TELECONFERENCE 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

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SACRAMENTO, CALIFORNIA

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CHICAGO, IL 60611

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9:30 A.M.

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.

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

S. Katharine Hammond, Ph.D.

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

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison, Scientific Review Panel

Mr. Peter Mathews, SRP Support Administration

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Melanie Marty, Deputy Director, Division of Scientific Affairs

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

Dr. Jim Collins, Air, Community and Environmental Research Branch

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

Dr. John Faust, Chief, Air, Community and Environmental Research Branch

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

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

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

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: I'll call the meeting to order. Now, we can start.

And I'm Mike Kleinman. I'm the Chair of the SRP. And on the phone today we have Dr. Glantz from Chicago. And in order to make sure that the record shows our, you know, attendance, what I'd like to do is start with Dr. Glantz and then go around the table, so everybody can briefly introduce themselves.

So, Stan, would you please, start?

PANEL MEMBER GLANTZ: Sure. I'm Stan Glantz obviously. I'm a professor of medicine at UCSF. And I'm happy to be on the phone with you from Chicago, where it's actually precipitated some, so it's very exciting.

CHAIRPERSON KLEINMAN: Thank you.

PANEL MEMBER GLANTZ: I'm also right across from the Trump Tower.

(Laughter.)

CHAIRPERSON KLEINMAN: Is that symbolic?

PANEL MEMBER GLANTZ: I guess. I guess. I think he's going to call it President Trump Tower.

PANEL MEMBER HAMMOND: Is it huge?

(Laughter.)

PANEL MEMBER RITZ: Let's not go there.

CHAIRPERSON KLEINMAN: Thank you.

Alan.

PANEL MEMBER BUCKPITT: Good morning. This is Al Buckpitt, former faculty member at UC Davis, now retired.

PANEL MEMBER HAMMOND: Katharine Hammond, faculty member from UC Berkeley, School of Public Health.

PANEL MEMBER BLANC: Paul Blanc. Professor of medicine at the University of California, San Francisco.

CHAIRPERSON KLEINMAN: Mike Kleinman, University California, Irvine, Department of Medicine.

PANEL MEMBER RITZ: Beate Ritz, Department of Epidemiology at UCLA and Center for Occupational and Environmental Health at UCLA.

PANEL MEMBER ANASTASIO: Corte Anastasio, Department of Land, Air, and Water Resources, UC Davis.

CHAIRPERSON KLEINMAN: Okay. Thank you very much. The Panel is going to address two agenda items for this meeting. We'll be talking about two RELs that have been prepared and have been submitted for review. But before we start that part of the meeting, I'd like -- we're going to hear a presentation from the staff at CalEPA and OEHHA about the recent passing of Dr. George Alexeeff. And I would like to invite Melanie Marty to start it off.

DR. MARTY: Thanks, Mike. We just wanted to take a few minutes to recognize George Alexeeff, our late

Director. This is the first time the Panel has been together in person since George passed. And George really had a special place in the Air Toxics Program. He came before this Panel many, many times over the years. Started work for the California Department of Health Services, which is where OEHHA used to be before the -- before CalEPA was started.

And he started work in the Air Toxics Unit in this particular program. He became unit chief, then section chief, branch chief, and eventually the Deputy Director for the Science Division and ultimately the Director for OEHHA.

He really loved his work, and he was a passionate public health scientist and committed to using science to protect the public and the environment. And during his 30 years of service, he became respected for his integrity and his advancement of risk assessment tools. So on top of that, he was just a great guy and a good friend and a mentor to a lot of young people, and fantastic meter. So I just wanted to take a few minutes to remember George and few moments on silence.

(A moment of silence.)

CHAIRPERSON KLEINMAN: Thank you very much, Melanie.

And before we actually start, I just wanted to

remind everybody who has a microphone to speak into it, because we are recording the proceedings and also because Dr. Glantz can't hear us without us talking through the microphone.

PANEL MEMBER GLANTZ: Thank you.

CHAIRPERSON KLEINMAN: You're welcome. We live to serve.

So this morning, we're going to hear a presentation from the OEHHA staff on the carbonyl sulfide reference exposure document -- reference exposure level document. We will have comments that have been received by the Panel's lead discussant, Dr. Blanc. And OEHHA will have an opportunity to discuss their response to the comments that were made.

And then we'll have an opportunity to discuss and provide feedback on the carbonyl sulfide REL, and then discuss approval of the document.

The second item on the agenda is going to be a Panel review of the reference exposure level for ethylene mono-n-butyl ether, otherwise called EGBE. And we will hear a presentation on the reference exposure level document, the levels for one hour acute RELs, 8-hour repeated REL, and a chronic exposure REL for both of the compounds that will be discussed today.

So I would like to start with the review of the

carbonyl sulfide REL document. And -- no, we'll start with a presentation from the OEHHA staff.

(Thereupon an overhead presentation was presented as follows.)

DR. FAUST: I just wanted to do a quick introduction of myself. I'm John Faust. I've been recently designated to fill the position of the Branch Chief of the Air Community and Environmental Research Branch filling the position that Dave Siegel vacated when he retired last fall.

I come from the Branch. I've recently been leading a group that's work on an environmental justice screening tool called CalEnviroScreen that identifies communities in California burdened by multiple sources of pollution. But I've been with OEHHA over 20 years and have variously worked on documents related to the Air Toxics Hot Spots Program, Prop 65, and the Drinking Water Program.

So I look forward to working with the group in the future. And with that, I'll just turn it over to John

DR. BUDROE: Good morning, Dr. Kleinman, and Panel members. My name is John Budroe. I'm the OEHHA Air Toxicology and Risk Assessment Section Chief. And I'd like to introduce Dr. Jim Collins. Dr. Collins is the staff lead for the carbonyl sulfide reference exposure

level document, and he'll be making the presentation on the document to you this morning.

DR. COLLINS: Good morning, Panel. Let's go to the second slide.

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DR. COLLINS: This document lets see I get to second slide. This document -- oh, let's see I go to the second slide.

This document, if it's approved will -- I'm sorry. Please stand by.

This chemical, if the reference exposure levels are approved, will become part of our Appendix D1. The last draft was revised in May. And since then, there's only been minor changes.

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DR. COLLINS: Slide 3 is a selfie of carbonyl sulfide. It's one of the simplest chemicals we've looked at in the toxic air contaminant program. It was actually suggested that we look at this in 1997 by the NRDC, and 20 years later we're coming to actually have a result.

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DR. COLLINS: Slide 4, carbonyl sulfide is a chemical intermediate. It's a byproduct of oil refining. And, at least an Australia, it has been suggested as a potential grain fumigant. Although it is not currently

registered in California either as a fumigant or as even applied to the -- as a fumigant. So it's a potential grain fumigant. It was declared a federal hazardous air pollutant in 1990, and a toxic air contaminant in California in 1993.

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DR. COLLINS: Slide 5. In 2012, the emissions in California were estimated to be 15,710 pounds from 56 sources. The top source in California was 7,706 pounds from a refinery in the Los Angeles -- in the South Coast Air Quality Management District. At the same -- for the same year, the federal government reported TRI, its inventory emissions as 34,916 -- 960 pounds from 15 sources. And we can get into some of the discrepancies, but one of the differences is a hot spots emissions are updated every four years, but not necessarily carried forward for the intervening years. Whereas, TRI emissions are reported every year.

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DR. COLLINS: Slide 6 shows a slide of the metabolism of carbonyl sulfide. Carbonyl sulfide may get into the body by breathing the pure material or as a contaminant. It may be formed metabolically from methionine. It also, if someone is exposed to carbonyl sulfide, it can form carbonyl disulfide can form carbonyl

sulfide under the influence of mixed function oxidase. And notice that arrow tends to go in one direction. It's not a reversible reaction.

Carbonyl sulfide then can react with water to form a mercapto formic acid under the influence of carbonic anhydrase. Again, another molecule of water can be added Mercapto formic acid to form sulfhydryl ion bicarbonate, and hydrogen ion and that's in equilibrium with hydrogen sulfide and carbon dioxide in water.

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DR. COLLINS: Slide 7. Reference exposure levels are based on the most sensitive an relevant health effects reported in the medical and toxicological literature. And they are derived as described in our document 2008 on *Hot Spots Risk Assessment Guidelines* for RELs. And this was reviewed by the Panel and adopted by OEHHA in 2008.

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DR. COLLINS: An acute REL -- acute reference exposure levels are levels at which infrequent 1-hour exposures are not expected to result in adverse health effects. And these are described in Section 5 of our technical support document.

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DR. COLLINS: Slide 9. The key study for carbonyl sulfide is an extensive study carried out by the

National Toxicology Program published in 2004. And the key study, the investigators exposed groups of five rats to several concentrations of carbonyl sulfide six hours a day for one day, and then followed them for 14 days.

Male rats exposed to the highest dose or six hours showed ataxia and head tilt near and slight somewhat after the exposure. And then they showed neuropathological lesions in the brain at 14-day follow-up. And this basically has the outline of how an LC50 determination is determined. But in this case, they were looking for non-lethal effects. Male rats exposed to 300 parts per million did not exhibit these nervous system effects. So the experiment yielded both a LOAEL and a NOAEL.

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DR. COLLINS: Here's our derivation on slide 10. The study population was groups of five male rats. And this is a deficiency in the study, there was only one sex looked at and a small number of animals. They looked at several concentrations of carbonyl sulfide, a single exposure of six hours, followed by follow up. LOAEL of 600 and NOAEL of 300. A benchmark dose was not derived, because there was an all-or-nothing response, either no animals responded, or in the case of the severest adverse effects, all the animals. You can mathematically develop

a benchmark concentration, but I'm not sure it's meaningful.

The effect of 1-hour exposure -- equivalent 1-hour exposure of 300 ppm is 542 ppm using our variant Haber's rule, whereas concentration cubed times time is a constant.

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DR. COLLINS: So in the top line of slide 11, the human equivalent concentration is the same as the animal continuous concentration, a 1-hour concentration of 542 ppm. We use a NOAEL, so the LOAEL uncertainty factor is 1. The interspecies uncertainty factor is we use a subkinetic -- toxicokinetic subfactor of 2, which is our default, and a toxicodynamic subfactor for animals of square root of 10 also our default. For intraspecies uncertainty subfactors, we used a toxicokinetic subfactor of 10, which is our default. In the case of toxicodynamic human subfactor, we used a factor of 10, because infants and children are potentially -- potentially have increased sensitivity to neurotoxicants.

We also used an uncertainty -- database uncertainty factor of the square root of 10, because the data -- limited database for this chemical is -- it's quite limited. The cumulative uncertainty factor was 2000, and the acute reference exposure legal was 270 parts

Per billion or 660 micrograms per cubic meter.

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DR. COLLINS: Slide 12, chronic RELs. The chronic reference exposure level is a concentration at which adverse noncancer health effects would not be expected from continuous chronic exposures. And these are discussed in Section 7 of the technical support document.

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DR. COLLINS: In this case, we used the same paper, but the animals in this case were also rats, but 10 per sex per exposure level. And they were subjected to discontinuous whole body inhalation of 0, 200, 300, 400 parts per million carbonyl sulfide, six hours per day, five days a week for 12 weeks. At 400 ppm, both males and females showed an increase incidence of necrosis or cavitation in the parietal cortex and of neuronal loss or microgliosis posterior colliculus. And 300 ppm, there were no similar effects. So that was a LOAEL -- NOAEL.

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DR. COLLINS: Okay. Here is the listing of the COS exposed rat brain pathology data after 12 weeks. And notice in both the males and the females in parietal cortex area one, there was a significant increase in necrosis or cavitation in both males and females at 400 ppm. And in the posterior colliculus, there was neuronal

loss microgliosis in males and females at 400 ppm. So we have a NOAEL and we have a LOAEL, and go forward.

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DR. COLLINS: After we developed -- the previous slide shows basically what would be classically used for LOAEL and NOAEL pathology. However, in the case of the carbon dioxide -- carbonyl sulfide, we had an additional consideration. Upstream biochemical perturbations may be useful for assessing dose response relationships.

And there was a workshop on this that was held in Berkeley several years ago to discuss this. For carbonyl sulfide such an upstream effect maybe the decrease in cytochrome oxidase level in certain areas of the brain.

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DR. COLLINS: The same study using the same animals also studied the levels of cytochrome oxidase in the rat brain parietal cortex, both males and females, and also in the posterior colliculus, we selected this data because it was monotonic. It shows that the cytochrome oxidase level of 1,711 units at 0 ppm decreased as one went from 200 to 300 to 400 ppm carbonyl sulfide in the exposure, such that at the highest level, the enzyme level is 50 percent of the control. And this is of interest, because sulfhydryl groups inhibit cytochrome oxidase.

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DR. COLLINS: So we took that data and did a benchmark dose analysis. We found there was at least one model, the exponential model -- slide 17, exponential model, which gave a acceptable fit, although barely acceptable, and gave a BMC of one standard deviation from the norm of -- from the mean of 55, and a benchmark concentration -- BMCL of 44.

And slide 18 just shows the graph of the decrease with concentration caused by carbonyl sulfide.

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DR. COLLINS: So our prosed chronic REL, again Morgan et al. 2004, rats, four levels of carbonyl sulfide, the critical effect low cytochrome oxidase. The LOAEL was 200 ppm, no NOAEL was seen. And the BMCL one standard Deviation was 44 ppm from the Exponential Model 2.

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DR. COLLINS: The exposure then was time adjusted from 44 ppm to a continuous exposure level of 7.9 ppm. And since the effect was internal, the human equivalent concentration was also 7.9 ppm. We used a subchronic uncertainty factor of the square root of 10, which is our default for a 12-week study. Toxicokinetic and toxicodynamic subfactors, interspecies, were the same, as with the acute, the defaults.

For the intraspecies uncertainty factor,

toxicokinetic subfactor, we used a 10, the default. In the case of toxicodynamic, we actually only used the square root of 10, because we felt we were looking at an upstream effect and could justify a small uncertainty factor. But we still left in our uncertainty factor for the database as square root of 10, getting a cumulative factor of 2,000, and a chronic exposure level of four parts per billion.

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DR. COLLINS: Slide 21. Proposed 8-hour REL. The 8-hour reference exposure level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures. Because chemicals that have the endpoint of neurotoxicity often have cumulative and sometimes irreversible effects, the 8-hour REL is the same as the chronic REL, four parts per billion or 10 micrograms per cubic meter.

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DR. COLLINS: Slide 22. Carbonyl sulfide is a TAC especially affecting infants and children. In view of the neurotoxic effects of carbonyl sulfide, exposure may disproportionately impact infants and children. OEHHA recommends that carbonyl sulfide be identified as a toxic air contaminant, which may disproportionately impact children pursuant to Health and Safety Code 39669.5

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DR. COLLINS: No written comments about the public review draft were submitted, but we did have extensive comments from the Panel. And I'll turn to Dr. Kleinman.

DR. BUDROE: And Dr. Kleinman, do you have any questions for staff regarding the document?

CHAIRPERSON KLEINMAN: Well, I thought we should start out with Dr. Blanc presenting his comments as lead discussant on the document, and then we'll open it up.

PANEL MEMBER BLANC: You guys are doing the review. You have the slides. Go ahead.

DR. BUDROE: So we should go directly to --

CHAIRPERSON KLEINMAN: Let's go through Dr. Blanc's comments --

DR. BUDROE: -- our response to comments.

CHAIRPERSON KLEINMAN: -- and your responses.

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DR. COLLINS: Dr. Blanc made extensive comments on the document. One comment was the U.S. EPA lists 13 refineries with greater than 40,000 pounds of total carbonyl sulfide emissions. The hot spots inventory lists two or three with less than 8,000 pounds total. That is only 20 percent of the EPA estimate. Emissions table is for low year 2008, not the year with 22,000.

Well, we did -- there are some problems with the reporting. We did -- we now list the 2012 U.S. EPA toxic release inventory and the hot spots carbonyl sulfide California emissions inventory. And this is now in the revised document. And you can see it's on Table 3 on page three. And the five top emitters are oil refineries in the South Coast Air Quality Management District.

The differences between TRI and ARB emission estimates reflect differences in reporting requirements. TRI reporting is annual. They have some different requirements from ARB. The hot spots are only updated every four years. And the facility reports are staggered. Any given year does not include all sources. So that's just a weakness of the reporting, which we don't have an influence over.

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DR. BUDROE: Yeah, there are also -- this John Budroe. There are also other differences in reporting requirements between TRI and the hot spots database, and that's just, you know, two different programs. One is federal and one is State. And there's always -- you're never going to have a one-to-one match up between the hot spots in inventory and TRI.

PANEL MEMBER BLANC: There are two separate questions. One is is the 20,000 pounds included in the

40,000 pounds or are -- or is there not 100 percent overlap in the facilities? So the argument that California is staggered so that you wouldn't get all reporting for any one year from all sites would be supported by all of the California sites being part of the TRI. But if there sites in the TRI -- sites in the California that are not in the TRI or vice versa, if you went back over the four years that would capture everybody, because what we actually want to know is is the true value 60,000? Should we be adding it together, are they apples and oranges, or as I recently learned in -- on a trip to Sweden what they say there is that's like comparing apples and pears, which wouldn't work in America. But I guess when you don't have any fruit in the winter, that's a big difference.

