responded well. You mentioned the 2 studies, and that show like positive data with the others that were not included in the analysis, whenever those

analysis were done.

What if I just mention those couple of -- those studies that they talk about in their response and reference to the previous documents and to have already --

PANEL MEMBER GLANTZ: Well, I just think it would be different from the -- it would be the first time anybody did something like that in one of these documents. I mean, the -- I think it's -- I mean, it's on the record in the hearing, and I think it's something that, you know, the Air Resources Board could take and Cal EPA can take note of.

But I don't think we really -- I think this -- these reports are fairly narrow -- for better or for worse are kind of narrowly focused. And I do think -- I mean, I did go back while I was listening to the discussion and look at -- you know, they're very clear in the document that in setting an inhalation unit risk factor for TBAc, it's -- they're not saying TBAc per se is a carcinogen. It's just the exposure to TBAc, that's metabolized into TBA, which is carcinogenic.

And so that -- I think that is an important distinction, but I think it's made pretty clear in the document.

CHAIRPERSON KLEINMAN: Sarjeet, do you have a comment?

PANEL MEMBER GLANTZ: Well, I just had one other --

CHAIRPERSON KLEINMAN: Oh, one other. Sorry.

PANEL MEMBER GLANTZ: -- one other question. And this is, I mean -- or maybe I'll come -- let me come back to it at the end. Let's hear whatever everybody else says first.

PANEL MEMBER GILL: Mine is actually just a question more than anything else, or a comment, because the -- irrespective of what mechanism of action of TBA or TBAc is, because there's some issue that is not there, it -- does OEHHA have a confidence that basically TBA is carcinogenic based -- and because there's only one value, correct, or actually 2 data points. One is thyroid, and the other one is actually in the Toxic Substances Program I mean, their testing program in NTP, that it's actually carcinogenic. So there are 2 data points, correct?

DR. BUDROE: Correct.

PANEL MEMBER GILL: So how much confidence that you have -- OEHHA has in that this is a relatively significant carcinogen?

DR. BUDROE: Well, we've got 2 different tumor types in 2 different species. And we're fairly confident that you're looking at a carcinogen here.

PANEL MEMBER GILL: So in the past, if there's

data points of this type -- of data information of this type, then that -- then that is considered a carcinogen that should be looked at, correct, that that's what it is?

DR. BUDROE: Correct

PANEL MEMBER GILL: All right. So that's one point. The other one is actually there is a lot variability in the genotoxicity data that you see that is presented both by you and by LyondellBasell, for example, different points.

I couldn't understand -- I couldn't understand the basis of why the variability was. And either it doesn't show in the document. It just is a stated fact. Is there away that OEHHA could explain that or not, by any chance?

DR. BUDROE: I think that actually the chromosomal TBA is pretty uniformly -- does not cause chromosomal damage. All the DNA damage assays are positive. It's the bacterial gene mutation data that is equivocal, right.

But, I mean, the important thing with this is is you're looking -- we're really looking at we're not trying to demonstrate that TBA is a genetox carcinogen. What we're doing is going to the IARC criteria. And one of the requirements is that TBA not be genotoxic in order to be considered to be -- it's an alpha-2u globulin mode of

action. And what we're really saying is there's not -- the data -- there's enough positive data that you can't make that determination that TBA is nongenotoxic.

PANEL MEMBER GILL: Okay.

PANEL MEMBER ANASTASIO: I had a few comments, mostly in terms of improving readability. So first, in page Roman numeral small 3, the list of acronyms. I don't know if MCF, molar conversion factor, is a State-mandated acronym, but it would seem like molecular weight ratio would be a better choice, right? That's the ratio of molecular weights of TBA and TBAc. And, of course, that's throughout the document.

Next one on page 1. So this is a complicated document, because you've got, you know, 2 chemicals that you're talking about, TBA and TBAc. And then within each one you've got different types of tests and different types of results. So I thought it would be helpful to have a more specific kind of detailed outline scheme. You know, you've got Roman Numerals I, II, III, but within that you don't have anything.

So I thought it would be helpful to have a more detailed outline, so I could understand where I was in terms of what's TBA, what's TBAc.

DR. BUDROE: Okay. The Roman numeral I, II, and III actually correspond to the other chemical summaries

that are in appendix B of the TSD. So that actually goes back to a structure. But having some headings essentially delineated a little bit better like, for example, cancer bioassays on page 5 or metabolism pharmacokinetics, we can do that.

