MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

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THURSDAY, NOVEMBER 21, 2013

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

COMMITTEE MEMBERS:

Ellen B. Gold, Ph.D., Chairperson

Laurence Baskin, M.D.

Isaac Pessah, Ph.D.

Meredith Rocca, Ph.D., D.A.B.T.

Catherine VandeVoort, Ph.D.

Tracey Woodruff, Ph.D., M.P.H.

STAFF:

Dr. George Alexeeff, Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

Dr. Jim Donald, Chief, Reproductive Toxicology and Epidemiology Section

Dr. Mari Golub, Reproductive and Cancer Hazard Assessment Branch

Dr. Poorni Iyer, Reproductive and Cancer Hazard Assessment Branch

Dr. Ling-Hong Li, Reproductive and Cancer Hazard Assessment Branch

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

Dr. Francisco Moran, Reproductive Toxicology and Epidemiology Section

Ms. Cynthia Oshita, Proposition 65 Implementation

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

STAFF:

Dr. Martha Sandy, Chief, Reproductive and Cancer Hazard Assessment Branch

Dr. Lily Wu, Reproductive and Cancer Hazard Assessment Branch

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

ALSO PRESENT:

Dr. Will Faber, Oxo Process Panel of American Chemistry Council, Lyondell Chemical Company

Dr. Arthur Lawyer, Technology Sciences Group

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 GOLD: Good morning. It's 10:00 o'clock, so I think it's time to get started. And I'm going to immediately turn the microphone over to George Alexeeff.

DIRECTOR ALEXEEFF: Good morning. George Alexeeff, Director of the Office of Environmental -- is it on? Can you hear me okay?

Okay. Clearly, I have to get a little bit closer. That's better. Okay.

I want to welcome you all to the Developmental and Reproductive Toxicity Committee -- Identification Committee. And let me give you a couple of -- before I introduce the members of the Committee, let me just give the basic information about in the event of some emergency. So we have emergency exits in the back of the room. And if there is an emergency, you can exit to the back. There's also some on the side here, and then proceed down the steps.

Also, if you -- for the restrooms, they're out the back exits and to the left. So let me introduce to you the members of the Committee.

To my left is Dr. Ellen Gold, the Chair of the -- what we call the DART Committee. And she is professor and Chair at the Department of Public Health Sciences at UC

Davis. And to her left is Dr. Isaac Pessah, who is professor and Chair of the Department of Molecular Biosciences at UC Davis. And then to his left is Dr. Tracey Woodruff, who is professor in the Department of Obstetricians, Gynecology, and Reproductive Sciences at the University of California, San Francisco.

And to my right is Dr. Meredith Rocca, who is the Director of Non-Clinical Toxicology at Janssen Alzheimer Immunotherapy Research and Development. And to her right is Dr. Laurence Baskin, who is the Chief of Pediatric Urology, professor of Urology and Pediatrics and surgeon scientist at University of California in San Francisco. And to my far right is Dr. Catherine VandeVoort, professor-in-residence in the California National Primate Research Center at the University of California, Davis.

We have two individuals that are not in attendance today. Dr. Ulrike Luderer and Dr. Aydin Nazmi.

At this time, I'd like to just go ahead and introduce the staff that are present here as well. You'll be hearing a lot from the staff today. First, directly in font of me is Dr. Lauren Zeise. And then to her left, to my right, is Carol Monahan-Cummings our Chief Counsel. So she'll be answering any legal questions that the Panel has or any questions -- legal questions that come up in -- during the discussion that need to be addressed.

And then to her left is Allan Hirsch, the Chief Deputy Director for the Office of Environmental Health Hazard Assessment. So going back on this side, we have Dr. Martha Sandy, and she is the Chief of the Reproductive, Cancer and Hazard Assessment Branch in OEHHA. And then to her left is Dr. Poorni Iyer, and then to her right -- and then to her right is Dr. Mari Golub. We have -- then we have Dr. Lily Wu, Dr. Francisco Moran, and Dr. Jim Donald, who is also the Chief of our section that works on reproductive and developmental toxicity questions.

I just had a couple comments. We have -- I hope you have the agenda today. We have -- we're going to be reconsidering the listing of chemicals via the Labor Code known to the State to cause reproductive toxicity. We'll also be having some discussion of consideration of epidemiologic data and how we might want to tabulate it and presenting it to the Panel, and then some staff updates.

So I will turn this now over to -- did you have opening remarks or should I turn it over to Carol?

Turn it over to Dr. Ellen Gold.

CHAIRPERSON GOLD: I really don't. I just want to thank everybody in advance for all their hard work. I know the staff worked very hard and I know the Committee

had a lot to read and review and think about, so I thank everybody for their hard work and effort and time. And we can turn it back over to you.

DIRECTOR ALEXEEFF: Okay. Oh, that reminds me, yes. So I did want to thank all the members of the public in attendance. And also we are broadcasting this via webinar. So it's very important that if either members of the Panel or members of the public or staff are providing some information into the record that they speak into the microphones clearly, so it can -- other people out in webinarland can hear it. And it's also being recorded over here up at the front, just to remind everybody of that.