DR. BUDROE: It's about apples and pears.

PANEL MEMBER BLANC: Right.

(Laughter.)

DR. BUDROE: In general, the two databases mostly reflect each other, but there are some differences numerically, since hot spots database only lists every -- you know, for a -- list a facility in that emissions inventory every four years, you know, they're never -- the numbers are never going to match up exactly.

PANEL MEMBER BLANC: That's not really my

question. My question is what would you estimate the -- based -- using both sources, what do you estimate the total emissions to be? I'm not telling you to go back and rewrite the document, but perhaps for the future. As a reader, it wasn't all that useful to see, well, so and so says 20,000, so and so says 40,000. What I really want to know is, you know, based on the limitations of both data sets what is a reasonable annual estimate?

DR. BUDROE: I think what you've got is a range, and you're somewhere within that range, but I don't think we can provide a bright line.

PANEL MEMBER BLANC: Well, it can't be less than the EPA estimate, so how could it be within that range? It's only got to be more, to the extent that the EPA has underestimated, right, or am I not understanding the point here?

This is just a generalizable thing, right, because you're going to come up against this with other chemicals, so I think it would be useful going forward. I don't think it's the be-all or end-all with this one. But it's -- I think what happens is sometimes we get into a -- you know, we get formulaic a little bit with these documents, which is understandable, but I'm just suggesting you think about what the formula is.

If what you're trying to say is how big a problem

is this, then what you want to say is, you know, not EPA says this and Hot Spots Program says that, without some analysis or commentary, right? It's -- the utility of the document can be in the analysis. But I don't want to monopolize. Maybe someone else has same the reaction or if others on the Panel think I'm off base, we should just drop it.

CHAIRPERSON KLEINMAN: Okay. Let's take this point and go around and -- Kathy.

PANEL MEMBER HAMMOND: Okay. No. Paul -- I actually agree with Paul. I think that it is useful to try to understand. And I understand that that's challenging in your situation. And I'm going to ask some questions out of ignorance in this. But, for instance, we know that refineries go down sometimes for maintenance, and so I don't quite know how that four-year cycle of reporting to California goes. And maybe you can check into that. But would it be convenient that they report for a refinery that's down for maintenance, you know, in that year, and not for four years. So could you have an underreporting if that kind of thing were happening?

So that's the question -- one -- I'll leave it at that for the moment.

DR. BUDROE: Okay. Well, yeah, you would -- I mean, say, for example, ExxonMobil in Torrance that went

down because they ended up -- an explosion, they're going to probably report -- if that year that they're down is a reporting year, then they're going to report fewer emissions of carbonyl sulfide

PANEL MEMBER HAMMOND: Who determines the reporting year?

DR. BUDROE: ARB. I mean, they have a scale.

PANEL MEMBER HAMMOND: ARB tells each refinery which year they're supposed to report?

DR. BUDROE: Right. I mean, they're the ones that come completely control how the emission inventory works.

PANEL MEMBER HAMMOND: Right. So. But if -- is -- do you have access to information that would enable you to determine whether a refinery was down and for how many weeks it was down in a reporting year, to see -- because that would an indication of an overall underestimate if that was happening?

DR. BUDROE: We potentially could, but it's not -- I, mean in the end, it's -- now, you're starting to get into ARB's purview, so --

PANEL MEMBER HAMMOND: Okay. Well, it's important in the sense of trying to understand what Californian's exposures are, correct? That is important.

And then the other question that's related that I

had was what about accidental releases or, you know, incidents like the Chevron fire, are those affected by this, are they incorporated in these numbers?

DR. BUDROE: No, they're not.

PANEL MEMBER HAMMOND: And is there any of estimate of those emissions

DR. BUDROE: I don't exactly know. I know there have -- the air districts for example, for the Chevron fire Bay Area AQMD may have attempted to make an estimate, but I can't give you an exact answer to that.

DR. COLLINS: You may learn more when the facilities have to revise their risk assessments and use these numbers for their carbonyl sulfide, to see whether it's an issue or not.

PANEL MEMBER HAMMOND: They do a risk assessment? The companies do a risk assessment?

DR. COLLINS: Health risk assessment is under the Hot Spots Program, but --

PANEL MEMBER HAMMOND: I see.

DR. COLLINS: -- but there are guidelines. There's a computer program they need to use called HARP. The air districts learn how to use it. The consultants use that. So really I think we'll find out something about carbonyl sulfide when a refinery is actually emitting it, is it actually affecting anybody?

PANEL MEMBER HAMMOND: I mean, will they -- are they required by those guidelines -- I'm sorry, I don't know those to --

DR. COLLINS: No. Once this chemical is listed --

PANEL MEMBER HAMMOND: Yes.

DR. COLLINS: -- or has an -- they have to use it. They have to apply that number to their emissions. So we'll see whether it affects anybody.

PANEL MEMBER HAMMOND: You mean the REL number?

DR. COLLINS: The RELs, yes.

PANEL MEMBER HAMMOND: So -- but when you say apply it to their emissions, is that their routine emissions?

DR. COLLINS: Routine emissions.

PANEL MEMBER HAMMOND: So what about accidental emissions?

DR. BUDROE: Yeah. Accidental emissions aren't included. And they -- actually, the hot spots facilities are required to report quantities of carbonyl sulfide now. They just don't have to do a health --

PANEL MEMBER HAMMOND: Comparison.

DR. BUDROE: Right.

PANEL MEMBER BLANC: So just to go back to the every four-year process. Is the 20,000 pounds that's

estimated for 2012, the reporting for the sample in 2012 only? That's what I understood you to say.

DR. BUDROE: Correct.

PANEL MEMBER BLANC: So isn't the true annual emissions adding together the values from the last four years?

DR. BUDROE: Possibly. I'm not that familiar in that kind of depth with the ARB inventory system -- hot spots inventory system.

PANEL MEMBER BLANC: Well, again, I think this would come back to -- I mean, we've seen in almost everybody meant some number like this, if it's a relevant hot spots chemical already. And we've probably never delved down to this level of granularity, but I would suggest -- it's not going to change this document, but I would suggest for future documents if what -- if the purpose of presenting the number is not simply, okay, we've checked that off, we have to present the number from some recent annual hot spots program. If the purpose is rather to say what do we think the California release is, and if you think that it's every four-year sample, such that over four years, you would capture the universe of exposures. And if you think they're more or less constant over time, then the annual exposure is the additive of the four samples, if they're not overlapping samples.

DR. BUDROE: Okay. We can have a dialogue with ARB and see what we can do for the --

PANEL MEMBER BLANC: That would be useful going forward.

DR. BUDROE: -- upcoming documents.

PANEL MEMBER BLANC: Don't revise this, but just going forward, I think.

CHAIRPERSON KLEINMAN: Yeah.

PANEL MEMBER RITZ: So this maybe because I'm ignorant about the chemistry, but it says here atmospheric half-life is more than two years. So that means it's relatively stable, correct? So could there be cumulative amounts in the air through these releases over time or how does it disappear?

DR. COLLINS: Maybe --

PANEL MEMBER ANASTASIO: Yeah, this is Cort Anastasio. I can speak to that. The lifetime is long, a few years, but it will be dispersed out of the area relatively quickly, over the course of probably days to a week, depending on the air flow.

CHAIRPERSON KLEINMAN: Kathy.

PANEL MEMBER HAMMOND: Along that line, following in a slightly different way, I've been thinking about the hot spots, and I have some new ideas as I've been kind of thinking about today's agenda.

And one of my thoughts is hot spots means we're talking about places not the overall average for the State. And this may be something more of an issue that goes -- it's just not for this. But if the major source of carbonyl sulfide is refineries, then clearly what we'd be interested in the concentrations nearby the refinery. Those are the hot spots, in fact, and it's not what the average in the whole State is. And to whatever degree we have that information, which I guess the answer is we don't always have that information.

DR. COLLINS: We should soon, because --

PANEL MEMBER HAMMOND: So ARB is going to do monitoring for that, you mean?

DR. COLLINS: I don't know that ARB --

PANEL MEMBER HAMMOND: Or who is doing that?

DR. BUDROE: The facilities that emit carbonyl sulfide have to do essentially a modeled inventory of how much they're emitting. And the modeling software generates concentrations.

PANEL MEMBER HAMMOND: Fence line?

DR. BUDROE: Fence line, maximum exposed receptor.

DR. COLLINS: Receptor grid.

PANEL MEMBER HAMMOND: And that's a requirement when it goes into D. So Appendix D and the hot spot, at

that point, that comes into play, is that correct?

DR. BUDROE: Correct.

CHAIRPERSON KLEINMAN: So just to put this in a little perspective, I did a little digging to see if I could find anything on ambient concentrations. And I found that in occupational environments, occupational exposures range from about 2.6 to 50 parts per million, so way above what we're talking about, but indoor air concentrations are less than one part per billion, in -- that they've measured.

What's interesting is there's a substantial amount of COS in cigarette smoke, which is mentioned in the document, and side-stream smoke also. So I calculated out what that turned out to be, and it's something on the order of 45 parts per billion in cigarette smoke.

PANEL MEMBER HAMMOND: Mainstream.

CHAIRPERSON KLEINMAN: In mainstream, and then about 10 percent of that in side-stream smoke. So in the presence of smokers, you have a substantial -- you know, you could have substantial --

PANEL MEMBER HAMMOND: That was say in a home, for instance --

CHAIRPERSON KLEINMAN: In a home.

PANEL MEMBER HAMMOND: In a home with smokers, that would exceed the chronic REL.

CHAIRPERSON KLEINMAN: But I don't think the RELs are applicable to indoor air, are they, or are they -- they're not intended as far as I know.

DR. BUDROE: No, they're not intended for indoor air quality.

PANEL MEMBER GLANTZ: Well, this is Stan. I mean, they're not regulatory -- you know, they're not to regulate indoor air, but I think they are informative in terms of, you know, considering the levels of exposure, you know and could be -- that's information that could be used in public education campaigns or something, because the biological effect doesn't depend on whether you're indoors or outdoors.

CHAIRPERSON KLEINMAN: Thank you, Stan.

All right. So let -- is there any more discussion on this particular point? If not, we can move to the next, or did you want to respond in any way?

DR. BUDROE: No, I think we can move on to the next slide.

CHAIRPERSON KLEINMAN: Okay. Let's move on.

--o0o--

DR. COLLINS: Slide -- okay. Comment. Thiess et al. 1968 data discounted based on Bartholomeaus and Haritos 2005 review should summarize all the animal experimental data, cat, dogs, and guinea pigs, 300 to 500

ppm.

Actually, OEHHA used two independent English translations, one of which staff did of the original Thiess study, which was published in German. We added to the reporting of Thiess results. There were no deaths after six hours at 300 to 500 ppm in cats, rabbits, or guinea pigs, with a total of two of each species.

PANEL MEMBER BLANC: This was just an example of OEHHA was responsive to my wish to see rather than the original document, which cited a secondary source of a review of primary data, and the primary data were absent from the document. So I made them go back and do this, so I was pleased to see that responsiveness. And I think, to me, the general point was when the data are so sparse and you have a study that does -- has looked at multiple species, maybe not the best study in the world, it actually needs to be included as -- in terms of its primary data. And so you did that, so that was good.

DR. COLLINS: Now, I don't know whether you want to go into the maybe overemphasizing carbon disulfide. Morgan makes convincing argument this is not the pathway and rather hydrogen sulfide is the ultimate toxin, which I would agree with. I would just -- I just didn't know how Thiess et al. were sure that it was carbonyl sulfide that was -- that was causing the problem. It just wasn't clear

from reading that paper. Now, maybe I'm missed some of the German idioms. I don't know.

PANEL MEMBER RITZ: I can read it.

DR. COLLINS: Your spare time, you want to read it.

CHAIRPERSON KLEINMAN: But as I understand it, the hydrogen sulfide and the carbon monoxide were co-pollutants to which the people were exposed.

DR. COLLINS: That's what they think and they ruled out hydrogen sulfide by it didn't react with lead paper. I don't know how they ruled out carbon monoxide. The only thing I could figure out is they knew they were working with it. And, you know, it was almost like a trade secret or something. It didn't really talk -- they just had, okay, this poor guy died and we know it's carbonyl sulfide.

PANEL MEMBER BLANC: Yeah, yeah. I should say -- clarify that the Thiess paper included a human exposure component. It wasn't just animal data.

DR. COLLINS: Right.

PANEL MEMBER BLANC: So -- and I did -- I didn't think the issue was carbon disulfide based on the data that were available. So I thought -- this is just a point as to what -- reemphasizes that I thought this was quite a relevant paper, since it was a human death. And I didn't

care for the way in which it was sort of discounted and the discounting was really based on this secondary review, and so you backed off on that, so that's fine.

CHAIRPERSON KLEINMAN: Yeah. I would imagine if they suspected carbon monoxide they would have done carboxyhemoglobin analyses on the blood. It would be, you know, pretty straightforward to do that. But if they didn't mention it, then there's nothing you can do.

DR. COLLINS: I'd have to go back and take a look.

--o0o--

DR. COLLINS: Carbonic anhydrase may be crucial to COS metabolism. We would certainly agree. How much is know about human carbonic anhydrase polymorphisms?

Well, there's lost of the polymorphisms, at least 15. Some are cytoplasmic, some are, I think, attached to endoplasmic reticulum. There's a few of them that are inactive. The problem is we just don't have a lot of data about carbonyl sulfide metabolism by carbonic anhydrase in humans. When they look at the various polymorphisms, they're interested in CO2 not in COS.

PANEL MEMBER BLANC: This comes down to an issue that emerged as one read the document in detail, which is that -- and we'll come back to it I think related to the ultimate values that were determined, but it would appear

that the mechanism of action of this toxicant is through its metabolism to hydrogen sulfide. And carbonic anhydrase is the critical enzyme in that regard. So theoretically if you had hyper metabolizers, they would be at risk of greater toxicity, but there isn't any data on it. There's surprising little data on the biological implications of whatever genetic variability there is in carbonic anhydrase activity, which surprised me, since it's a pretty important enzyme, but there you have it. And I think your approach was to try to take that into account in your uncertainty calculations.

CHAIRPERSON KLEINMAN: I did find a reference that showed that if you block carbonic anhydrase, you actually reduce the COS toxicity.

DR. COLLINS: That's mentioned in our summary.

CHAIRPERSON KLEINMAN: Yeah, so looking at that, I was thinking in support of that hypothesis, you ought to put that into the diagram in Figure 6 or in slide 6 where you talk about metabolism.

DR. COLLINS: Yeah. Yes.

CHAIRPERSON KLEINMAN: Because I think it's important to show that if you block that, you do block the toxicity.

--o0o--

DR. COLLINS: Comment. The acute REL uncertainty

factor human toxicodynamic equals 10. Chronic REL equals square root of 10. Not convincing the data justify a chronic REL square root of 10.

Well, I don't know. We -- this is certainly negotiable, but basically we used the square root of 10 for the chronic REL toxicodynamic subfactor, because an upstream effect was used as the REL basis. And there was an effect seen at 200 ppm and 300 ppm, whereas the pathological response wasn't seen until you got to 400 ppm. So that was the rationale. I'm certainly open to negotiation.

PANEL MEMBER BLANC: Well, you know, this is a situation where the effect you're talking about is not apoptosis of nasal epithelium, but brain cell death. So that does concentrate the mind a bit. And I think that was the motivation of my discomfort with sort of backing off on the uncertainty, since the uncertainty has to do with things like how much carbon -- how much hydrogen sulfide is really being produced from the parent compound?

So this -- if I had, you know, felt intensely about it, I would have then come back to you and said, you know, unacceptable blah, blah, blah, you know. But I would certainly welcome the thoughts of the Panel. And I think it's just a -- you know, it's the mechanics of when you're the single reviewer of something, I don't think --

I don't think I feel like I unilaterally should be, you know, setting ARB policy or something.

So I would certainly welcome, to the extent that people want to comment on this. And if there's a consensus, either way, I'd certainly be comfortable with it, as I'm sure you would be. So I don't --

CHAIRPERSON KLEINMAN: Yeah. I'd like to ask the other Panel members chime in. Beate.

PANEL MEMBER RITZ: Yeah. First of all, I want to congratulate you for using that data on cytochrome oxidase. And when I read that being from the Parkinson's field, it really started scaring me, because mitochondria are it, and the dopamine neurons don't divide after we're born. So if we're born with not enough dopamine neurons, we are likely to come down with Parkinson's earlier, because we lose about one percent while we're aging. And at some point, we are hitting that 60 to 70 percent where we're showing motor symptoms, which could be earlier or later in life, hopefully never.

So dopamine neurons are very high in stress, because they are autonomic pacemakers, and they have certain ways of not -- they have a very high oxidative stress level. And mitochondria are extremely important and we all agree now that oxidative stress and mitochondrial dysfunction is what contributes to dopamine

neuron death. So anything that inhibits, in my mind, the mitochondrial cytochrome oxidase is actually something we should be looking at twice.