PANEL MEMBER ANASTASIO: Right. And especially, because, you know, you'll have metabolism or you'll have, you know, carcinogenicity and you'll have it for TBA and then you'll have it for TBAc. So being able to understand without having to go back through the whole outline structure to know where I am would be helpful.

Related to that, I felt like there were a number of points where, as someone who is outside of the field, it would have been helpful to have a sentence or two explaining why a given issue was important. For example, the alpha-2u, it took me towards the end of the document before I understood why it mattered whether it was acting through alpha-2u or not.

So when you first have, say, the alpha-2u information, it would be useful to say, you know, this is significant because if it's this, it matters, if it's this, it's something else. So just a sentence or two to orient the reader.

Let's see, page 21. Okay. So page 21 is the alpha-2u that I just mentioned.

Page 29. So this is under Section 6, Quantitative Cancer Risk Assessment. Again, I thought an intro there would have been helpful, because you're kind of mixing what did you do before, and then what are you doing now with some different assumptions in terms of inhalation fraction. So it would be helpful in this portion to say, you know, these are the previous calculations we did. These are the assumptions we used.

Now, we're going to change some of these assumptions. And so based on the new assumptions, or at least the new data, this is what we find to really guide the reader through it a little bit better, especially in that second paragraph where you talk about the 70 percent fractional absorption, and the 100 percent metabolism of TBAc to TBA. You indicate in that paragraph, you know, these are old data. We're going to have updated values in the next section, you know, better data. We have better data than this, but this is what we did before. Again, just to help orient the reader to understand what's going to be changing.

Page 30, table 6, you've got the poly-3 corrected tumor incidence. I thought it would be helpful to put the not-corrected tumor incidence next to it, which is from table 1, just so that the reader can see how things change without having to flip back and forth.

And then page 34 --

PANEL MEMBER BLANC: You mean, having the actual proportion might even strengthen that more.

PANEL MEMBER ANASTASIO: Yeah, that's a good idea.

PANEL MEMBER BLANC: Have in the actual proportion in a separate --

PANEL MEMBER ANASTASIO: Or the percentage.

PANEL MEMBER BLANC: -- column --

PANEL MEMBER ANASTASIO: Yeah.

PANEL MEMBER BLANC: -- or underneath it or something, right?

PANEL MEMBER ANASTASIO: Right.

PANEL MEMBER BLANC: Those are just the raw numbers.

PANEL MEMBER ANASTASIO: Right.

PANEL MEMBER BLANC: You'd have to do all the algebra in your head or whatever.

PANEL MEMBER ANASTASIO: Right.

PANEL MEMBER BLANC: Long division.

(Laughter.)

PANEL MEMBER ANASTASIO: Page 34. So this is the CSF. So you're going off the TBA oral exposure to determine a TBAc inhalation CSF. And so the implicit assumption is that an oral exposure to TBA has the same

efficacy or adverse effect as an inhalation of the precursor. And is there any data for or against that? Does the route of exposure matter?

DR. BUDROE: Potentially for any chemical, but we have -- don't have any data that indicate that there's a route -- a difference between routes, you know, that would affect toxicity. So in the absence of the information indicating that, we assume that you have equal toxicity between the different routes.

PANEL MEMBER ANASTASIO: Yeah, so maybe just a sentence that explicitly states that for that calculation.

PANEL MEMBER BLANC: Don't you need to say something about your what assumption is about first-pass metabolism in that case? I mean, don't you need to actually explicitly say that?

DR. BUDROE: Yes, we will need to do that.

PANEL MEMBER ANASTASIO: And then my last comment is something that Jesús brought up. There is nothing about ambient concentrations of TBAc here, which again sets kind of the significance when you take the unit risk factor times the ambient concentration, you get some sense of the cancer risk. So it would be helpful to have, you know, whatever information is available from the literature about what ambient concentrations of TBAc are.

DR. BUDROE: I don't think you have any.

PANEL MEMBER ANASTASIO: Okay.

DR. BUDROE: I mean, I really don't. There is such a small data set for TBAc that -- I mean, because just -- it's not used that much.

PANEL MEMBER ANASTASIO: Yeah. So that would be helpful to know as well.