So I think right now what I'd like to do is turn it over to Carol Monahan-Cummings. And she'll be giving us some information regarding the first item and other sort of housekeeping kinds of issues that she may provide.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Good morning. Can you hear me all right?

Okay. Before I get into the details of what we're going to be doing today, I just wanted to give you my usual reminders for this Committee. I know you don't meet all that frequently, except for this year. And so just a quick reminder I sent out a note to you all a couple weeks ago about ex parte communications, which

means any communications you may have that are not in this public forum with third parties. And just to remind you that if you had any of those discussions that are related to the substance of what we're talking about today, my recommendation to you is to disclose those on the record and just give the general content of what the discussion was, who it was with. That would include media contacts or other interested parties that may have contacted you.

And then just to give you just some of the general guidance for this Committee. This is a scientific committee, and we'll go into, in just a minute, the exact wording of what your charge is, but you're actually applying what's called the "Clearly Shown Standard" to the scientific evidence that you're going to be hearing today. That is not a legal standard. Although, it can have a legal effect once you make a decision. It is a scientific decision.

And because of that, you don't need to worry about things like if you've ever been on jury duty, you might have gotten an instruction about beyond a reasonable doubt standard or preponderance of the evidence or something like that. And those are not the standards we're using today. What we're using is the language in the statute, which is really -- it's a scientific finding. You were appointed to this Committee by the Governor,

because you're scientific experts. And so you don't need to worry about the law, and that's me. And all the lawyers back there will take care of it.

Related to that, you are looking at the weight of the evidence, the scientific evidence, that you're being presented. In your binder, you've got the tab for the guidance document that was created by prior members of this Committee that goes into detail on what the weight of evidence and issues that you might be concerned about how to approach those.

I want to remind you that you can and should list chemicals if there's sufficient animal evidence of reproductive effects. And there need not be any human data available in order for you to list. You don't have to find a chemical isn't -- is a human reproductive toxicant. Also a couple issues that frequently come up in the public comments are the effect of a warning like -- or the effect of a listing like we're going to have to have a warning of some sort or we're not going to be able to use this chemical anymore, or it's going to affect market share, that sort of thing. And those are not issues that you need to be concerned about at this meeting.

Also, at the end of each of the presentations, you're going to be asked to vote on whether or not the chemical has been clearly shown to cause either male

reproductive toxicity, female, or developmental toxicity or all the above. The quorum today is going to be five members, and so five members have to vote in the affirmative in order to take an action to keep these chemicals on the list.

You have the option to vote or not to vote. You can recuse yourself, which has the effect of a no vote, and -- but you also have the opportunity to say that you aren't ready to vote. You're not required to make a decision today. So if there's information that you feel like you need or you just need to think about it some more, that's entirely fine. Just let the Chair know that when you get to a point of needing to vote.

Any questions on that?

Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: In the communication piece, you mean that's related to interested parties, right? Parties that have an interest in the outcome?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. In terms of your communications within the Committee, the concern there would be if there was a discussion between a quorum of the Committee, which -- or a majority of the Committee, and that would be five of the individuals on the Committee, either discussing together our in series about something that is significant in front of the Committee.

So those obviously need to be disclosed, if there are those kind of discussions. But if one or two of you talked about something -- you know, you talked to the Chair about how to present the information today, for example, that's entirely fine.

Does that answer the question?

COMMITTEE MEMBER WOODRUFF: (Nods head.)

CHIEF COUNSEL MONAHAN-CUMMINGS: You look like you had another one.

COMMITTEE MEMBER WOODRUFF: Well, what if we had had a -- like I have a post-doc that works with me and I asked her some questions about the papers. She's not an interested party though.

CHIEF COUNSEL MONAHAN-CUMMINGS: No, that's fine.

COMMITTEE MEMBER WOODRUFF: Okay. All right.

CHIEF COUNSEL MONAHAN-CUMMINGS: But you just disclosed it, so it's fine anyway.

COMMITTEE MEMBER WOODRUFF: I just disclosed it, right, so there we go.

CHIEF COUNSEL MONAHAN-CUMMINGS: What's her name.

COMMITTEE MEMBER WOODRUFF: Her name is a Hanna Vesterinen. I probably just pronounced her name incorrectly on the cast, so I apologize.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Any other questions?

All right. Cindy, if you could put the slides up.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: As everybody has mentioned, I'm Carol Monahan-Cummings, the Chief Counsel for the Office of Environmental Health Hazard Assessment, and I'm also counsel for this Committee. I'm just going to go over kind of the legal posture of what we're doing today. It's a little bit unusual for this Committee, particularly related to the number of chemicals that are being presented to you for reconsideration.

So if you could go to the next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The outline for my discussion today is that we're going to talk about the proposed change of basis for certain chemical that are already listed under Prop 65. Some of them have been listed since the very early days in the eighties.