PANEL MEMBER BLANC: But, Beate, specifically in terms of the uncertainty factor?

PANEL MEMBER RITZ: I would think so, because from what I read, the brain of the developing fetus already has the enzyme to convert into H2S. And if that happens in a part of the brain where the neurons are not able to divide much longer after birth, or at all, then you know you're just setting up susceptibility. I'm not saying that a kid will be born with any problems. It will just be born with not enough dopamine neurons, and then, you know, 60 years later we see the effect of that. So that's my uncertainty to that question.

And you wouldn't see that in other brain areas where you still see developed -- I mean, neuronal division and, you know, replacement, et cetera, even if some cells are affected, but you see it for certain cell types. And you wouldn't -- nobody has looked in these animals. I just wish somebody would be looking and count the dopamine neurons. You can count them. That's an experiment that I would like to suggest somebody does at some point.

CHAIRPERSON KLEINMAN: Well, I think this is an important point, because the carbonic anhydrase is not

only an upstream effect, but it is mechanistically tied to the toxic effect downstream. So it's not like we're seeing an enzymatic change that has some, you know, foggy relevance to the problem. This is -- it appears to be directly applicable.

So I think, you know, it may be that the square root of 10 is, you know, an underestimate. I don't know. I'd like to, you know, sort of get a feeling from the rest of the panel whether this is something that ought to be reviewed and revised within the document.

PANEL MEMBER ANASTASIO: I think it's an important issue, but I don't have the expertise to be able to distinguish between the two.

DR. COLLINS: I'd like to direct you to the comparison REL on page 26 of the document, in which we used the pathology and the toxicodynamic factor of 10, we ended up with a total uncertainty factor of 6,000 and a higher REL of 22 micrograms or nine parts per billion. So even using these assumptions, with the upstream effect, we got a lower number.

PANEL MEMBER BLANC: Say that again.

DR. COLLINS: If you look on page 26 --

PANEL MEMBER BLANC: I mean, I think what you're saying is if you used -- if you didn't use the cytochrome data, but used the animal data. But I don't think that's

what we're suggesting. I think what we're saying, or the question is, is the use of the cytochrome data ipso facto take care of enough uncertainty such that the square root of 10 is sufficient rather than 10. I think that's the question.

So the question is not if you didn't use the cytochrome data, which no one is supporting, and you used 10 and not square root of 10, would that be a better approach? And I think you misinterpreted. I don't think that's what -- that wasn't what I asked.

DR. COLLINS: No, I don't think it's a better approach. I'm just saying it ended up with a -- even using that sensitive enzyme, we ended up with a lower REL, a more health protective REL than we would, had we used the more traditional approach of the pathology.

PANEL MEMBER BLANC: Yeah. No, I think that's great. I don't -- the question is should you be more? Because obviously, if you use 10 and not square root 10, then your chronic REL will be three-fold lower, right? Is that right?

DR. BUDROE: Right. Well, part of the question is usually we would use a quote classic pathology and point for example, like with the frank brain pathology. Here, we're using an effect that's considerably more sensitive, and it --

PANEL MEMBER BLANC: And that increases your certainty? Does that increase your certainty, therefore, that you've captured all of the variability or all of the unexplained potential? Because this -- this part is for the toxicodynamic piece, is that right?

DR. BUDROE: Correct.

PANEL MEMBER BLANC: So is the -- do you believe that because you're using this enzyme, you have the cytochrome data, you have therefore captured all of -- or sufficiently -- have you captured three times more of the toxicodynamic uncertainty, such that it warrants reducing the factor, because one could say if you had the terrible -- the animal data of brain dead versus not brain dead, the uncertainty factor, in fact, shouldn't be 10, it should be 100, right?

I mean, so it depends on if you're mitochondria are half empty or half full, right?

DR. BUDROE: It's going to capture more of the uncertainty. Exactly how much is always -- is a hard question, but it's -- we felt that using the upstream effect would justify, you know, keeping the toxicodynamic factor that is square root of 10. And eventually, it gets it to a point where if you load on too many more uncertainty factors, we've got a cumulative uncertainty factor now of 2000. That would push it to more like

6,000, which gets outside the range of what we wind up considering -- at least, what's in the 2008 guidelines, as being the acceptable risk assessment.

PANEL MEMBER RITZ: But 6,000 is what you use for the pathology.

DR. BUDROE: Well, that was a comparison, but we actually wouldn't use that for a REL document. It would be outside the range of what we would general consider to be acceptable, as in the guidelines.

CHAIRPERSON KLEINMAN: Well, looking at the model fit in the benchmark dose model, you do add a level of conservation by taking the lower 95 percent line to get the BMDL. So to some extent, the way the model is constructed also introduces a level of, you know, safety in that. So it may be that, you know, using the square root of 10 is reasonable, because you've already added another level of conservatism to it already in the way you construct the model. But perhaps that could be discussed in the -- where you talk about what the benchmark dose is -- you know, has involved.

PANEL MEMBER BLANC: Well, it's kind of interesting, because in our dialogue the point was not brought up that were you to actually do that, you'd be outside the range of an acceptable multiplicative factor, based on your own guidelines. So if that's really the

case, that's helpful to hear it. But I might -- could I ask for confirmation of that statement? Is that policy -- I don't think I was ever aware of that there was an absolute cut-off that -- of uncertainty past which one would abandon the attempt to set a standard.

Maybe -- I don't know, is there somebody from staff that wants to address that specific issue, because it would also touch on other guidelines going forward. You can just keep that in mind, and --

DR. MARTY: Yeah. This is Melanie Marty. The guidelines advise that we avoid using uncertainty factors larger than 3,000, but it is not an absolute cutoff. We just really try to -- in a way, it tells you you don't have enough data to generate a number. And U.S. EPA uses the same cutoff. And they generally don't like to use larger uncertainty factors than that, but it doesn't mean you don't have to. It doesn't not mean that.

PANEL MEMBER BLANC: And tell me again for this with the square root of 10, what's the uncertainty multiplicative factor we're using, 2,000?

DR. MARTY: Right. So right now we're using a 2,000-fold total uncertainty factor. And, you know, keep in mind, these are -- you know, it's kind of like putting a step function over something really complex --

PANEL MEMBER BLANC: No, no. All right.

DR. MARTY: -- as uncertainty factors. So it's -- there's a lot of judgment in it. There's no question.

PANEL MEMBER BLANC: Yeah. Well, again, is there any -- can I just ask a mathematical question, given our, yes/no bridge points, which are generally 10 or a square root of 10, and then another 10 for a lousy data set, which we've put in here also in the chronic, I believe, right?

DR. MARTY: (Nods head.)

PANEL MEMBER BLANC: So is there any way you could ever get to 3,000 or would it have to be 2,000 or exceeding 3,000, just out algebraically.

DR. MARTY: Yeah. No, we do -- we can get to 3,000 if we're using root 10 rounded to 3 times 10, for example, times 10, would be another 10.

PANEL MEMBER BLANC: I see.

DR. MARTY: So you can get to 3,000. The 2 is the default kinetic -- toxicokinetic uncertainty factor when you've used a human equivalent concentration adjustment. So that's where there's a 2,000. That's how you come up with 2,000 or 6,000 in the case of comparative REL.

PANEL MEMBER BLANC: Okay. Well, I mean, I --

DR. MARTY: I think your points are well taken

and, you know, it is a little bit unnerving, given the dose response for this chemical, which is --

PANEL MEMBER BLANC: Very steep.

DR. MARTY: Yeah, it's very steep. You go from almost nothing to pretty serious pathology. So, yeah, that --

PANEL MEMBER RITZ: Holes in the brain.

DR. MARTY: Exactly. So there -- you know, there -- I think we could consider that. Another issue is we do have carbonyl sulfide in our breath and in our guts. So you have to be a little bit careful. I mean, we don't want to get so low that we're below what we're normally breathing out anyway.

PANEL MEMBER BLANC: Right. Well, I'm okay with leaving it where it is. In the final analysis, the key thing is that you've finally generated a standard. But I do think these discussions are applicable to other situations. So I think it's -- I'm happy that we took the time to do it.

CHAIRPERSON KLEINMAN: Okay. Let's move on to the next comment.

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DR. COLLINS: Yes. This actually continues what Dr. Blanc is talking about. Suggest more COS dose response discussion, given steep COS dose response curve.

Possibly include discussion of similar toxicants hydrogen sulfide.

Basically, there is this very interesting paper from Brown and Strickland that looked at eight time points between five minutes and 16 hours and showed a very steep dose response curve for everything except for the longest time frame. The problem is we just don't have enough data on COS for a similar analysis.

Dr. Blanc did send -- found a study by Benson et al., which was the basis for the abstract by Nutt that we cite in our study. And again, that showed a very strong reaction -- there was nothing at 450 parts per million in the 6-hour period, but at 500 and 550 lost of the animals showed neurotoxic effects. I think we're just dealing with we only have so much data on carbonyl sulfide that we can look at.

--o0o--

DR. COLLINS: The acute REL for carbonyl sulfide is 50 times higher than the 8-hour and chronic REL. It seems out of line with the difference between the acute and chronic REL for H2S.

In this case, the staff felt that the acute REL for H2S is based on a human study where the adverse effect is a LOAEL for odor perception, whereas the chronic REL was based on the inflammation of nasal mucosa in mice, and

that these were not really comparable for what was used for COS.

And if you look at hydrogen cyanide, which also had cytochrome oxidase, it has a steep dose response curve. And acute REL for hydrogen cyanide is 38 times the chronic REL. And I think this again is that just the amount of data that's available, it's limited. We don't all have all the data we would like.

PANEL MEMBER BLANC: I thought it was interesting. It was an interesting exercise, and it underscored some of the limitations of the state of the art. And how you end up using, you know -- it actually comes back -- it will circle back for the discussion of the next chemical where, you know, you're -- you end up using a certain endpoint because that's the endpoint you have the data for.

So it was illuminating to me that the endpoint for hydrogen sulfide was related to odor and not related to things, you know, one would really care about, so that's why. But I think, in general, I've certainly found these exercises of comparative data or a little paragraph in the report, which says now if you look at such and such, which acts in a very similar manner, here's where we are with that.

And so just to -- I'm not suggesting that you

rewrite it, but just saying this is, you know, if you want to get --

DR. COLLINS: Stop smoking, Stan.

(Laughter.)

PANEL MEMBER BLANC: -- if you want to get the point across, it is helpful sometimes.

PANEL MEMBER ANASTASIO: Yeah. I'd like to actually second that point. I thought it very interesting the comparison between the H2S, which appears to be the downstream actor in COS toxicity. To have those RELs in the COS document, I think is helpful. It also points out the fact that we don't have RELs for CS2, as far as I can tell.

DR. COLLINS: Oh, yeah. Carbon disulfide.

PANEL MEMBER ANASTASIO: There is a CS2.

DR. COLLINS: (Nods head.)

PANEL MEMBER ANASTASIO: Oh, I couldn't find it. Okay. So it would be useful to put that in the document as well, since they're all linked physiologically.

DR. COLLINS: The CS2 causes psychosis.

PANEL MEMBER BLANC: And Parkinsonism just to point out.

--o0o--

DR. COLLINS: Okay. This has to do with strict adherence to a two-week exposure acute study, while a

three-week exposure data exists that shows 300 ppm to be a LOEL. I think there was just some confusion that what we want to use for acute REL is a single short duration, and with, if possible, follow up for some time to see if there's any delayed effects. And that the reason we didn't use -- we did not use a two-week exposure for acute study, we used a single exposure with two-week follow up. So I don't know, I think it was just --

PANEL MEMBER BLANC: Confusion on my part.

--o0o--

DR. COLLINS: Why does the 8-hour REL use Morgan 12-week exposure data since the study also provides 24-day data demonstrating a LOEL of 200 ppm.

I think this was -- basically, the 8-hour REL is applied to repeated 8-hour exposures up to a lifetime, and is based on chronic exposure, if available. So we use the longest exposure, the 86-day exposure rather than the 24-day exposure. And as the exposure got longer, the effects seem to be greater on inhibition of the enzyme.

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CHAIRPERSON KLEINMAN: Going back to that last slide. Just as a matter of clarification, you say it's a repeated 8-hour exposure over a lifetime. Are you -- you're considering that 8-hours a day for the entire -- every day for a month?

DR. COLLINS: It could be. It could be a work schedule. It depends on what it is. It's just a -- that, thing -- 8-hour exposure came up and the 8-hour REL was in response to specific problems certain air districts had, and they wanted -- thought that this REL might help alleviate the problem of exposure -- or inappropriate exposure.

DR. BUDROE: It's directly related to off-site worker exposure. On site would be covered by occupational standards for good or for ill. But off-site workers districts had a concern with, so that's why the 8-hour REL was developed, also for day care centers.

CHAIRPERSON KLEINMAN: But it applies for 365 days a year, as opposed to, you know, a standard 5-day work week kind of thing. I just wanted it --

DR. BUDROE: Correct.

CHAIRPERSON KLEINMAN: -- clear in my mind.

DR. BUDROE: It gets modeled in.

CHAIRPERSON KLEINMAN: Okay. Thank you.

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DR. COLLINS: Add expanded data from Benson et al. and the Lovelace Annual Report. We actually did that, and it was a conformation of the acute REL data that we got from Morgan. It's unfortunate they didn't give actual incidences, because it certainly would have helped

strengthen the database for the acute REL.

So the results were consistent with what we had. Unfortunately, Benson did not give incidents of the various adverse effects. It would have been very useful for quantitative determinations.

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DR. COLLINS: And expand description of COS in natural sources as a Captan breakdown product, and in environmental tobacco smoke. And basically, all those have been put in as well as a paper last year about ambient levels of carbonyl sulfide in Beijing China.

Sorry about all the tongue twisters.

(Laughter.)

CHAIRPERSON KLEINMAN: Thank you. All right. So I'd like to invite any other comments from members of the Panel.

PANEL MEMBER GLANTZ: This is Stan. I don't have anymore.

CHAIRPERSON KLEINMAN: Thank you, Stan.

PANEL MEMBER ARAUJO: I do have some comments. I think that it was a very, very good review, but I want to -- I would like to bring attention to the comment from Melanie, that one of the products of the -- this compound is hydrogen sulfide, and which is present in our body.

And as a matter of fact, and this is something

that is missing in the review, is that it almost appears like everything that is related to the carbonyl sulfide is bad and is toxic. And it turns out that the hydrogen sulfide is not only present in our body, but it can have like beneficial effects. It has presently been recognized as a possible neurotransmitter. And in some models of ischemia/reperfusion and models of diabetic cardiomyopathy and inferred toxicity, it has been shown that it actually can be protective.

And it is not clear how, and it's been hypothesized that it is via induction or activation of the Nrf2 pathway and of regulation of antioxidant genes.

So I think that it is just very complex, and it's an area that we're having a very small molecule that has been over a very long time, and it's surprising how much is really unknown.

In the entire review, I think that we're sort of like a hand waving. You know, the review is good in the sense that is this is the state of the field, that we're hand waving. You know, we don't really know how is it toxicity?

It seems that you discuss it like several times during -- throughout the document. You know, it could be due to this, it could be due to that. I think that it needs to be even more put forward, you know, that it's

just not known. And then put up a prong, what other possible mechanisms how that it induces toxicity, and also show that some of these compounds, and it could actually exert beneficial effects and put some references about these actions that I'm mentioning.

So one possibility that I bring out, whenever I see these controversies or, you know, whether something is toxic or something is beneficial, is that it may be dose related. You know, it may at very low doses, and whatever doses that he's found in the body or the endogenous levels of some of these compounds, it is actually good.

So in that case, when we regulate, we don't really want to go that low, I mean, below the endogenous levels and -- because and -- we could be inducing actually some harm.

And above certain concentrations, so you could activate other pathways that makes it toxic, and what are these other pathways. And I don't know. I don't know if it is just like the inhibition of the cytochrome oxidase of which appears to be a good candidate, or there are any other pathways that haven't been investigated.

But I think this actually should really just put more up front. And I don't really have any good comment about, you know, how to estimate like the uncertainty factors and when there is so much that is unknown, and

especially when we have a compound that generates compounds that could have like a beneficial effect.

So if we go too low, so maybe it's actually not good, but we don't really have data to say that we should go below a certain level or not.

So honestly, I don't know what to recommend, you know, in that regard, and -- but I do recommend to be cautious at least, and to present the data and to show it, and to say -- and to discuss it. I think that that portion is missing.

DR. COLLINS: You're saying like many small molecules, like carbon monoxide and NO have found almost hormonal effects into the body.

PANEL MEMBER ARAUJO: Absolutely. Carbon monoxide is the same situation. Carbon monoxide is -- also has been shown to be -- to act as a neurotransmitter, has also been shown to process anti-inflammatory and antioxidant and actions at those levels. But you do -- you give very high doses of carbon monoxide, so it induces like, you know, a toxicity at the respiration level by binding it to the hemoglobin.