PANEL MEMBER ARAUJO: That review that I mentioned, the Bus from Critical Review Toxicology has a lot of data actually, tabulated and referenced. They say that some of it is actually here from the ARB or reviewed by the ARB. And I was surprised to see things like the concentrations can vary a lot from ambient concentrations that are in the order of 0.59 in Southern California -- 0.59 parts per billion concentration of 2.8 micrograms per cubic meter as a worst case TBAc air concentration.

It can go as high as 532,000 micrograms per cubic meter in an occupational exposure of a personal brake shop work space. And so there's a whole table. And you have like different concentrations, so that the range is humongous. It's very large.

DR. BUDROE: Okay. Well, those aren't actually measured concentrations. Those are -- what ARD -- ARB did was to create a series of scenarios, and say if we use this much of this chemical, then here's what the concentrations were going to be. But they didn't actually

go out and measure like what concentrations were at brake shops using this stuff, or where industrial paints are being applied use TBAc, because they haven't -- don't really have those kind of opportunities. They're not really using TBAc in those kinds of applications that much at this point.

So this is all -- this is all essentially modeled scenarios. And that's where we're getting these concentrations from. And this is out of the 2000 -- january 2006 ARB document, Environmental Impact Assessment of tertiary-butyl acetate.

PANEL MEMBER ARAUJO: Right, that's what I was going to say. They also reference the AQMD, some documents from the AQMD, and -- look at table 10 of that review that I mentioned, and then see if it is the same thing that you are talking about, because it --

DR. BUDROE: Right. Well, they mention this ARB document and then they also mention some of the modeled concentrations that South Coast Air Quality District did in theirs, but those are all -- those are all modeled scenarios. Those aren't actual measured concentrations. So those are more worst case, this is as bad as it could be if they used this much.

PANEL MEMBER ANASTASIO: John, are there emissions data at all?

DR. BUDROE: I haven't seen any. I looked at the hot spots inventory and there wasn't anything in there. At this point, probably not.

PANEL MEMBER ANASTASIO: Even stating that would be helpful. You know, pointing out some of these knowledge gaps. That's all I have.

PANEL MEMBER RITZ: Well, I have very little. I had actually the same problem with the kidney cancer, not realizing what it really meant until I finally went -- came to page 20. And I think you might just want to take a few of the paragraphs from the male rat kidney tumor discussion to the front, so that when you're reading this, you are actually knowing what this is about. And why the alpha-2u is important.

And the only other note I have is about the female thyroid. So the male kidney, that's one thing, you know, the discussion is pretty thorough, but you have no discussion why only the female thyroid would be affected. Is there nothing known about this that this animal species is strictly vulnerable or the females are?

I mean, it's very clear that thyroid cancer is more common in females in humans as well. Why? It's not clear. Sex hormones are a candidate, but nobody really knows. So I'm just wondering does that need some explanation?

DR. BUDROE: Do I have an answer for why it was significant in females as compared to males? No.

There was a slightly elevated incidence in males actually, but it wasn't statistically significant adding the dose points. So we could check the literature to see if there's anything out there that would suggest why male -- females may be more sensitive than males, in general, to thyroid cancer.

PANEL MEMBER RITZ: Yeah. It's just because it's known that females -- female humans have a higher risk. So that kind of tracks, but if it's just, you know, a fluke of the animal species, maybe that would also be important to know.

CHAIRPERSON KLEINMAN: Okay. Alan, do you have any?

PANEL MEMBER BUCKPITT: I had a couple of issues, one of which actually is that I agree with some of the comments from LyonBasell[sic] on 2 of the assays for genotoxicity. One is the AMS determination, and personally I don't believe the data. I don't have good proof of that, but unless they isolate the adduct and show it by HPLC, AMS, any protein that's adducted in those samples is going to show up on a very sensitive technique. Any other material incorporated into amino acids is going to show up as a positive.

And again, the technique itself is so sensitive, that unless you're very specific about what you're measuring, you're likely to be incorrect.

Okay. Remember that Jim Felton spent half of his career doing these sorts of studies. He's one of the authors of the letter. So again, you have a situation here that you have a publication, and I know it's in the peer-reviewed literature, that may not be correct.

The other issue relates to the 8-hydroxydeoxyguanosine. And I think if you go back in Blair did a really nice study. It's got to be a long time ago. But unless you have OCD when you're isolating the DNA, you will get 8-hydroxydeoxyguanosine. So you have to be extremely careful when those measurements are done to get accurate data.

There's all sorts of literature out there. And correct me if you think I'm wrong, Sarjeet, but there's all sorts of data out there where people are showing, same chemical, same amount, and they show 100-fold deviations in the amount of 8-hydroxy that they derive from it. And it's all based on whether they do the assay correctly, carefully.

DR. BUDROE: All right. Well, is there anything in the study outlined in the document that gives you pause?

PANEL MEMBER BUCKPITT: I can't say, because you don't know how careful people were in doing the assay. So I do bring it up, because I think it would be -- I'd be remiss in not saying something. It may be absolutely correct, but I think there's a good chance that it may not be. And that puts you in a very difficult position. There's no way of knowing, unless you do the studies, unless you have complete confidence in the person doing this work. That's all I have.

PANEL MEMBER GLANTZ: But what should they -- other than like worry about the fact that every study has potentially got problems, I mean, what are they going -- what should they do in terms of the report, other than like say, gee, we worry about this.

PANEL MEMBER BUCKPITT: I mean, that's the problem, Stan. I think to accept them on face value without a comment saying that there have been some issues in the analysis of these adducts by accelerator mass spectrometry or the measurement of 8-hydroxydeoxyguanosine. I think that comment might be enough to certainly satisfy, but I think there's a significant chance that these studies are not.

DR. BUDROE: Okay. Well, with the AMS study, the mass -- accelerator mass spec, we haven't altered the document to say that that's a shortcoming of the study.

It would have been a better study if they'd actually done adduct isolation.

PANEL MEMBER BUCKPITT: Yeah.

PANEL MEMBER GILL: Yeah, well the 2 studies are different. The AMS one is actually easier to discount it than the other ones, because AMS if they did not say what it is, is a bit more problematic.

But you have stated comments, but it may be vetted, may a bit more forceful a bit, but you have stated it. Whereas, the other one is a bit more difficult because we really do not know how they did it.

PANEL MEMBER BUCKPITT: Right.

PANEL MEMBER GILL: But he AMS one is a bit more clearer, because there is no -- otherwise, they would have said it if they analyzed the data.

PANEL MEMBER BUCKPITT: Well, I think Jim actually had some instances where he measured just radioactivity, which is what was done in this study. And when he went back to look for specific adducts he couldn't find them. Okay. So it's easy to get a false positive, if you have anything contaminating in that -- that sample that has radioactivity with it.

And it could be lipid, it could be protein. A 260 to 80 ratio of 1.8 is not proof that there isn't protein in there. It wouldn't take much.

PANEL MEMBER BLANC: Just make a comment before Dr. Ritz leaves. So in your previous document that we heard the revised addition of today, you had received feedback that unless you tested whether the difference between the response in the males and the females was actually different, you should pool them, if you recall.

DR. BUDROE: Yes.

PANEL MEMBER BLANC: So do you -- other than the fact that you have a test for trend, which is significant in the females and not in the males, if I just look at the date, it's hard for me to believe that the data are actually statistically different by sex. Do you have reason to believe that they are?

And I think your test for trend will be more substantive if the data were pooled, frankly, if you just look at the numbers.

DR. BUDROE: That is something --

PANEL MEMBER BLANC: That your positive test for trend is driven entirely by the high dose in the female thyroid cancer. It's not -- there isn't a monotonic increase in response by any means. And it will be a far more convincing pool, because it will be 3 out of 60, 3 out of 60, 6 out of 60, 11 out of 60, if they were combined.

DR. BUDROE: All right. So you're talking about

the mouse data -- mouse tumor data?

PANEL MEMBER BLANC: Yeah, where she asked why is it just the females?

DR. BUDROE: We can take a look at that, and run an analysis.

PANEL MEMBER BLANC: I mean to be consistent, right?

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER RITZ: Yeah. Otherwise, I think you need an explanation why it's the females, not the males, if you want to make that argument.

DR. BUDROE: We well definitely examine that issue.

PANEL MEMBER GLANTZ: So I just have one -- before you run off, just I have one. So my last question is, I mean, I've heard a lot of discussion about ways to improve the way the report is written and the discussion, but I haven't heard any criticism of the broad bottom-line conclusion or the unit -- the actual unit risk number. And so -- and this is, again, I'm not a toxicologist, but the -- would I be correct to walk out of here and think that while there's lots of improvements to the report, that when this thing comes back to us we wouldn't expect to see a change in the basic conclusion, the basic modes of action, or the unit risk, or would some of these

criticisms maybe affect the unit risk calculation?