So it really depends on the dose. It also depends on whether it is at the cellular level versus a multi-organ system, like in the body. And I was doing some searches to see whether just at a cellular level,

just if you take cells and you put carbon sulfide, if at least that has been elucidated, and I don't see much of any literature, and it is surprising to me.

DR. COLLINS: Well, there is something called know hormesis.

PANEL MEMBER ARAUJO: Right.

DR. COLLINS: And hormesis is an effect where there will be a dose response curve. And at the very lowest level, there will be a beneficial effect, and -- but it's sort of like some toxicologist except that some think that it's being pushed like people -- like lead -- showing that lead -- well, lead might have this little beneficial effect. So, you know, just don't get there and a little bit of lead is not going to hurt you. Yeah.

DR. MARTY: So just to comment on considering the endogenous versus exogenous exposures to really anything. So, you know, it's clear that there is benefits to endogenously-produced compounds, including H2S. So we just had a little look-see at that from the Aliso Canyon gas leak where there were measurements of H2S in the ambient air.

So when you're thinking about it from a toxicological perspective, I think you have to be really careful about adding on to endogenous levels of any sort of chemical, because what you're doing there is that --

and, in fact, the toxicity that you measure is the result of additions to the endogenous levels for a number of compounds.

So it's -- I think it's important to be careful about how much uncertainty factors you use, because you don't want to get, you know, below what is a natural background, for example, which is an issue with the ozone standard. There's one example of that.

But I -- you know, I think it's, you know, a cautionary tale, be careful about saying, oh, it's okay, because we have endogenous levels of this stuff. If we're adding to that endogenous level, we really don't know what we're doing at the low end of adding, but you can see if you add more and more, you start to get into toxic effects, so it's a tricky business.

PANEL MEMBER ARAUJO: May I add -- also comment on that. I agree, and I think we -- we are faced with a question of could it be that it is good or beneficial after whatever is in the body, and if you supplement it somehow, so you're already crossing that threshold, and you start seeing the toxic effect, and -- however, I am surprised by some of these papers that have been appearing presently.

So I have here in front of me one paper published lasts year, where they administer -- they did administer

carbonyl sulfide. They administer sodium hydrosulfide, which is a donor for hydrogen sulfite, so it's metabolized and it induces -- it produces hydrogen sulfide, and that's clearly induced toxicity. So they're adding on top of.

Now, they're just adding one compound that comes from the metabolism of the carbonyl sulfide. I'm not saying that this is what is going to happen, and I haven't seen any work or where actually they give like a low dose of carbonyl sulfide and they see beneficial effects. No. But it not means I'm saying that, but I'm just saying that some of the compounds that we're attributing toxicity to may actually be good at certain concentrations, and that should be expressed in the document, because this is part of the -- this is part of the general lack of sufficient knowledge, you know. And perhaps one of the things that we need to consider when we use one uncertainty factor versus another.

PANEL MEMBER BLANC: Well, I guess I would take a somewhat temporizing view, and I don't think I would insert an explicit statement saying carbonyl sulfide could be good for you because it -- you know, hydrogen sulfide could be good for you. It's a little bit too many things.

But I think it's certainly fine to have a statement that says this is a complex and poorly characterized area of metabolism, and it includes

biological effects at low levels that are not well characterized, or something like that.

But the problem with a statement that says it could be good for you is that it really could come back as a club to be used against regulatory interventions. And so I would -- and that's not your intent, but that's, in fact, how it would potentially be used. And that that's clearly been the intent of people who may have, in some way, tried to argue that a little bit of lead is a good thing.

So perhaps I'm a little overly cautious, but I think I would shy away from that. One come accomplish what you're saying in terms of emphasizing the uncertainty with a more neutral sentence or two.

PANEL MEMBER ARAUJO: One of the problems is this approach is that if we will be just ignoring a whole body of literature that is -- that is there. And I think that the responsibility of the agency, and it is at least in the portion of where he presents in literature, that the literature is presented in an unbiased way. So by no means, I am suggesting that we should include a statement where we hypothesize and that carbonyl sulfide could have some beneficial effects. No. I mean, there is no data whatsoever that it is presented.

The data that I have referred to is in relation

to the hydrogen sulfide. So there is a portion in the document where it discusses the mechanism of the toxicity induced by the carbonyl sulfide. And it says that it produces like hydrogen sulfide and some other compounds, and hydrogen sulfide is an inhibitor of cytochrome oxidase, and that's a possible mechanism of how induces toxicity.

That is a portion where actually they could include. However, hydrogen sulfide has also been reported to be an endogenous gaseous molecule that could exert in some, I don't know if you want to say beneficent effects or you could say just an anti-oxidant and anti-inflammatory effects.

So doesn't say -- that shouldn't be really interpreted that because of the issue of what is -- what the hydrogen sulfide is doing that now then we need to conclude that mostly carbonyl sulfide is also doing. That could point out is to -- in the direction is that maybe hydrogen sulfide is not really the mediator of the toxicity induced by the carbonyl sulfide.

We cannot attribute all the toxicity to the hydrogen sulfide because the hydrogen sulfide could actually be doing some positive things. And that is just not known.

PANEL MEMBER BLANC: Well, it is very well known

that, in fact, hydrogen sulfide is a cytotoxic anoxic injury at levels of which it exceeds by orders of magnitude low endogenous levels. So I think -- I think what you're saying is comparing two different things in a sense. If one makes the argument that at the levels we're talking about, the one-for-one metabolism to hydrogen sulfide, you'd get one hydrogen sulfide molecule for each molecule of carbonyl sulfide. That we're not talking about exposure levels that are in the experiments that they're citing, because they're referring to the data that they have, the animal studies that they have.

Those are not levels that are in the range of endogenous biological hydrogen sulfide. And so again, I would just say I think there's ways to say this without overstating it to a level which would be prone to misinterpretation or miss -- even misuse, thinking to the regulatory intention of the document to inform public health policy.

CHAIRPERSON KLEINMAN: But I think Dr. Marty's comment about the distinction between the endogenous and the exogenous is really important, and that endogenous what we're worried about is an exposure that really raises the internal level above the normal physiological background. And under that physiological background, we have defenses to deal with it, but above that, you start

to see the toxic effects.

And I think one of the key things is if you block the conversion of COS to sulfide -- hydrogen sulfide, the toxic effect drops off. So there's a real mechanistic link to toxicity at these more than physiological levels. Unfortunately, we don't have enough knowledge to be able to actually do the toxicokinetics and dynamics to calculate what those physiological levels are. So we have to be a little more conservative, I think.

PANEL MEMBER RITZ: Plus, we don't really know what the brain levels are versus the levels maybe in the urine or in the blood, right?

CHAIRPERSON KLEINMAN: Right. That is true.

So are there any other points?

Dr. Buckpitt.

PANEL MEMBER BUCKPITT: I've got one very minor comment, but mixed function oxidase is really a term that went out in the 1970s. So if we can just update it to monooxygenase. You find that in Gillette's old book 1971, but not probably beyond that.

PANEL MEMBER BLANC: A little bit later than that.

(Laughter.)

PANEL MEMBER BUCKPITT: I've been around long time, Paul.

PANEL MEMBER BLANC: Too long.

PANEL MEMBER BUCKPITT: That's right. I get the point.

PANEL MEMBER ANASTASIO: This is Corte Anastasio. I had just a few points. On page two, the hydroxyl radical rate constant, I think there's a typo there. I think it should be -- it's written as 2 times 10 to the minus 5. I that should be 2 times 10 to the minus 15. The highest value you can have is 10 to the minus 10. So that's just a typo.

And then on page four, part of this mirrors what Kathy had said earlier, I think a little more granularity on the ambient data would be helpful. For example, are COS levels higher when you're refining these? One would expect that. No.

DR. COLLINS: I don't know.

PANEL MEMBER ANASTASIO: Oh, we don't. Okay.

DR. COLLINS: I don't think we know.

PANEL MEMBER ANASTASIO: So I guess maybe the thing to do then is for some of these values that are slightly higher, I don't know in the literature if there's any evidence of nearby sources. That would be helpful.

I think also you can see that there's a problem with the range that you give for the U.S. values. You know, you say --

DR. COLLINS: That was from two different papers. I quoted from a review, and I'm going back and working on that.

PANEL MEMBER ANASTASIO: Okay. So those -- yeah, those two pieces are inconsistent in that sentence.

DR. COLLINS: Yeah.

PANEL MEMBER ANASTASIO: So to the extent you classify sites as rural, urban, you know, near a refinery, that would be helpful, but maybe the data is not there.

The other part is the new data that you put in for the Beijing concentrations. Actually stating what those concentrations are would be helpful.

DR. COLLINS: Okay.

PANEL MEMBER ANASTASIO: And again, any information about nearby sources that might be contributing to higher concentrations would be useful to know. Yeah, those are the only comments I had.

CHAIRPERSON KLEINMAN: Are there any other specific changes that the Panel wants to recommend before the document gets finalized?

PANEL MEMBER ARAUJO: I just have a very small comments. One has to do with the numbering of the figures and tables. So you're having a sequential ordering in this document. Figure 1 -- figures and tables together, and then you start with Table 3.

DR. COLLINS: Okay. We can -- yeah, we started to get in the habit of numbering the tables to sort of identify what part they were with. But if you want to -- if you just like one to four, we can do that.

PANEL MEMBER ARAUJO: Oh, got it. Okay. All right. Yeah, I'm just seeing that both documents used like different ways. This is -- one uses --

DR. COLLINS: They're in Oakland and we're in Sacramento.

(Laughter.)

PANEL MEMBER ARAUJO: Okay. And the other is also very small. On page 22, on the table for the current reference -- the current RELs.

DR. COLLINS: Yeah.

PANEL MEMBER ARAUJO: So you're showing the chronic reference exposure at the bottom in micrograms per cubic meter, and in between parentheses parts per billion. However, before you've shown exactly the -- you always show the parts per millions before, and then the micrograms and here you invert it. So just be consistent throughout it.

DR. COLLINS: Okay.

PANEL MEMBER ANASTASIO: Can I add on a related note? I mean, I know it's confusing, right, sometimes you've got a mass-based concentration, sometimes you have

a ppm mixing ratio. Sometimes in the document -- well, generally you give both --

DR. COLLINS: Yes.

PANEL MEMBER ANASTASIO: -- which is preferred, but there are times where you give only one or the other. So it would be nice to always have both.

DR. COLLINS: Okay. Good.

PANEL MEMBER HAMMOND: I was going to bring up in the other document, but this is true. I brought this up before. Along that line. Within that, if you're going to do a mass base, I think decide for the entire document to be either milligrams or micrograms per cubic meter or ppm or ppb throughout, and do the conversions as necessary, because it's very easy for a reader to get confused by that. So just -- I know that --

DR. COLLINS: We do some of that in here, because some of the things we said were parts per trillion and I had made them to parts per billion just for consistency.

PANEL MEMBER HAMMOND: Right, right. No, no. That's fine. And I -- but I was thinking that was a comment I head for the next paper that we're going to talk about. But, in general, I brought this up before. It does get confusing. And trying to carry some numbers around as you're reading it and your suddenly going from milligrams to micrograms. And since there were all these

uncertainty factors that are factors of 10, 100, 1,000, well, then suddenly we're getting in the same realm.

So if, within a document -- I agree we should have both the mass-based and the volume-based units, but keep the same units, and do the conversions as you need to for the papers, whatever is most convenient, in a report. But either milligrams or micrograms per cubic meter, either ppm or ppb.

PANEL MEMBER BLANC: I'd like to make a motion that we approve the document, bearing in mind that there may be some minor corrections, including an expansion of the discussion of the limitations of the knowledge base on metabolism consistent with Dr. Araujo's comments. So I would move that we accept the document with that in mind.

PANEL MEMBER ANASTASIO: Second the motion.

CHAIRPERSON KLEINMAN: All right. Can we get a consensus on that.

Jesús?

PANEL MEMBER GLANTZ: Stan votes yes.

CHAIRPERSON KLEINMAN: Okay.

PANEL MEMBER ARAUJO: Yes.

PANEL MEMBER ANASTASIO: Yes.

PANEL MEMBER RITZ: Yes.

PANEL MEMBER BUCKPITT: Yes.

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER BLANC: Yes.

CHAIRPERSON KLEINMAN: Very good, I agree too.

So the State law requires OEHHA to seek the advice and recommendations of the Panel and to take the recommendations to heart and incorporate those into the final document. And I think with the discussion today, which I think was a very good approach to looking at these documents, I want to congratulate everybody on putting the comments on a slide, so that we could all see them, and see how they were responded to. I think that's a great approach.

So I think we've fulfilled our statutory obligation in this regard.

PANEL MEMBER GLANTZ: This is Stan, just one kind of procedural comment. Since the motion was to accept the report subject to the small changes that were discussed, I think I'd like to -- I don't know if we need to make a motion, but what we've done in the past is that we've delegated to the Chair the authority to review the revised document and accept it on behalf of the Committee. So I don't know if we need to --

PANEL MEMBER BLANC: No, but that's consistent. Thanks for reiterating what has been our standing approach.

PANEL MEMBER GLANTZ: Yeah. So just to have it

on it the record, so -- because the Panel does have to actually approve the final, final, final document. So we're just delegating, Mike, you -- the authority to you to offer that approval.

CHAIRPERSON KLEINMAN: I'll be happy to act in that regard after the document is finalized.

So the Panel didn't have any additional changes to recommend, other than the ones we've already discussed. And I think that allows us to wrap-up this part of the agenda. So thank you very much.

I think, at this point, before we start with the next document, I'd like to offer people a 5 to 10 minute break, and then we'll reconvene at 10 after.

(Off record: 11:04 AM)

(Thereupon a recess was taken.)

(On record: 11:17 AM)

CHAIRPERSON KLEINMAN: Okay. I'd like to call us back to order, and reconvene the meeting.

And before we move forward with EGBE, I just wanted to mention that Dr. Araujo wasn't here when we went around the table earlier, but he did come in shortly thereafter, and has been here for the whole discussion. So he is -- I just wanted to make sure that everybody knew that was here.

Stan, are you still with us?

PANEL MEMBER GLANTZ: I am.

CHAIRPERSON KLEINMAN: Terrific.

All right. So we're now going to take up the discussion of the reference exposure levels for EGBE, which stands for ethylene glycol mono-n-butyl ether.

DR. BUDROE: And the -- we're going to have a team presentation here. So Dr. Jianming Yang will be presenting the actual EGBE REL document, and then Drs. Daryn Dodge and Rona Silva will be presenting the response to comments.

(Thereupon an overhead presentation was presented as follows.)

DR. YANG: Good morning. I will present a draft of the non-cancer reference exposure level for ethylene glycol mono-n-butyl ether, EGBE. My name is Jianming Yang, staff toxicologist.

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DR. YANG: So EGBE is a solvent. In terms of solubility, it has characteristics of both alcohol and ether. So no surprise it is got a wide application, such as use in consumer products and the building materials. It is a high production volume chemical. It's a low volatile chemical. EGBE, the vapor pressure is 0.88 millimeter mercury at 25 degrees.

EGBE is a major toxicity in human including skin,

skin, respiratory system irritation, which is different from the EGBE the major toxicity in rodent, such as hemolytic red blood cell and damages in the liver and forestomach.

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DR. YANG: Slide 3. Since EGBE has been used widely, its production is huge. For example, about 180,000 tons of produced in U.S. This in 1992 data. And about 150,000 tons produced in the European Union. The world wide estimated production is as high as 500,000 tons. EGBE's major use in the paints and the coatings is about 13 -- about in 75 percent, and 18 percent for the metal cleaners and the household cleaners.

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DR. YANG: Slide 4. EGBE toxicokinetics. EGBE can be absorbed through the inhalation, ingestion, and dermal exposure and distributed to the tissues rapidly. EGBE's metabolism is mainly through the alcohol and aldehyde dehydrogenases. In rats, there are three metabolic pathways including: 1, oxidized to 2 butoxyacetic acid, called BAA; 2, conjugated with UDP-glucuronide acid; and 3, conjugated with the sulfate.

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DR. YANG: Slide 5. EGBE's elimination is mainly through its metabolized form of BAA through the urine.

Its half-life in the human is about 40 minutes. And elimination for half-life for the BAA through the urine about six hours. In occupational exposures peak excretion of BAA in urine is between 6 to 12 hours after exposure.

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DR. YANG: Slide 6. This figure shows EGBE metabolic pathways. EGBE in the rat, like I mentioned before, can be conjugated with the glucuronide and sulfate. EGBE can be metabolized to the BAA through the alcohol and aldehyde dehydrogenases. In human only, the BAA can be conjugated with glutamine and glycine.

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DR. YANG: Slide 7 is for the acute reference exposure level. It's based on human inhalation studies. One LOAEL at the 98 ppm was identified. Actually, this is, however, three human studies. Each study has two to four human subjects. And the exposure for either eight hours or four hours. Eight hours include 98 and 195 ppm exposure in chamber. Four-hour exposure is for the 113 ppm in the room exposure. EGBE critical effect is in human acute exposure is ocular and nasal irritation.