PANEL MEMBER ARAUJO: That was one of my first comments. And it actually -- it does affect the values.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER ARAUJO: But it's going to be -- it's going to take a little bit of time. Maybe I get together with Cort and --

PANEL MEMBER GLANTZ: Okay. Well, I just was -- that was for my own benefit, but okay. Thank you. That's helpful to know.

PANEL MEMBER BLANC: Can I just -- well, I have another question, which is based on your initial back and forth, this is a revision -- not a revision. This is a revisiting of a previous unit cancer value?

DR. BUDROE: Not exactly. We did an informal number for ARB, but it wasn't -- it didn't get run through either the TAC process or the hot spots process.

PANEL MEMBER BLANC: Okay. And in that previous -- how many years ago was that?

PANEL MEMBER ARAUJO: Ten years ago.

DR. BUDROE: 2006, over 10 years -- really over 10 years ago.

PANEL MEMBER BLANC: And, at that time, did you conclude it was a carcinogen acting through this metabolite --

DR. BUDROE: Yes.

PANEL MEMBER BLANC: -- or did you have some fundamentally different conclusion?

DR. BUDROE: No, we concluded it was a carcinogen because of the TBA data.

PANEL MEMBER BLANC: So, I mean, to me, that's kind of useful in terms of consistency too. You know, I just want to mention that. I don't know if it fits into your -- it would fit more into your response to the critique than it does fit into the document itself. Although, I would say for full disclosure purposes, a sentence which says, said formal -- this had previously been -- this question had previously been addressed, but not in a formal unit risk dose process.

CHAIRPERSON KLEINMAN: Well, there actually was a cancer slope factor and a unit risk factor in 2006 in the ARB document.

PANEL MEMBER BLANC: Or however you want to word it, but I mean, to me, that's useful.

CHAIRPERSON KLEINMAN: Okay.

PANEL MEMBER ARAUJO: Could I just comment on Alan's point of the uncertainty on some of the methods and to assess the DNA damage? Right. So the -- out of the 7 criteria, OEHHA says that there is only one criteria that is not met to consider these tumor and alpha-2

microglobulin remediated. And two of them that are not completely met, but only one that is not met, which is exactly that, the non-genotoxicity.

So let's say for -- that you were to discount in that data, could you feel comfortable in the other data that is provided in still saying that this does not meet the criteria for non-genotoxicity? Based on -- the other point would be the bacterial, and the other would be the Comet assay, right?

PANEL MEMBER BUCKPITT: So those weren't without issues, right, and they were discussed in the report, I thought well discussed in the report. So it's -- you know, you're essentially between a rock and a hard place. This is -- your data are not --

PANEL MEMBER BLANC: Perfect.

PANEL MEMBER BUCKPITT: -- perfect.

DR. BUDROE: No, but that's not the only criteria that TBAc --

PANEL MEMBER BUCKPITT: That's correct.

DR. BUDROE: -- TBA didn't meet. It also doesn't meet the dose response similarity between the purported MoA in the tumors.

PANEL MEMBER ARAUJO: But that is another criteria. But as far as the non-genotoxicity, you're really relying on this bacterial Comet assay and in vitro

data, right? I mean --

DR. BUDROE: Right. And there it's a question of, you know, is there enough data there to really say that it's not absolutely -- you know, stick to the point that it's non-genotoxic. And like I said, I wouldn't be -- we're not trying to show that this is a genotoxic carcinogen. What we're saying is there's enough positive data out there, and it may have its warts and, you know, flaws, but there's enough out there that you can't really come to the -- you can make the definitive conclusion that TBA is non-genotoxic.

PANEL MEMBER ARAUJO: Yeah, so that's a good point. Did you say it like that in the document, or just in the response letter? So you can be confident there is not enough data to say it is not genotoxic, but you don't have enough data to say it is genotoxic. I understand. And so if you don't -- I don't remember what actually they say like that in the document, but that would be really good to have it, basically phrased in that way.

DR. BUDROE: Okay. We didn't -- we address that a lot more in response to comments than we did in the document itself, so we can add some of that to the document.

PANEL MEMBER BLANC: Does the Chair want to entertain a motion?

CHAIRPERSON KLEINMAN: Well, I just wanted to make sure that, you know, everybody has had an opportunity to comment. And I don't see any other comments, so yes, I will entertain a motion.