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DR. YANG: Slide 8. The point of departure, we use the LOAEL 98 ppm. Because this is for the acute REL derivation, so no time adjustment is needed. And the

LOAEL uncertainty factor equal to 10. This is just default by OEHHA guidelines. And interspecies uncertainty factor equal to 1, because we use human data. Intraspecies toxicokinetic equal to 1. This is mainly for the acute effects that is from the site of action. It's not considered from the systemic effects.

Intraspecies toxicodynamic equals to 10 because of the small sample size. And also for the children. If the children have asthma, may be more sensitive to the EGBE. The calculated cumulative uncertainty factor equal to 100, so we calculated the acute REL about 1 ppm.

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DR. YANG: Slide 9. EGBE chronic toxicity is based on NTP, National Toxicology Program, 2000 study. The use of the two species, rat and mice, inhalation studied for two years. Animals were exposed to EGBE six hours per day, five days per week at concentration 31, 62.5, and 125 ppm. This is for rat. For the mice, the exposure for the 62, 125 and --

PANEL MEMBER GLANTZ: That is Stan. What slide are you on? I've got --

DR. YANG: Slide 9.

PANEL MEMBER GLANTZ: Okay. Okay. All right. I'm on 9. I was just -- I was afraid --

DR. YANG: Okay. Okay. The exposure to rat and

mice was different. Dose group was -- each group was with 50 rats or 50 mice. The highest study exposure dosage was selected based on -- produce the 10 to 15 percent differentiation in hematologic indices.

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DR. YANG: Slide 10, the chronic toxicity. Our major focus on the non-neoplastic effects. In rats, it is included hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation in livers. In mice, include forestomach also and epithelial hyperplasia, hematopoietic cell proliferation, and hemosiderin pigmentation in the spleen and the Kupffer cell, also have the bone marrow hyperplasia. The major effect in rat they cause the rat blood cell damage and cause anemia. So later those indices are actually from the anemia.

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DR. YANG: Slide 11. Show you how we selected point of departure from the chronic derivation. When we selected the point of departure, we considered the toxicity between species with specific endpoints, such as for the hemolysis effect, Compared to rodent, human is sensitive. The hepatic Kupffer cell pigmentation is a secondary effect from EGBE's hemolytic effect, and was not considered at the point of departure.

Rat nasal olfactory epithelial hyaline

degeneration was the most sensitive toxicity endpoint in NTP study. So that's why we selected this endpoint as the point of departure.

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DR. YANG: Slide 12. This table summarizes some chronic toxicity incidence from NTP 2000 study. There are included four endpoints, the nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, forestomach epithelial hyperplasia, and forestomach ulcers.

The first two endpoints include both rats and mouse studies. The latter two endpoints is only for mice. From the dose group design, we can see the rat have the exposure doses for the 31, 62, and 125 ppm. And for the mice is exposure for the 62, 125, and 250 ppm exposure. This gives us the general idea, you know, the rat is more sensitive than the mice. And liver Kupffer cell pigmentation because it is the second effect from their blood cell hemolysis, because that is not as sensitive in the human. We are not considered that endpoint as a point of departure also.

So we will focus on the nasal olfactory epithelial hyaline degeneration. We can see in the control group both male and female rats is incidence is 13 out of 48 or 50. And the no dose group for the male rat

is 21 out of 49, and for the female it is 18 out of 48. But the data for the male and the female rat in the no dose compared to control grown is not significant by the status analysis.

If we combine the male and the female rats together, you can see the no dose group have the incidence 39 out of 97. That is significant. It is higher than the control group. This shows you the sample size the power in the statistical analysis. And we can see how the -- where good dose response in the rat for this endpoint.

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PANEL MEMBER BLANC: Did you show what the dose response was there statistically?

DR. YANG: Yeah. Actually, I have -- the last slide I have, you know, the batched doses that have occurred will show the dose responses were less than. You see you -- if you see, you know, the stated significant level, you see the force for the male rat. The no dose is 21 out of 49 compared to control is not significant. But for the -- neither dose, the 62 ppm, 23 out of the 49 is significantly higher than the control. And if you see the high dose exposure 125 is much higher. You have three studies. That means the P value is less than the 0.00.

PANEL MEMBER BLANC: So I was making the point --

DR. BUDROE: If you're asking did we do --

PANEL MEMBER BLANC: -- that what you've tested here is not a dose response. What you've done is a series of pairwise comparisons. And the fact that the P maybe point 0.05 and then it may be 0.01 and then it may be 0.001 is not a statistical test of a dose response. Maybe it's in your text. It's certainly not in your table.

DR. YANG: Significant levels less. Yes, that's correct.

PANEL MEMBER BLANC: So you just need to be cautious. I don't doubt that it does look on the face of it, but if you wanted to do a test for trend or some statistical test that showed there was a monotonic relationship between dose and response, you could easily do that, and I think your table would be strengthened by doing that. So you just need to be cautious when you -- not to confuse the test that you've done with what it is that you're testing.

DR. YANG: Yeah, that's a good point. Actually, that --

PANEL MEMBER BLANC: And that's why you get into trouble -- not into trouble. That's why, you know, you end up saying, well, I can't show that there's a difference between -- at 31.2, unless I combine the two sexes. But, in fact, I don't know what your test for trend would be in just the males or just the females,

because you don't present that, at least in the table.

DR. YANG: Yeah, yeah, that's correct.

DR. BUDROE: Correct. We could do a trend test and we'd certainly consider adding that to the document to that table.

PANEL MEMBER BLANC: And maybe Stan has a comment.

PANEL MEMBER GLANTZ: Yes, Stan. I just wanted to agree with what Paul said.

PANEL MEMBER BUCKPITT: How do the numbers for your controls look like the historical controls, are they in line with what they see historically?

DR. YANG: Historical controls.

DR. BUDROE: We don't -- I don't have that comparison at hand.

PANEL MEMBER BUCKPITT: It might be worth looking at --

DR. BUDROE: Looking at the NTP as historical control database.

PANEL MEMBER BUCKPITT: -- because you've got -- I mean, that's significant, right 30 out 50 -- or 13 out of 50? So it would be interesting to look back to see what the historical controls were.

DR. YANG: The background level is high -- is a little high. If you look at the liver Kupffer cell

pigmentation, the male rat that's actually in the control group is pretty high, 23 out of the 50. That's 46 percent. Yeah, yeah, I agree with that. Yeah, actually next slide -- Slide 14 --

--o0o--

DR. YANG: Maybe I show slide 14, you know, the first -- the impact to slide 13, you know, this may show the dose response relationship. This actually -- we can see -- we use the female rats, you know, for the endpoint of the rat and nasal olfactory epithelial hyaline degeneration indices. We can see the three doses -- three exposure groups and the control group who feature this very well dose response issue here. And the more important, you know, the BMDL and BMD is very close. That means those data free to BMD is the more aware. And we now back to slide 13.

Slide 13 is show you the benchmark dose analysis of BMDL05, and NOAEL and LOAEL. This is just summarize from NTP study. For the BMDL05 is down by OEHHA used the EPA benchmark dosage software. We can see the first in endpoint nasal olfactory epithelial hyaline degeneration. For the male rats, we've got eight. All this used dichotomous model. And submodel inside the parentheses, this is generated from the Probit Model has got bad statistics we rely on a lot. And then for female rat is

7.6, we use the model is Logistic Model.

So this is why we select the same point. BMDL05 as the point of departure, because a little lower than the male rat, and the more sensitive. And also this endpoint is more sensitive. And on the other endpoint, and I mentioned it before, we are not considered as a point of departure, because of like the liver Kupffer cell pigmentation, I heard before OEHHA submitted the talk to the SRP and just got it rejected because that is the second effect from the rat blood cell hemolysis.

PANEL MEMBER BLANC: So let's come back to something related to the first thing I asked about. You combined the male and female rats in your previous table, because you argue that there really isn't any difference in the pattern of the response.

DR. YANG: Yes.

PANEL MEMBER BLANC: And the statistical test that you used to show that there was no difference statistically between the females and the males was what?

DR. YANG: You know, I think that maybe how the better answer, you know, when -- you know, the data, you know, distribution maybe is normal, you know, the distribution the sample size does, you know, play a bigger role. You know, if a small sample size, you may not see a significant effect that got the P value less than 0.05.

But the bigger sample size, you may got a significant level, unless -- that's then reflecting, you know, representative. Because a big sample size, you know, is representation. Maybe in the battle. You know, human clinical study, you know, FDA uses it. You know, they have a different phase study. Each number is different.

But when you want to use the medicine to the human, they need a bigger sample size.

PANEL MEMBER BLANC: Well, go back to the slide where you have the rats, the females, the males, and everything else.

DR. YANG: Okay.

PANEL MEMBER GLANTZ: What side number are you going back to?

DR. YANG: This -- I think that slide is 12. I think it is statistics issues, you. And you may have, you know, better --

PANEL MEMBER BLANC: So, okay, you could make the argument that you don't have a lot of power there to show a difference between -- actually, you're not going to show a difference between the females and the males. I mean, if you did a model where you put in sex as a predictor variable, it --

DR. YANG: Yeah, not a --

PANEL MEMBER BLANC: But you'd get a point estimate of the effect too, will be like 1 or 1.006, or something. There is no difference. And if that's true, and since these data indicate that, in fact, 31.2 is not a no effect level, but it's a low effect level, as you see with the combined. And the reason why I would say that is because if you did the correct statistical test, you'd show that there's a dose response.

Then, in fact, whether or not your statistical model gives you a slightly lower level using just the female rats, it's actually bad science. You should use the pooled data and model it where you assume that 31.2 is a low effect level not a no effect level. I think that's --

DR. YANG: That's a good point. Yeah, we use that as, you know, the, yeah the NOEL for the combined, the male and female. And we may use the LOEL uncertainty factor of 10 and generated value may be even more small than currently, you know, the chronic dose we propose.

And this rule is already -- is lower than the other regulated agents. And like U.S. EPA you -- because we got the public comments from the American Chemistry Council, they argue that OEHHA generated, you know, the numbers really is just too low. They say it's how many times? I forgot. It is -- ten times or even to the 100

times lower than the other regulated agents. And like, I don't know. But yeah, you are -- definitely, it was a good point, if we use that as the NOAEL, you vet a lower numbers.

PANEL MEMBER BLANC: Well, you seem to come with -- I don't know if that's because of your correction factors or whatever. But in the slide you presented with the modeling, if you go forward back to where you were, didn't one value come out to 7.6 and the other 8.2 or something?

PANEL MEMBER GLANTZ: Are on you slide 14 now?

DR. BUDROE: No.

PANEL MEMBER BLANC: You're going the wrong way.

Yeah, well, was it the slide before that?

CHAIRPERSON KLEINMAN: Slide 13.

PANEL MEMBER BLANC: Yeah. So one is 7.6 versus 8.2 with the Probit model.

DR. YANG: Yea, they are pretty close. You know, yeah, pretty close.

PANEL MEMBER BLANC: But doesn't at least the science support using the combined?

DR. YANG: You know, for risk I would have a general idea when you use the BMDL05 or NOAEL, usually we select most of the endpoints and pick the less -- the smallest number.

DR. MARTY: So the reason that the combined male and female rat data has a higher number for the BMDL is because you have a larger sample size. So your 95th percent upper confidence bound is going to be a bit bigger than with the smaller sample sizes. So that's -- and we could use the male and female rat combined, because as you point out, there isn't a difference.

PANEL MEMBER BLANC: I mean, you must have -- guys must have had some discussion internally when you were trying to decide what to use. I'm curious from -- it just seems -- it seems sort of weighted statistically. And maybe Stan or Beate, somebody, should -- maybe I'm off base. You know, maybe I've just looked it the wrong way or something.

Stan, do you have any?

PANEL MEMBER GLANTZ: I don't quite understand the point you're trying to make.

PANEL MEMBER BLANC: They use the female rats because the pairwise comparison -- well, they use it for two reasons. One is because they got a lower number when they just used the female rats, but that assumes that the data do not show a no effect level -- a low effect level, and so they have to use 31.2 --

DR. MARTY: Paul, actually, it's --

DR. YANG: Actually, I can saw --

DR. MARTY: Jianming. Sorry.

So it's not because the data don't show a NOEL or a LOEL.

PANEL MEMBER BLANC: Okay.

DR. MARTY: The benchmark dose modeling takes into account the sample size. It takes into account the entire dose response curve. So it's just a better way to get a point of departure than just choosing the NOEL.

PANEL MEMBER BLANC: Okay. I got you. But even so, if you -- maybe you do think the females and the males are different, and therefore you shouldn't combine them and then you should make that argument, or -- but if you do otherwise think they are not really biologically different based on the data you have, then the better science would be to use the bigger numbers.

DR. MARTY: Yeah, I think I agree.

PANEL MEMBER GLANTZ: I mean, going back to the earlier discussion about slide 12, I mean, I agree, at least as I understood the comment. I mean, I think you should explicitly test for dose response in those data, and you can also at the same time put a variable in for gender and test whether there's a significant difference between the male and the female rats.

And I -- you know, if you're looking at all the data at one for a given outcome, that ought to give you a

big enough sample size. They have enough power to -- you know, to see if there's a gender difference. And then depending on what that shows, that would then affect what you do in slide 13. So I think -- I don't think we can resolve this right now, but in terms of, you know, how I think OEHHA ought to proceed, I mean, that's what I would suggest doing.

And all of this current discussion would become moot, because you'd actually have a quantitative assessment of what made sense to do.

CHAIRPERSON KLEINMAN: I'd like to also chime in on the mouse data, which shows no dose response whatsoever. It's totally flat across the exposure doses, and they're barely more than the background dose. And I really question whether you can insert that data and calculate a BMDL.

DR. YANG: Yeah, I did.

CHAIRPERSON KLEINMAN: You can do it, but I don't know that it's legitimate. In fact, it looks like it's getting better as you go to the higher doses. So I think perhaps the mouse data is at best misleading.

DR. YANG: BMDL slide.

PANEL MEMBER ARAUJO: Do you know why they use these type of mice in the --

DR. YANG: Yeah, you're right, because, you know,

in the mice, the dose response some is not good. And that's why we got the BMDL is a big number. And, you know, the forestomach also is a male. We got the 64, female got a 17. You know, the male/female has been -- yeah, you are right, but I didn't, you know, show you all the benchmark dose analysis occurred. The most data -- you know, the fact of the dose response is not that good.

PANEL MEMBER RITZ: So I'm not an animal experimenter, but when I look at the data, it looks to me that it's informative to see that there's actually nothing in the mice, but it's. And so I would lead that in that table, but I would suggest to take it out of the dose response analyses, because it makes no sense. It's just in comparison to the rats where we see a dose response, at least eye-balling it, I imagine the P value will also be significant. Then we should base it on those.

And in the zero category, it seems like the rats either spontaneously have a lot of the nasal outcomes, and therefore they also react and the mice may not, so -- but that's how I would read this data. And I'm not an animal.

DR. MARTY: Okay. So just to be clear, we usually run the BMDS modeling on all of the data before we choose where we're -- which data set we're going to use for the reference exposure level. So the -- we do let the data do the talking on it. And maybe it's a waste of time

in some instances to do the benchmark dose modeling, but it's really fast, so -- and sometimes you can see things that you don't necessarily see just looking at the data, but we have not included -- the actual number is not based on the mouse data.

CHAIRPERSON KLEINMAN: I agree, but once you put it in there, then you might get somebody arguing, well, you've got a BMDL for mice, why didn't you use it? Yeah, I would think that taking it out and just parenthetically saying in the text that the mice did not show a, you know, reasonable dose response, therefore not -- they weren't used in the REL setting.

DR. MARTY: Yeah, I mean, we can take some of it out. But as a practice, we run them all. The best fitting models are the ones that generally get chosen that also are -- that show that there is a dose response. So embedded in the BMDS is a trend model. So it won't fit the data, if there isn't a trend.

PANEL MEMBER ARAUJO: But the value of the data is also -- depends on the value of the model. And so they're using rats that are impreg rats. So when you're using impreg rats, you're really looking -- you can really evaluate like at different concentrations and the effects of the different concentrations.

However, the mice are F1 mice from across in

between black 6 and C3H mice. So none of the mice are equal. All of the mice are actually different in terms of the genetic makeup. That could maybe be the reason why we cannot really see a dose response. And they just hit sort of like a threshold effect, right, either they see deletions or not or the effects or not.

But that's why I'm asking if anybody knows why in the toxicology program they like to use these mice?

DR. YANG: Cheaper, compared to the rest.

PANEL MEMBER ARAUJO: They're cheaper.

PANEL MEMBER BUCKPITT: No, they're not cheaper. They're not cheaper.

DR. MARTY: That's a question for the National Toxicology Program people.

PANEL MEMBER ARAUJO: Yeah. They use it very frequently, I know.

DR. BUDROE: Yeah, that's been their mouse model of choice for a long time.

PANEL MEMBER RITZ: Maybe to address genetic diversity.

DR. MARTY: Well, actually, they don't even do a very good job of that. So, you know, just a side-bar, they are moving to genetically outbred strains to better mimic diversity.