PANEL MEMBER BLANC: So my motion would be that the document be revised in light of the comments made and returned for a brief review by the leads, re-review.

PANEL MEMBER ARAUJO: Can I ask how we do -- do we address in that unit of the values and the CSF and all that, because I understand that we cannot discuss outside this room in between reviewers or with --

PANEL MEMBER GLANTZ: No, that's not true. You can meet with the staff. It's just that we can't have a quorum of the Committee, meaning --

PANEL MEMBER ARAUJO: Can I discusses it with Cort, for example.

PANEL MEMBER BLANC: Yes.

PANEL MEMBER GLANTZ: You could do that, yeah, but you can't have a quorum. So we know there's a long history of the leads working directly with the staff to resolve these kind of issues before the report comes back to the Committee. It's just we can't have a -- we can't have a meeting of the Committee, or if we had 4 of us or 4 of us meeting with the staff, we can't do that.

But I guess my question --

PANEL MEMBER BLANC: They can't buy you lunch either.

PANEL MEMBER GLANTZ: Yeah, that's right. They can't even by you a cup of coffee.

But the -- but my question for you, are you saying that we tentatively accept the report subject to this or --

PANEL MEMBER BLANC: I think we heard from Jesús that it would be more comfortable that it come back to us --

PANEL MEMBER GLANTZ: Okay. That's what --

PANEL MEMBER BLANC: -- but with be an expedited review at that time, I would presume.

PANEL MEMBER GLANTZ: Okay. So is what your suggesting that OEHHA work with the leads to get all this fixed, and then it would come back to the full Committee for a final action?

PANEL MEMBER BLANC: That's my motion.

PANEL MEMBER GLANTZ: Okay. I would support that. Second that.

CHAIRPERSON KLEINMAN: Okay. We have a motion on the table.

All in favor?

(Hands raised.)

(Dr. Ritz and Dr. Gill not present.)

CHAIRPERSON KLEINMAN: It passed unanimously,

In that case, I -- so we've done our due diligence on this. We will have this document revised. The leads will review the revisions, and then at the -- we'll bring it back at our next meeting for a brief re-review.

PANEL MEMBER GLANTZ: That may be, you know, depending on how -- whether or not there are any issues of controversy, we might even be able to do that by an Internet meeting, rather than having everybody have to travel, because it doesn't sound to me like there's any huge points of controversy.

PANEL MEMBER BLANC: So I think there are 2 questions. One, is there some time sensitivity to this chemical for which there's virtually no use and no exposure, but in a larger sense I would ask now, since we've completed this part of the agenda, what our anticipated coming projects are? It is somewhat frustrating, and it's not your fault, that there had to be such a lengthy response to a 70-page letter or whatever on this document, which was actually the revision of an existing cancer potency factor for non -- low exposure chemical.

But might we expect something substantive in terms of a public health-related chemical assessment?

DR. BUDROE: We have chemicals in the pipeline that we're working on, but we don't have a -- I'd hate to put us on the record as committing to bringing up a specific chemical at the next meeting.

PANEL MEMBER BLANC: Heaven for bid, but will there be -- should we anticipate that there might be a specific chemical or two at the next meeting?

DR. BUDROE: We dearly want to bring at least one new chemical to the Panel at the next meeting.

PANEL MEMBER GLANTZ: Well, you know, this brings up a kind of broader point. This is the benefit of me being on this Panel since the Pliocene age. But we actually have had this discussion in the past about like how are priorities set. And we did develop a prioritization algorithm a long time ago. And it might be worth at the next meeting having OEHHA come back with some sort of, you know, logic of like what chemicals are coming in what order with some rationale for why it's hose chemicals.

Because I remember when I first joined this Panel a very long time ago, we did coke oven emissions. And it turned out there were no coke ovens in California. Now, coke oven emissions are quite toxic actually. But since -- but there weren't any coke -- and when we said to ARB and OEHHA why are we doing coke oven emissions, they

said, well, we have the data. And that's when we did the first prioritization document.

So I think it would be a good idea to sort of -- you know, I think it's been done 2 or 3 times over the life of the Panel to really just come back and say we want to make sure that we're bringing things here where there's actually going to be some impact to make it worth all the work by you guys and by us.

DR. BUDROE: Okay. Well, some of this has been kind of on an ad hoc basis. Like, for example, TBAc, the reason it came before the Panel is because ARB, and even more so, the districts were interested in it there's been a long -- Lyondell is -- it's been wanted to be used by industry in applications for a while as a VOC substitute.