PANEL MEMBER ARAUJO: Right.

PANEL MEMBER BUCKPITT: But I think that's going to come with its own set of problems, in terms of the variability of the data. We always used outbred animals in our work, which meant that we had to use higher Ns and got a lot of criticism for doing that.

PANEL MEMBER ARAUJO: What Ns did you use?

PANEL MEMBER BUCKPITT: We used the Swiss, which is an outbred animal, Swiss mouse.

PANEL MEMBER ARAUJO: How many animals were grouped and were --

PANEL MEMBER BUCKPITT: Eight to 10 rather than three to four.

PANEL MEMBER ARAUJO: They're using a good number. They're using 50 animals per group.

DR. MARTY: Yeah.

PANEL MEMBER BUCKPITT: But if you have a small effect, and that's the issue, you've spent two years doing this, you have a small effect, then you're caught between a rock and a hard place. You say, well, is this one of the outbred animals that's just an outlier or is this a real effect.

So if you have to go to 100 animals per sex, then you're doubling the expense of some of those studies.

DR. YANG: Now, we are continuing on to slide 15 for the 8-hour REL derivation. The critical effect is a

nasal hyaline degeneration of female rat olfactory epithelium. And the point of departure we use the 7.6 ppm from the BMDL05.

As I mentioned before, the rat exposure for the two years and six hours per day, five days per week for two years inhalation exposure. Time-adjusted exposure, we use the point of departure times six hour per day and times five days per week, and we also times 20 divided by 10.

What does this means? Twenty divided by 10 represents the active worker in the 8-hour worker period we'll breathe the half air of the resident would breathe during 24 hours. And the human equivalent concentration at issue is equal to the time-adjusted exposure times regional gas dose ratio.

--o0o--

DR. YANG: Slide 16 is about the uncertainty factor. Actually, all these uncertainty factor is just use the default for the OEHHA guideline, such as the interspecies toxicokinetic uncertainty factor UF A-k equal to 1, UF A-d equal to square root of 10, and UF H-k equal to square root of 10, UF H-d equal to the square root of 10. So that's the total UF equal to 30. We got the eight-hour REL equal to the 0.032 ppm.

--o0o--

DR. YANG: Slide 17 is for the chronic REL derivation. This is pretty much same with the 8-hour REL development is except the time-adjusted exposure without multiple 20 by 10 formula, because this is continuous exposure.

--o0o--

DR. YANG: Slide 18 also for the uncertainty factor is UF A-k equal to 1, UF A-d equal to the square root of 10, UF H-k equal to the square root 10, UF H-d equal to the square root 10. The cumulated UF total uncertainty factor is 30, the same as the 8-hour REL. So the chronic REL equal to 0.016 ppm.

--o0o--

DR. YANG: Slide 19 is just a summary for the acute REL and 8-hour REL and the chronic REL, that we proposed here.

--o0o--

DR. YANG: Slide 20 is public comment, I will turn the time to John.

DR. BUDROE: All right. Dr. Kleinman, we'd entertain questions on the document before moving on the response to comments.

CHAIRPERSON KLEINMAN: I think let's move ahead to the comments, and then we'll have our lead discussants start with those, and then we'll move on to the ACC

comments.

PANEL MEMBER BUCKPITT: Okay. When I look at the these documents, I always look to see whether the RELs make sense, and whether they're based on the best available science. I will say, as an overall general comment on the document itself, it's far less a good critical review of the literature than what we saw with TDI and MDI. It seemed like with those two documents whoever wrote the review went through the literature, but also evaluated the quality of what was done.

It brings me to my first big comment. And I want to make sure that the Committee understands that I think OEHHA scientists are kind of between a rock and a hard place here. You're basing your acute REL on the carpenter studies that were published in '56, but actually probably done in the late 40s and early 50s. If you look at some of the numbers from the animals, a lot of that was done earlier.

I have three issues with those studies. They may be absolutely the appropriate studies to base your acute REL on, but I think the Committee needs to understand that this is pretty -- it wouldn't meet today's standards of science, by any stretch of the imagination. So they used methylthiazole with unstated purity. Essentially, it was commercial material sold under the trademark of the name

during the year that they purchased it. That may have been technical grade material.

They never essentially redistilled it. They never checked the purity of the material that they were using for their studies. So we really don't know what was in that batch of material.

Their conduct of the inhalation exposures was not very precise. The temperatures got as high as 29 degrees centigrade. They were monitoring the concentrations with something called a interferometer. And maybe you can help us out here, Cort. I scanned the internet, and I could not find out. Near as I can tell, it's a refractive index detector. But I'm just clueless, okay? And I went back and tried to figure out what that was.

They did do some calibrations to take samples, but they essentially said that they evacuated a flask and got about a liter of air in that flask, and then did a -- essentially a titration to determine how much butoxyethanol was in those samples. They sampled four times during these exposures, but never gave any indication of what variability in their numbers were. They never said anything about standard curves.

I mean, again, standards were different at that point in time, but these kind of aren't even close. I remember as a graduate student, it was back in '56, Paul.

We always ran standard curves for the things that we did. None of that in any of the write-up.

The methods may have been fine. The inhalation exposures may have been fine. One of the concerns that I had, they exposed some of their individuals to 195 parts per million, and they had one individual that gave them 10-fold less butoxyacetic acid. Now, maybe it was bad assay for the butoxyacetic acid. Maybe that was all going to the glutamine conjugate. But it's clear that there may have been some substantial issues associated with those exposures, and with the levels that they were recording for the exposures.

I'm not advocating that we move away from these studies as the benchmark point of departure, but I certainly think the document has to point out the weaknesses of this study, and it doesn't do that. And it really, really needs to be done.

DR. YANG: Yeah, I agree. Yeah, yeah, because that is where all the, you know, the publication. And we also try to find most recent and better design -- you know, better the publication and the key study. Unfortunately, later they only have one dose exposure for the toxicokinetic study. That's, you know, just cannot use it as, you know, the key study because they cannot compare each other. You know, that's where risk if we

only use -- that only one dose. No matter you're using one dose, it adds, you know, the NOEL or LOEL, because they -- when they use human study, they put human into chamber exposure to the -- you know, the new harmful Chemical. They cannot use it. You know, a lot of the human volunteer are some only in three or four people. You know, the one dose you just cannot risk.

Yeah, I agree. Yeah. We may need to, you know, update the document, you know, point to start the weakness. Yeah, that's great. Yeah.

PANEL MEMBER BUCKPITT: The question I have, if you started with the 20 part per million exposures, of -- what is it Jonathan -- Johanson, and did the calculations from there use that as no observable adverse effect level? What sort of acute REL would you come out with, if you started with that?

I know all of the -- I mean, you did a very good job answering the ACC and pointing out where you were essentially bound to the carpenter studies. But what would happen if you started with those 20 parts per million exposures and you said, okay, this is a no observable adverse effect level, what would your acute REL look like? Because you can trust those data.

DR. YANG: I think maybe we use the 98 ppm as the LOAEL. And that is about 100. If you count 100. And

this use 20 as the NOAEL. So that will remove the LOEL and also uncertainty factor of 10. I think we got the big number for that.

PANEL MEMBER BUCKPITT: Okay. I think it might be worth a discussion in your document. Again, this is going to be certainly a concern. It was a concern of ACC, but I think probably the Committee needs to think about these things. The carpenter study was probably so poorly done that I just have no faith that what they have in there is -- and I may be completely off base. But when somebody uses a chemical off the shelf that was produced in that era, it's likely that it was not very pure. The standards have gone way up. There may have been formaldehyde, acrolein. I mean, you don't know what was in that bottle.

Okay. So the chronic RELs. Again, we've had -- we've already had a good discussion. I think there's no question that you base those -- the fact that the human is not sensitive to the hemolysis, unless you have heroic doses. People have tried to commit suicide with ethylene glycol containing products. I think that all makes sense. It's based quite well, so I don't have any problem with that.

I'm going to go down through some of the other parts of the document and have some additional -- I'll

give you the paperwork when I finish.

DR. YANG: Okay. That's great. Okay.

PANEL MEMBER BUCKPITT: Put I found the document itself not all that well organized up front. So it would be nice to have some tables separating out the studies done with animals, and what they found -- how many, what they found, what they -- so that we're able to parse that out in the writing. We don't have to try to sort through all of the writing.

So if you can say, all right, these are the acute studies with animals, these are the chronic studies with animals, these are the human exposures that are controlled, these are the studies where humans took large amounts of this as acute poisonings, that would help, I think, put the document in a readable format.

The other thing that I didn't find in the document was available levels on butoxyethanol following if I clean my kitchen floor with a cleaner, okay. And those data are out there. In fact, I think, what was his name, Nazaroff -- he was on this Committee earlier -- has published several papers on that. I think it would be important to know what sort of air concentrations we get when we're using some of these cleaners. So I think adding more of that to the document could be really helpful.

DR. YANG: Yeah.

PANEL MEMBER BUCKPITT: The toxicokinetic parts. Again, this goes back to being evaluative, being critical. If you look at those initial studies by Johanson and Boman, 1991, it's clear that Dick Corley in his PBPK modeling and his evaluations have shown that the uptake in -- by dermal is much less than by inhalation.

They used finger pick analysis to do the blood levels and Johanson study. And Corley quite clearly showed that that was -- that led to values that were way out of whack. And it's not just one person saying this person is wrong. It was a very well studied phenomenon. I think for you, you need to put Corley's work in front and say, all right, this is what we know about if somebody is exposed by dermal and by inhalation, that inhalation is really a more important route of exposure, and then come back and say, by the way, there are other studies that suggest that that's not the case, but they were flawed by the fact that they took blood samples by essentially needle prick. Okay. They're finger tip samples.

So it's important again to indicate that the inhalation exposures are more important, I think, than the dermal exposures. And there's lots of literature to suggest that.

The metabolism and elimination. Again, this part

of the document seemed pretty disjointed to me. Maybe, I just can't read anymore, that you discussed species differences, age differences, differences in metabolite patterns, but there's no consistency. So up front make us a table, okay? Say, you know, the human doesn't really excrete much of this as the glucuronide or sulfate. That's an animal issue. We end up making glutamine conjugates of this.

So we have a good sense of how the animals differ from how the humans work with this. And, you know, butoxyacetic acid has been used as a biomarker of exposure. But if that's already metabolized to the glutamine conjugate, unless there are ways that they use to split, to essentially hydrolyze that, they're going to get misinformation from those.

And I know the European Union uses butoxyacetic acid as a biomarker, but they recognize that it's probably not ideal. So again, some evaluative comments there would be very helpful. I think it would make your document much better.

Let's see. Yeah, there were just some areas. So this is -- this is quite specific, but you have oral studies suggested that human stomach tissues would be less capable of accumulating and localizing butoxyacetic acid than rat stomach tissues. That's stuck right in the

middle of another paragraph that has nothing to do with that.

Try to sort out, you know, for each section, what points you want to make and go through that process, okay, so that things are clear where it's coming from and where it needs to go.

Again, separating the studies in animals and humans, I think would really help clarify the document -- the differences in metabolize, I've already said something about.

Let's see. Because you have a sentence in there that says, "Because butoxyacetic acid is excreted in the urine in both rats and humans following ethylene glycol to butoxyethanol exposure, it has been suggested that the production of BAA through the formation of BAL by ADH is applicable in both rats and humans".

I didn't even understand what that was saying. The any species with alcohol and aldehyde dehydrogenase is likely to take this through the aldehyde and into the acid. So it's sort of a throw-away sentence.

And it says, "Lesser amounts of the glucuronide and sulfate conjugates of EGBE is -- really should be BAA, right, which is the conjugating species.

DR. YANG: Yeah.

PANEL MEMBER BUCKPITT: I don't understand, and

I've done some kinetics in my years, what an elimination half-life in urine is. Can you explain that to me? I get an elimination half-life in blood, but --

DR. YANG: Blood is about 14 minutes in human occupational exposure. And BAA elimination in half-life is about six hours, but in the occupation exposure scenario is a longer, like between 6 to 12 hours.

PANEL MEMBER BUCKPITT: But I guess the question that I have is how do you do a half-life in urine?

DR. YANG: We didn't do. We just review the publication.

PANEL MEMBER BUCKPITT: I know, but --

PANEL MEMBER BLANC: How does one do?

PANEL MEMBER BUCKPITT: Can somebody -- yes. How does one do a half-life in urine.

DR. YANG: Maybe --

PANEL MEMBER BLANC: You would take serial urine samples and you would see when the amounts clear of the metabolite. So it would be like --

PANEL MEMBER BUCKPITT: With a clearance in the urine, a half-life?

PANEL MEMBER BLANC: Well, let's say I measure -- well, you don't know when the urine was produced, but you're presuming -- you're using it as a surrogate. So maybe -- maybe there's a -- maybe clearance is the more

correct term, but I think that's what they mean. I'm assuming that's what they mean.

PANEL MEMBER BUCKPITT: It didn't make sense to me. I mean, I understand half-life in the blood.

PANEL MEMBER BLANC: Well, it's also clearance from the blood, isn't it? I mean, I don't know if -- it's somewhat semantic the argument.

PANEL MEMBER BUCKPITT: Okay. Let me put it to you this what. In any of the kinetic journals that I've reviewed for, I've never seen somebody report a urine half-life. I've seen them report accumulative metabolites. I'd be very careful of that, I guess.

Okay. I'd suggest you'd just use stick structures for your structural formula, rather than the CH.

Sorry.

And then the human case reports, so again, consider dividing this into accidental inhalation, dermal exposures, high dose oral, intentional exposures. That would allow you then to say all right, this is what we know about controlled exposures, this is what we know about high dose inhalation oral ex -- I'm sorry, high dose oral exposures where there's been a poisoning and intentional use.

And the point here is that erthrocyte hemolysis

does occur in humans if the dose is heroic. We're just much less sensitive. And I agree with OEHHA's assessment that that would not be using that as a point of departure in animals would not be good to set these standards.

DR. YANG: Yeah, I agree. That's why, you know, for the chronic REL, you know, for the risk assessment, our REL is protective of humans and the environment. They have a ways to still use that endpoint, you know.

PANEL MEMBER BUCKPITT: Yeah. And then there were a couple of additional human exposures study that I found. You can -- I'll give you the references here, that really should be in there and should be evaluated.

Again, a table that lists the approximate doses along with the toxic endpoints and the references. And then I think my final comment was with the acute toxicity of the children. So the document states all 24 children in an accidental exposure were asymptomatic at the time of ingestion. But it was actually asymptomatic at the time of report, and subsequently 24 hours later.

Now, I only saw the abstract to that. I couldn't get the real paper, but that's a distinction that I think you want to make.

DR. YANG: Yeah, we may make that more clear, because the children -- 24 children, children -- only two children trigger more than a 15 --

PANEL MEMBER BUCKPITT: Right.

DR. YANG: Yeah, I mean it literal. And that is may consider more -- more safe way, you know, take that children in the hospital, you know, observe her or do something, you know, 24 hours. And then --

PANEL MEMBER BUCKPITT: But I think being clear that even 24 hours later there was no symptomatology with these individuals.

DR. YANG: Yeah. We need to make it more clear.

PANEL MEMBER HAMMOND: Just a quick comment, since we're on that particular section. That section you conclude with EGBE at these concentrations appears to have low acute toxicity by the oral route. But I said to myself, what do you mean by these concentrations? And, in fact, what we're talking about, I mean, these are cleaning materials. We don't really know. We have, you know, a variety of things that -- that seems like a strong statement for something we don't know well. And I found that -- I mean, maybe you mean the concentrations in the cleaning materials, but I found that a very strange statement in the midst of that story.

DR. YANG: Yeah, I actually, you know --

PANEL MEMBER HAMMOND: Too strong.

DR. YANG: Yeah. Some people just say, you know, the next clean agent or something. They didn't say how

many the EGBE or was it a percentage in that agent or something. Yeah, sometimes that suggest --

PANEL MEMBER HAMMOND: Oh, I understand the information isn't strong. It is not good. It's not good information, but the last statement sounds much stronger than is supported by the paragraph.

DR. YANG: Yeah, we may need to revise that. Yeah. Yeah, that's a good point. Yeah.

PANEL MEMBER BUCKPITT: Dr. Kleinman, that's all I have.

CHAIRPERSON KLEINMAN: Okay. Dr. Hammond has comments, I believe.

PANEL MEMBER HAMMOND: Yes. Thank you. So these are all, you know, very challenging to deal with. I'm going to focus most on the Occurrence/Major Uses section, because I think Dr. Buckpitt said quite a bit about the health effects.

First of all, the usage that is given here is over 24 years old, you know, and, in fact, I could quickly find on the internet data that was, you know, 25 percent higher for 1999. I think, and this may be something kind of useful, the American Chemical Society publishes every year production, you know, volumes of major chemicals. This is a high production chemical, so you should be able to get much more recent data.

DR. YANG: Okay. I will search for that.

PANEL MEMBER HAMMOND: So we should be -- you know, you shouldn't in your paper be presenting 1992 data. We can get much more, and the usage has been increasing as far as I quickly could find over time. And as I say, seven years later, it was 25 percent higher.

DR. YANG: We need make extension search. Actually, I search meta-analysis or some related literature and also Google seems is not bring all the -- some of the news is. But you mentioned American Chemistry Council may have valid -- look at that.

PANEL MEMBER HAMMOND: Right. This is not like the peer-reviewed literature, but it's probably the strongest information you can get and it's probably even better than the peer reviewed literature that's going to be older. And so I would suggest you check with them, because I'm almost certain they'll have that -- those data.

DR. YANG: Definitely. Definitely. I will check, yeah.

PANEL MEMBER HAMMOND: And so a comment kind of paralleled what we talked about earlier in the earlier discussion has to do with the hot spot reporting in California. So the number that was reported in here -- let's see, here it is, that the statewide emissions

reported under Air Toxic Hot Spots Programs were 282,760 pounds in 2011. And given what we were saying earlier, is this the every four years reporting, once again, is that correct?

DR. BUDROE: That is correct.

PANEL MEMBER HAMMOND: So actually what -- let me -- help me to understand this. In 2011, one quarter roughly of the facilities that might emit this reported 282,000 And say in 2010, there's another number for a different quarter. So I do think that we need to talk about reporting things if, in any four year period, if you were to sub four years, you would actually get all the facilities in the State reporting. Then a true reporting of an annual emissions would be a four year sum, is that correct?

DR. BUDROE: Well, we'd have to project across each of those. For example, year one, you've got a quarter of your facilities reporting.

PANEL MEMBER HAMMOND: Right.

DR. BUDROE: Year two, second quarter. So we could project across a four-year period how much, but it would -- how much material was being emitted, how much EGBE, for example, but it would be a projection. It would be an estimation.

PANEL MEMBER HAMMOND: Okay. It would be an

estimation, but we have errors. We can think about what are the size of the errors. So the errors if you were just to add any four adjacent years, you would be at least covering all the facilities. What the error would be that the facility that was four years ago might have changed its production, increased or decreased its production each of the -- so I understand that. But when you report only one year, we know we're grossly underreporting, like on -- if I had to bet my money, we're reporting only about a quarter of the emissions that are actually happening in that year.

So in 2011, we have 282,000 pounds reported emitted by one quarter of the emitting -- now, also, they may not be evenly spread over those four years. But if, in a four-year period, we get all the facilities reporting, we're getting a four-year average by adding those together to know. That would be, if I had to put my money, what the best estimate of a yearly emission is.

DR. BUDROE: That make sense, and that's something we can look into for sure.

PANEL MEMBER HAMMOND: So I would suggest, you know, if you want to be clear. And I understand that there is this error because you're doing it in different years, you can say, for instance, and you could pick the best way to do this from between 2008 and 2012, you know,

the -- it appears that the average annual emissions were, and that would be your -- you know, your assumptions are going to be a constant emission per facility, but it's a lot better than leaving three-quarters of the facilities out, as far as the size of the error.

DR. BUDROE: Right.

PANEL MEMBER HAMMOND: Okay. So my suggestion -- and you know your data better. You may come up with a much better way to do that. But let's not neglect three-quarters of the facilities.

DR. BUDROE: Okay.

PANEL MEMBER HAMMOND: And this would apply not only here, but going forward. I don't think that had registered from me until today, that quadrennial.

DR. BUDROE: Right. Well, actually we picked up on this a couple years ago. And it's where they actually -- the reporting requirements are actually, to the best of my knowledge, set in statute actually, not even in regulation.

PANEL MEMBER HAMMOND: See, you're just quicker than me, but good. That's great. Yeah, but let's think about that, you know, and think how -- what is the best way to characterize it, but I think that picking any one year clearly has a huge error. We should find a better way to characterize that. And you could do a rolling four

year and see what -- you know, from 2000, the rolling four year and see what the trend is, so 2000 to 2004 average 2001 to 2005, 2002 to 2006. Just roll it along and you can that way at least get a sense of trends if you want to look for that. And I'm sure you'll come up with even better ways to do this with a little more thought. Okay.

Yeah, so I do think there's significantly more being emitted. I also think that there -- I know there are more data about outdoor concentrations. And I guess I'm finding myself now moving into what do we want in these documents, what's needed. But for instance, if we want to say what are the levels outdoors, even -- they're indirectly, for instance -- for instance, Joan Daisey's study that looked at 12 office buildings and reports the concentrations inside of the offices, they also collected outdoor samples and they reported what they saw outdoors.

So you can -- we have an outdoor sample there. So you can look for even things that are looking at indoor levels may have done a comparison of outdoors to know how much is penetrating. So there are data kind of hidden there. Is that clear? You look a little confused.

DR. BUDROE: No, that's entirely clear, I guess. But is a question for the Panel is how much, for example, exposure assessment information should be in this document as compared to toxicity information.

PANEL MEMBER HAMMOND: Right. I guess --
DR. BUDROE: You know, the focus of the document.
PANEL MEMBER HAMMOND: -- I always thought there was supposed to be a sense that there was an exposure here, and that's part of why I was on the Panel.
PANEL MEMBER BUCKPITT: Well, I think there should be --
PANEL MEMBER HAMMOND: I have to justify.
PANEL MEMBER BUCKPITT: -- because again, when we look at these RELs, I think it provides a basis for saying, geez, we're way over, we're way under. You know, whatever that is.
PANEL MEMBER HAMMOND: We have a problem.
PANEL MEMBER BUCKPITT: So I think it really does provide a platform.
PANEL MEMBER HAMMOND: A context -- a context for the Toxicology. So as an example, if one is doing that, and I think we may need to think about that outside of just this document where we want to go with it. And I'm sure some of -- you know, all the scientists that OEHHA thoughts on this, we should work it through. But it's not clear to me whether we want to do indoors or not. I mean, I understand that part of what this is -- hot spots are about is outdoor. On the other hand, you do have indoor data here. And if we have indoor data -- and indoor data,

to me, as a -- somebody I feel a responsibility to the citizens of California, I think letting them know what we know about where they can be exposed is important, even though it may not be here. But I'm open to what the appropriate place is -- roles for us to play are here.

But I think the fact that painting with a latex paint can clearly, in some of this information, lead to exposures that are above the RELs that you have. This is a way an individual citizen can be exposed or cleaning with certain cleaners.

So, you know, there are issues about -- so I think we need to think about that and come to a conclusion and decide what we want to do with that. And I will defer eventually to, you know, what ARB wants or CalEPA. But leaving it for now, assuming that we are interested in that, I have concerns when we have sentences like the highest geometric mean EGBE was 81 micrograms found on a certain day after some of the water-based paints were used.

Well, that -- a geometric mean does -- is not a good representation of the high concentrations. And it's not the geometric mean that -- in this case. It might be important for an epidemiology study. It might be important to another study, but it's not important if we want to know are there any Californians overexposed? And

does this represent -- does this activity represent something that can expose Californians to something that is of risk, given what we're finding for the REL?

So I would be willing to guarantee that if the 8-hour REL is 150 and the geometric mean is 81, that if I had to bet my money, I'd be saying, yeah, there are going to be people overexposed from that. So those are the -- again, the context there.

DR. BUDROE: Okay. Well, that's -- I mean it's correct that this -- the information we develop in this document will be informative for indoor air issues, but it's not directly regulatory for indoor air issues.

PANEL MEMBER HAMMOND: So, if it's going to be there --

PANEL MEMBER GLANTZ: Well, this is Stan.

PANEL MEMBER HAMMOND: Stand before, let me just finish. Let me answer and then I'll let you say something. So if I -- I understand, and I'm not clear where we're going to go with all of this, but to the degree -- if it's going to be there, I want it to be accurate, all right, and to fully represent what it is.

If we feel that we don't want to be talking about indoor air, that's a different thing. But if we're going to talk about it, we need to talk about it in a way that's truly informative of what those exposures could be.

DR. BUDROE: Correct, and we can -- we can re-evaluate that information and make it more descriptive.

PANEL MEMBER HAMMOND: Right. And maybe represent more --

DR. BUDROE: Address those concerns.

PANEL MEMBER HAMMOND: We all know that it is generally true that concentration -- exposure concentrations are log normally distributed or something like that. There's a skewing of the data. But those high points are not to be ignored. They're actually really important in the health of Californians. So that's why we don't want to neglect that.

So, okay, Stan.

PANEL MEMBER GLANTZ: Well, I just wanted to comment on the indoor air thing. And while the ARB doesn't regulate indoor air, they do have responsibility for informing the public about it. So I think the representation of the indoor air data being accurate is important.

I mean, we went through this with several things in the past, secondhand smoke and formaldehyde are two that instantly jump to mind. So what's in the report about indoor air needs to be correct. We shouldn't -- and because there is substantial indoor exposure, I don't think we should just drop it.

DR. BUDROE: Okay. And if you have specific written comments that you can provide us with, that would be extremely useful.

PANEL MEMBER HAMMOND: Okay. I will try to prepare those for you.

And then there's a comment that Microorganisms or molds have also been identified as possibly emission sources. Leaving that just staying like that, we have no idea whether that's this minuscule 0.03 percent of the REL or whether it's six times the REL. How does it compare with paint? How does it compare with cleaning materials?

So I think -- and now it maybe that someone just detected it and that was it, but it can -- something should be said more about that, so it's not so easy to dismiss. So I do think that letting people know about cleaning products, about painting -- at the very least, it might just be, you know, having windows open or being careful not to be residing in things -- in rooms.

I also found it interesting that it was at day 19 that they get these high levels or, you know, it's not the day after they painted, which I would have thought. You know, so it's interesting how some of this is happening, and what does that mean for people, is kind of there.

So -- and I guess the other issue for me is because this is a hot spot as opposed to some of the other

things we've been doing, some of this -- and maybe you can help me understand this -- some of what happens is we call this -- we approve this for this thing, there's then a mandate to ARB to do more sampling, is that correct, that this becomes the beginning of sampling as opposed to the ending of sampling?

DR. BUDROE: No. This is -- well, the ARB doesn't sample for these emissions. What happens is -- I was about to carbonyl sulfide. EGBE is on the list of chemicals that must be quantified. So facilities have to report --

PANEL MEMBER HAMMOND: Their emissions.

DR. BUDROE: -- their emissions to the air district, and then the air district reports that back to ARB. So what this really means is this will now -- EGBE will go into a hot spots risk assessment, so to look at cancer risk, if the chemical is a carcinogen or non-cancer health effect risk. And there's hazard indices that -- cumulative hazard indices that get essentially put together by effect class.

So like neuro-CNS effects, for example, respiratory effects. So once these RELs are adopted, they'll actually be able to be used to generate a quantitative estimate of risk from this chemical at each of those facilities and emitted.

PANEL MEMBER HAMMOND: You just said something really important to me, in terms of how this -- I think it is helpful to me to understand how this document gets used, what the consequence of it is. So among other things, you're saying it's the cumulative effects. So if there are three different neurotoxins that are -- that have been identified that one is going to try to actually look at that cumulative effect on the brain, is that correct?

DR. BUDROE: Yeah, it's -- and probably a better word to use would have been combined effect.

PANEL MEMBER HAMMOND: I'm sorry?

DR. BUDROE: Probably a more accurate word would have been to say combined effect rather than cumulative.

PANEL MEMBER HAMMOND: Okay. Oh, right. Okay. Yes. Yeah, I agree.

PANEL MEMBER RITZ: I think I don't understand how would that be done? Because each toxin has different toxicities and, you know, how would you combine that? I mean, micrograms and ppm of one agent is not the same as for another.

DR. BUDROE: Well, what one is being generated is a hazard index for each chemical, so it's the amount in the emissions inventory divided by the REL. So you --

DR. MARTY: Concentration in the air. So

there's -- this is Melanie. There's risk assessment guidelines that have actually gone through this Panel and been adopted for use in the hot spots. And the way it works is the hot spots facilities are required to report emissions of a set of compounds. If there is a reference exposure level then, those facilities that are required to do risk assessments have to do air dispersion modeling to come up with concentrations in the communities nearby. Those concentrations are compared to the reference exposure level.

So John was referring to the hazard index approach. So what we do, because we don't know lots about the mechanisms of toxicity, we do it by target organ. So the respiratory system is considered a target organ. So if you have multiple respiratory toxicants coming from a specific facility, they would do these ratios of the model concentration to the reference exposure level. And those ratios get added. So it's a way of trying to account for multiple chemical exposures and impacts on a single target organ. And it's -- you know, it's a relatively cruder estimate, but that's how it works.

PANEL MEMBER HAMMOND: Okay. And moving on to a slightly different topic. On page 25, the statement is made, "Epidemiological studies suggest cleaning products, including those products that utilize EGBE, increase the

likelihood of an asthmatic episode in susceptible individuals". That needs a reference that statement. And I think that that's an important finding, you know, that we need to understand a little more about that, maybe understanding what are the concentrations that people are exposed to during cleaning, whatever. I don't know the study, what that study is, what the study -- you know, whether that was just a -- without any effort to look at what the exposures were then.

But certainly asthmatic episodes are very important to health outcomes. And this is looking in humans. And so -- and I do know later that you say there's currently sufficient evidence to consider EGBE a chemical for which children are more sensitive compared to the general population. You know, so -- and, you know, further studies need to be done you say a couple more times, which I -- it's good to say that, but we do kind of think that children are more susceptible to asthmatic attacks.

And so again, I would probably, you know, turn to, you know, one of the respiratory people to get more information on that. But I think -- let's think that through, you know, what do we know about asthma, what do we want to say. And I don't know what the study is without the reference to be able to look at it to say what

else can we deduce from that study.

DR. MARTY: So we do need to reference these things. I'm just going to get up to talk about the asthma issue. So in our guidance, actually, let's go back to 2001, we had to prioritize the toxic air contaminants, so we had criteria for prioritizing to determine in a separate function those toxic air contaminants that may disproportionately impact children. And it's a "may" not a "will".

And asthma came up as a disease that, in and of itself, disproportionately impacts children, higher prevalence lets, higher hospital admissions, smaller airways so they get in trouble easier than a larger airway.

PANEL MEMBER HAMMOND: Yes, I remember this actually.

DR. MARTY: Okay. Great.

PANEL MEMBER HAMMOND: Right, I'm right there with you.

DR. MARTY: Okay. So that --

PANEL MEMBER HAMMOND: That's why I've been studying asthma for a long time in children.

DR. MARTY: And when we're looking at our reference exposure levels, this is one way, as we go through the chemicals, that we add to that list of toxic

air contaminants that may disproportionately impact kids. If something we think is either an asthmagen or has the potential to exacerbate asthma, then we consider, okay, maybe that should go on that list. So that's where that comes from.

PANEL MEMBER HAMMOND: And I totally agree with all of that logic. That makes really good sense to me. But therefore, I want to see more -- make that stronger, make it a -- you know, it's just a line -- it's a sentence there and then it gets repeated later, but not -- let's get a little more meat onto that, a little more information about what that's about. And I didn't have the reference to look it up.

So thank you. And I'll try to get you some written comments. Do you have any questions for me on that?

CHAIRPERSON KLEINMAN: Okay. I'd like to open it up to the rest of the Panel for any comments that they may have.

Stan, anything from you?

No.

Okay. All right. Let me ask this, I'd like to talk about the response to comments from ACC. And you both have had a chance to review the agency's response to those comments. What I'm looking to do is if it's not

necessary to go through them point by point, if you've already reviewed those responses and the rest of us have had a chance to look them over too, if we don't have any glaring disagreement with the agency's response, we might be able to just do that more rapidly.

PANEL MEMBER BUCKPITT: Dr. Kleinman, that makes sense to me. I did look over the ACC comments. They were also concerned about the carpenter studies. But again, this is an issue that I think the entire Committee needs to take a look at. There may be no options for that. Other than that, I thought that the responses from OEHHA to those comments were absolutely right on the money.

CHAIRPERSON KLEINMAN: Thank you.

Kathy.

PANEL MEMBER HAMMOND: I looked them over. I didn't look at them that critically. But from what I read, they look fine.

PANEL MEMBER BLANC: But just to clarify, there was -- the most substantive change that was made in response to these comments was a change in one of the calculations of the -- one of the RELs, isn't that correct?

DR. BUDROE: That is correct.

PANEL MEMBER BLANC: So since that's the most substantive thing, I mean, there were here and there minor

text changes. Although, I would characterize most of the responses as an explanation or justification or amplification of what you had done, but there was no action item that flowed out of most of those responses. So could you just walk us through the change that you made and the rationale, since that's the most substantive, the change to the REL?

DR. BUDROE: Okay. Well, the change in the acute REL --

CHAIRPERSON KLEINMAN: So I believe this is the ACC comment number 13 or the responses to that.

DR. DODGE: So, Dr. Blanc, we are referring here to -- I'm -- this is Daryn Dodge who assisted in some of these response to comments.