And eventually, the districts and ARB said you need to get -- we need to have a number. This question needs to be settled.

PANEL MEMBER GLANTZ: Okay. Well, I mean, I think that's a legitimate point, you know. I don't think this needs to be a completely academic process. But I do -- I've had the same kind of frustration that Paul is talking about. So I think it would be useful.

PANEL MEMBER BLANC: I didn't say -- I didn't say frustrated. I just was curious.

PANEL MEMBER GLANTZ: Or the same curiosity that

Paul has.

(Laughter.)

PANEL MEMBER GLANTZ: But I think it would be useful to, you know, come forward and say here's how -- you know, here are the things that we're working on, here's why, and to make the case that the -- I mean, if it's a thing where a bunch of the air districts are saying we're getting requests to permit this, and we want a scientifically peer-reviewed number, I think that's fine, you know.

And it may be, if this ends up being like really -- it may be that there's not a lot of use now, but there could be, so that wouldn't be bad. But I think that having some sense of like what's in the pipeline and why, and making sure that the important things are getting addressed would be a -- there is a protocol that's been -- was developed and updated at least once. It might be worth going and digging that out of the archives and taking a look at it.

DR. BUDROE: Right. And I kind of remember that, but that hasn't been updated, I know, for things like, for example, the children's health.

PANEL MEMBER GLANTZ: Right.

DR. BUDROE: And I know we have a number of --

PANEL MEMBER BLANC: That's not true.

PANEL MEMBER GLANTZ: No, it was updated for the children's health.

PANEL MEMBER BLANC: The children's health. There was a -- we developed the first 10, and I don't think we've gone through those 10. I would be really shocked if we had. Maybe we have.

DR. BUDROE: There are some better memories out there than mine.

PANEL MEMBER GLANTZ: Yeah. No, I was the lead person on that one.

PANEL MEMBER BLANC: And, Mike, I would also ask that in the interim, between now and our next meeting, if you could reach out to the Department of Pesticide Regulation. Has it been 5 years since we've had a pesticide here? Four years?

(Laughter.)

PANEL MEMBER BLANC: Ten?

PANEL MEMBER GLANTZ: Thousands.

PANEL MEMBER BLANC: Anyway, you know.

CHAIRPERSON KLEINMAN: I agree that, you know, it would be very useful to get, you know, some view of what is being considered as being important. And if nothing else, it will give us an opportunity to sort of do some homework in advance figuring out which of us want to do which chemical.

PANEL MEMBER GLANTZ: Yeah. And also, we did have something to say about the prioritization.

No, in fact, as I recall, we first -- after the coke oven emissions thing, there was a prioritization document. And that was updated when the -- when the -- I think it was SB 25 or something passed. And there were 10 -- the law required 10 compounds to be identified. And then I think that that's true they have -- whatever happened after that.

So I think if you look at those two documents, and see what would it take to update them.

DR. BUDROE: Okay. Is my understanding correct that the prioritization is actually an ARB process?

PANEL MEMBER GLANTZ: I don't remember.

It came -- I know that the documents officially came to this Committee. Now, I don't remember who handed them to us, but the documents exist. You know, I would just go back and look at them.

CHAIRPERSON KLEINMAN: Going back to our TBAc document, from what I've heard -- I haven't heard anything that says we're asking for a revision of the cancer slope factor or the unit risk factor.

PANEL MEMBER BLANC: I don't think that's what Jesús said, he said it could change --

CHAIRPERSON KLEINMAN: Oh, okay.

PANEL MEMBER BLANC: -- in fact, so that's why we had the resolution in the form that it did.

CHAIRPERSON KLEINMAN: Okay. If it did change.

PANEL MEMBER BLANC: It doesn't mean -- I'm not anticipating an 80-slide presentation. That's just a hint.

(Laughter.)

DR. BUDROE: Seventy?

PANEL MEMBER GLANTZ: That's 100 slides.

(Laughter.)

PANEL MEMBER BLANC: All right. You want a motion to adjourn?

CHAIRPERSON KLEINMAN: Yeah, if there's other new business, then --

PANEL MEMBER BLANC: I'll move that we adjourn.

PANEL MEMBER ANASTASIO: Second.

CHAIRPERSON KLEINMAN: We are adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 3:30 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, 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 meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 9th day of January, 2017.

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