We're referring to slide number 25, if we want to take a look at that. Okay. So the comment here was, "The acute REL for EGBE should be five parts per million, based on the 50 parts per million no observed effect concentration from Jones et al...", which was a physiological study. I'm sorry, a pharmacokinetic study -- "...and then apply a cumulative intraspecies uncertainty factor of 10, 10 for the pharmacodynamic portion and one for the pharmacokinetic portion", instead of the 30 that we had originally intended to use.

Our response is that OEHHA still believes that

the LOAEL of 98 parts per million by Carpenter is probably the most appropriate point of departure for the REL. However, we do go on to say that OEHHA concurs that the total intraspecies uncertainty factor be reduced from 30 to 10, following the same guidance here that the commenter had discussed. The toxicodynamic uncertainty factor portion would be a 10, and the toxicokinetic would be going from a 3 to the 1.

Now, per our guidelines, when we're dealing with direct-acting sensory irritants, which is what EGBE appears to be doing here, we go to a uncertainty factor of 1 for the toxicokinetic portion, because these kind of direct-acting sensory irritants, there really isn't much variability in the population for -- the original reason why we had it a 3 is the concern that there could be some sort of systemic issues going on, for example, Carpenter et al. saw headache, perhaps nausea. Although, that was probably due to the high temperature in the chamber. And, you know, the concern with metabolism going to butoxyacetic acid, which is a legitimate concern in rodents, but it doesn't appear in the acute REL at these levels really to be a concern at all.

So we concurred here that we should probably -- we should go to 3 to 1 for this uncertainty factor.

PANEL MEMBER BLANC: Yeah. I mean, I thought it

was a reasonable response. I just wanted to make sure that everybody caught that, because that was the major change. Unless I missed something, would you also characterize that as the major change in response to the critique?

DR. DODGE: Yes.

DR. BUDROE: Yeah, that would be the major document change.

PANEL MEMBER BLANC: And because you're talking about toxicokinetics and -- so this is not -- there's no metabolism issue, because it's the parent compound. It's directly doing what it's doing.

DR. DODGE: Yes, that's what we believe, yes.

PANEL MEMBER BLANC: Then the toxicodynamic uncertainty factor relates to potential within human variability in the response, absent the change in metabolism, because there is not a metabolic issue. So is that correct?

DR. BUDROE: That would be correct.

PANEL MEMBER BLANC: Some for example, there might be some humans who have an epithelium conjuctival response, that even with the same amount of chemical might be more intense. I mean, that's the variability we're talking about essentially.

DR. BUDROE: Yes.

PANEL MEMBER BLANC: I just wanted to be clear. I mean, I think that's reasonable. You know, I don't know if this touches on the response or the parent document, but the issue of apoptosis.

DR. BUDROE: For the chronic endpoint?

PANEL MEMBER BLANC: Right, right. So the apoptosis that was described was changes down the pathway towards apoptosis or it was actual apoptosis, because apoptosis is -- it's a term everybody loves, but it's like on the way to sell death, right?

DR. SILVA: My name is Rona Silva. I guess I'm not quite sure what you're asking?

PANEL MEMBER BLANC: Well, I'm asking the biological -- the key biological phenomenon that was driving the chronic REL was connected to the issue of apoptosis. So, I mean, Jesús, probably -- you could probably ask this question better than I could.

I mean, there's apoptosis and then there's cell death. And it's part of -- it's on the way -- it's program cell death, right, we're talking about, not --

PANEL MEMBER RITZ: Not necrosis.

PANEL MEMBER BLANC: No, it's before the cell is dead, but it's committed to dying, right?

So, I guess, I'm asking whether or not the endpoint that was seen was truly apoptosis or upstream

effects from apoptosis. There wasn't -- the response -- you know, the way the wording was I wasn't completely clear, and I think that -- it would be -- it probably matters. I don't know.

DR. BUDROE: I think it's one of the things where it's an upstream effect and you wouldn't necessarily have to go to apoptosis. But what you're saying is essentially a rough ER disruption, which kind of makes sense because what you're talking about is a detergent. And so you're disrupting the -- you know, the structure of the rough ER. And, you know, you can wind up downstream with apoptosis.

But, you know, basically the argument that we were making was is that this is not just an adaptive response. It truly is a deleterious response.

PANEL MEMBER BLANC: But not to belabor the point, but isn't there an issue of reversibility or irreversibility. That is to say once you really are committed, the whole issue of apoptosis is it's not a reversible process particularly, is it, or am I overreading the terminology?

DR. SILVA: So with the NTP study specifically, all they did in order to characterize the histopathology was to stain -- it's a basically stain H&E, hematoxylin and eosin. And that doesn't necessarily show you cells that are dying of apoptosis. There was no further

characterization of the eosinophilic globules aside from that in their study.

What I found while I was doing literature reviews is that eosinophilic globules will form kind of along with the process -- they go along with the process of apoptosis. So you could potentially have them earlier on whether the ER is stressed and the cell is trying to survive, and it's doing sort of and autophagy sort of response.

But that can, you know, also go forward and lead to apoptotic events. A lot of the research that I found that are -- that's cited in the paper, they noted usually in the presence -- whenever they had these eosinophilic globules, they would note nuclear fragments -- pyknotic nuclear fragments within the globules. The globules stained for plasma proteins. And so the -- and these globules were not necessarily found in normal tissues or -- if they were looking at the prostate, they weren't necessarily found in males younger than 50.

But -- so it's difficult for me to say that this is -- this is something that you'd only see in an apoptotic event, but it definitely will occur along the pathway to apoptosis. And it definitely can appear at the beginning stages when the ER is stressed out or when the cell is stressed.

PANEL MEMBER BLANC: Right. So my -- I don't disagree with you. I think what I'm trying to say is that there's a difference between saying that the eosinophilic droplets are a marker for increased likelihood of apoptosis. There's a difference between me saying that, and therefore its's not just a trivial finding versus saying that eosinophilic droplets are a marker -- are, in your words in the response, is an adverse effect indicative of cellular apoptosis.

I mean, I read that statement as saying this is the step -- an irreversible step down the pathway to apoptosis. This cannot be a reversible pathological injury, because apoptosis is not reversible. So I wasn't sure -- and I my note to myself was indicative of later incipience, increased risk? I mean, I don't know what you mean.

I'm not saying that it is a trivial indicator or that it's a non-pathological change, but the use of the language as it's used in this response, and therefore perhaps in the document itself, perhaps presents vulnerability if it's overstating what you really mean, without taking away from using it as an endpoint for toxicity or a not nice biological event.

DR. BUDROE: All right. So if I'm getting this, you're suggesting that we modify the language to state

that this -- that eosinophilic globules are a step in the progression that could result in apoptosis, for example, but is not definitely going to.

PANEL MEMBER BLANC: It's a marker for increased likelihood of apoptosis maybe or there are a lot of ways you can say it, if that's -- if the -- if I understand the biology correctly, and maybe I don't. But if that's what the data are -- because you're argument is appropriately that eosinophilic droplets are not just a benign thing and are not necessarily -- and are not a guaranteed reversible phenomenon that's temporary.

But you're not saying that once you see them, you're on the pathway -- the irrevocable pathway of apoptosis is not what you mean either, right?

DR. SILVA: Not always, yeah.

PANEL MEMBER BLANC: Well, most of the time, some of the time, right? I mean --

PANEL MEMBER RITZ: Actually, I would have a different question. It's not really clear to me what this epithelial hyaline degeneration really is as an outcome, because epithelial cells are dying all the time, and are being replaced all the time. But is this like a structural change, like a fibrosis? So maybe that is something you might want to add.

DR. SILVA: Okay.

DR. BUDROE: A better description of the pathology?

PANEL MEMBER RITZ: Yeah, yeah.

DR. BUDROE: Okay.

PANEL MEMBER ARAUJO: So maybe you can call it like a marker of stress or a marker of injury that could lead into apoptosis. It would be a way of rephrasing the description.

PANEL MEMBER GLANTZ: So it's a little hard to react when you're not in the room, but is that part of the discussion finished, because I had a couple of questions about the response to comments, but I'm happy to wait till an appropriate time.

CHAIRPERSON KLEINMAN: Well, why don't you go ahead, Stan, and --

PANEL MEMBER GLANTZ: Okay. Well, there were -- I agreed with the others who said generally I thought the agency did a quite good job of responding. And in -- and I was pleased to see that there were some changes made to the document in response to the comments, so -- but there were just a couple things.

One of them looking at the public comment document with the responses, it's comment number 5. "Hematoxicity is more generally recognized and accepted as the critical adverse effect". And I didn't really find --

I mean, the answer that you gave starting at line 161 seemed a little bit circular to me. So I was just wondering if you could kind of talk me through your response to that comment. I think you have the slide -- the slides are not numbered the same, but it starts on line 155 -- 153 of the document, or if you want I can read it to you.

PANEL MEMBER BLANC: While they're looking, Stan, I just want to say from my point of view, I actually thought that was pretty lucid response. I'll tell you what I understood from it. It's that hemolysis is not a relevant -- the blood -- the blood cells are not a target organ of toxicity in humans --

PANEL MEMBER GLANTZ: Right.

PANEL MEMBER BLANC: -- because humans are resistant to hemolysis in both children and adults. And therefore, because Kupffer cell hemosiderin is a reflection of hemolysis one wouldn't use that as animal endpoint to model risk for humans, because that's not a target organ that's relevant for humans.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER BLANC: And that's what I understood from what they were saying. And I didn't -- actually, I thought it was pretty clear. So I'm not sure what in their response wasn't clear.

PANEL MEMBER GLANTZ: Okay. Well, I think what you just said is much -- I understand now.

DR. BUDROE: Right. And we have a more detailed response to that essentially in response to comment -- the ACC comment number 44. So we could move --

PANEL MEMBER GLANTZ: No, no, no. You don't need to waste your time on that, but I just -- you know, the -- because when you got -- when you talk to it, it's later in the document. It made sense. I just didn't make the connection. So you don't need to bother.

And then the other thing I just thought would be I just wanted to ask about is this is comment 42. And if you look at line 119 -- or a pardon me 1119. And I just -- I'd just like you to talk where they had -- you said that there was response in 3 out of 49 female rats. And then you went on and said, so that -- that you said well, based on that, they may be a more sensitive subgroup.

And 3 out of 49 is -- you know, that's like 8 percent or 6 percent. And I was just wondering if you could just say a little bit more to justify your decision there?

DR. SILVA: So, I agree with what you're saying is that it could be associated with just chance. And what we have done is we've contacted NTP to get their raw

severity data. That was actually -- the number 3 out of 49 was actually something that was stated in the ACC comments to us initially. And that was not something that I found -- a number that I found in the NTP report or any additional government reports from the EU or EPA.

And so we're looking more into that, but I do agree that that is a low number, but we also do know that, at least from some of the studies that female rats tend to be more susceptible to EGBE effects than the male. So I mean, it is -- Because we present most of our comments with respect to the eosinophilic globule endpoint, you know, I'm okay with removing that from the document.

PANEL MEMBER GLANTZ: Yeah. Well, I think -- I mean, I just -- I always read the response to comments before I read the document, so I didn't realize that number wasn't in the document. But I think if you're going ahead to try to just clarify this, I mean, I think that's the appropriate response for now.

DR. BUDROE: Okay. And we are going to try to get that -- actually get that severity data from NTP.

PANEL MEMBER GLANTZ: Yeah, I think, if you could, that would be great. And then I just had one minor editorial almost comment just on the next page. And this was language in the report. At line 1133 where you talk about new information undocumented in reviews.

DR. SILVA: Right.

PANEL MEMBER GLANTZ: And I found that kind of odd terminology. And I think what you really mean something like not highlighted in the reviews or not stressed in the reviews or not discussed.

DR. SILVA: Not stated at all.

PANEL MEMBER GLANTZ: Yeah, so I would just -- because I didn't -- I got a little confused by what undocumented meant.

DR. SILVA: Okay.

PANEL MEMBER GLANTZ: And that is the language in the report. But otherwise, I thought you did a very nice job of responding. So that's all I have to say.

DR. SILVA: Thank you.

PANEL MEMBER BLANC: So if you really do combine the male and female rats, doesn't the issue of female susceptibility fall out, or am I off track there?

DR. BUDROE: Well, yeah, for the hyaline degeneration, that -- I guess it would depend on getting that severity data, if we can find that, because it might mean that -- we might be able to say that female rats do have increased severity compared to males, in which case, you might not want to combine the two groups.

PANEL MEMBER HAMMOND: I think that that depends on which outcome you're looking at. I think for some

outcomes that's not so true, and for some, it might be true. And I'm trying to find it right now, but I thought I had seen some that was the reverse. That there were some outcomes where the males were more susceptible. So I want to be careful not to just characterize it as the females are more susceptible.

DR. BUDROE: Right. Well, I'm hypothesizing at this point, we got -- we have to get the data before we can really make a statement in that regard.

PANEL MEMBER HAMMOND: Yeah, I would say look at that, and don't just take that as a statement carefully. Thank you.

PANEL MEMBER BLANC: So in terms of my read of the critique -- well, first of all, you guys have a lot of energy, because your response was longer than the original document in words, wasn't it?

(Laughter.)

PANEL MEMBER BLANC: I think or very close in length. Starting on line 589 of the response, "Finally, Kane et al. presents the RD50 concentration-response relationship for EGBE in a figure. At the lowest dose examined, the data show there is a 20 percent reduction in respiratory rate at about 140 ppm in the mice. This finding suggests sensory irritation is present in the exposed mice at this concentration".

That -- you know, A equals B was not intuitive absent some parenthetical, because respiratory rate is a well known gauge of respiratory irritation or something. I mean, there are many, many ways to get to an increased respiratory. So is that an established marker of sensory irritation in mice. That's a model. Then say it parenthetically.

You don't have to change your text of your response. But just as a reader, you know, it may come down to something you know so well that you don't think to say it explicitly.

DR. DODGE: Are you familiar with the RD50 studies that are -- have been done by Alarie's group? Over a number of years, they built up a huge database in mice looking at irritant gases, in particular in how they would cause a reduction in the respiratory rate in mice due to the irritation and excitation of the trigeminal nerves. And it's a form of a way to get the mice to reduce their exposure to irritant gases.

PANEL MEMBER BLANC: And I would just -- don't rewrite this, but it would have been more -- it would have been clearer with little parentheses, a well established marker of, you know --

DR. DODGE: Okay.

PANEL MEMBER BLANC: And then the paragraph just

before that, when you say something like the proposed REL of EGBE at 0.33 parts per million appears to be reasonably close, saying reasonably close to this other estimate, I mean, in general, what is reasonable mean, half an order of magnitude, an order of magnitude, three orders of magnitude? I mean, in general, try to avoid those words, unless you then say what you actually mean in some kind of quantifiable way.

DR. DODGE: Right. Okay. I understand. Okay. It's like, I think there was one other place where you guys said significant, and it actually wasn't clear whether you meant biologically significant, statistically significant, you know, so just -- it's just a word of cautionary thing. I'm not telling you to rewrite it or doing anything, but just, you know, be careful.

PANEL MEMBER RITZ: Yeah. You're also asking for a statistic of two -- when they compare two people. I wouldn't ask for that, a statistical comparison.

PANEL MEMBER BLANC: In fact, it might even be more words than the actual parent document. Is that possible?

(Laughter.)

PANEL MEMBER BLANC: Did you do a word count?

PANEL MEMBER GLANTZ: I think that's not necessary.

(Laughter.)

CHAIRPERSON KLEINMAN: All right. Are there any other comments from the Panel?

Okay. It looks like we have a lot of editorial changes requests. And the only thing that might be substantive is if the combining of the male and female data and the BMD model would give a slightly different point of departure.

PANEL MEMBER BLANC: Well, it's going to.

CHAIRPERSON KLEINMAN: Yeah, it should. So we have, I guess, two courses of action. One would be to have the document revised and brought back to the whole Committee, which given the large number of comments and the large number of things that are going to be changed and the possibility that we may end up with a different REL, I think we probably need to do that, rather than having it go back just to the reviewers.

So I think we should have this document revised and resubmitted to the Committee for the next available meeting, I guess, or, you know, whenever you can get it done. Time is an issue.

So having done that, so we're agreed on doing that. If we have no other comments on either the documents, then I think --

PANEL MEMBER BLANC: Do you want to just have --

perhaps have the minutes reflect that there's consensus on that approach.

CHAIRPERSON KLEINMAN: I think that's a good idea. There -- are there any objections?

PANEL MEMBER GLANTZ: Stan agrees.

CHAIRPERSON KLEINMAN: Yeah, Stan agrees. I'm getting nods of heads from everybody on the Panel. I guesses we're all too hired to --

PANEL MEMBER GLANTZ: I'm nodding my head too.

CHAIRPERSON KLEINMAN: He's nodding his head too.

Okay. Having said that, we have an agreement to have the document returned. And in that case. We've really concluded our business for the day. I'd ask for a motion to adjourn.

PANEL MEMBER HAMMOND: So moved.

PANEL MEMBER RITZ: Second.

CHAIRPERSON KLEINMAN: Kathy was the motion, Beate was the second.

And therefore declare the meeting adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 1:13 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 18th day of March, 2016.

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