We'll give you a legal background on why these are being presented to you today, talk about what our next steps are, and then I'll answer any questions. I'm happy to answer questions as we go along, but it may be that the slides will cover that. And so if you want to wait till the end, that's fine too.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So what we're talking about today, as I mentioned, is a change of basis for certain chemicals that have been listed under Prop 65. These -- we are looking at a change from an administrative listing, which was based on some provisions of the Labor Code, California Labor Code, that I'll talk about in a minute.

And so what happens when we have administrative listings that -- where there's been a change in that -- in the basis for that listing, we refer those chemicals to this Committee for consideration of whether to keep them on the list.

We do that in terms of authoritative body listings, Labor Code listings, and formally required listings. If you recall, a few months back when we did the kind of general discussion of how chemicals get listed, we went over those -- there's four bases for listing.

So next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: We have I believe it's eight -- is it nine chemicals or eight today?

DR. ZEISE: Nine.

CHIEF COUNSEL MONAHAN-CUMMINGS: Nine.

Okay. So we've got nine chemicals that we are going to present to you today, which we'll go over in detail. But what we're -- what we're doing is we went through and looked at chemicals that had been listed based on the American College of -- Conference of Governmental Industrial Hygienists. We call them the ACGIH. It's easier to say. And they -- they establish threshold limit values for chemicals that are present in the workplace.

In the past, we were able to list those chemicals based on what we call the Labor Code provision of Prop 65, but we have had to reconsider those because of some changes at the federal level. So we have looked at other basis for administratively listing some of those chemicals that we identified. And so this slide just gives you an idea of what we're planning to do with some that aren't being presented to you today.

So in the first box, we have four chemicals that we're proposing for listing -- actually, it looks like three -- that are based on findings from the U.S. EPA., and also on NIOSH, which is a -- kind of a subdivision scientific arm of OSHA. And so we're proposing those listings under those different authorities and formally required, which we don't use all that often anymore, but it's -- we're proposing the listing of the chemicals in

the second box based on requirements -- formal requirements by OSHA for specific warning requirements for those chemicals.

And actually the notices on these are not actually going to be the formally required ones that are being posted tomorrow. So you got advanced news.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the chemicals that are being presented to you today are in the left-hand box that's highlighted there. And then there's also we're going to have a number of them for a future meeting, which we're thinking about having in the spring of next year that you'll consider under the same standard that you're doing today, and generally under the same process, unless we determine that something -- we need to improve the process.

So next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the chemicals that we're considering today and we'll consider next year are the way this is going to work is the chemicals will only remain on the list if, in your judgment, they are --

have been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity. So it's the same standard that you use when you do a de novo review of the scientific evidence for a chemical listing. It's just that what's the difference here is that these chemicals are already on the list.

That shouldn't make much of a difference to you at this point, because how they were listed really doesn't matter, because you're reconsidering that listing and determining whether they should stay on the list.

Okay. You can skip the next slide and go two.

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CHIEF COUNSEL MONAHAN-CUMMINGS: All right. So the background here, as I mentioned, is that there's a provision in the statute that incorporates by reference what we call the Labor Code, which is California Labor Code subsections that are related to identifying chemicals that are known to cause reproductive toxicity. That provision actually incorporates by reference a federal set of regulations that are developed by federal OSHA. And it's called the Hazard Communication Standard. And we're going to call that the HCS.

You may be familiar with that if you do work in the occupational exposure area. The federal standard and

the State standard that follows that requires certain kinds of communications, including product labeling, employee training, and some other documentation like the -- they used to be called MSDSs and now they're called SDSs under the new standard.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So previously, until March of last year, the Hazard Communication Standard specifically referred to the ACGIH list of threshold limit values, and what's called subpart Z of the federal regulations as a definitive source for identifying chemical hazards.

And so it actually said specifically -- if you look at the next slide --

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CHIEF COUNSEL MONAHAN-CUMMINGS: Actually, the language is not in there. Sorry. It specifically said that you -- that chemicals that were identified by the ACGIH were conclusively considered hazardous. And so what we did is we looked at the threshold limit values for those at that time, and listed those that had a basis for the TLV of a reproductive endpoint or developmental endpoint.

So on this slide, you can see that there's a

couple of legal decisions that are -- or a legal decision that was related to listings under the Labor Code that was decided in 2011. We had been listing chemicals under the Labor Code since the beginning of the Program, but were challenged in the mid-2000s for listing those. And we went through the trial court and the court of appeal and our -- the requirement that OEHHA list chemicals under the Labor Code was upheld at that time, and that remains true today. And that's why we use the ACGIH TLVs for listings.

However, in 2012, as I mentioned, we're still required to do the listings, but because federal OSHA changed the Hazard Communication Standard, we can't list these chemicals based on the TLVs anymore.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So what we did, as I mentioned, is we reviewed all of our listings that have been done under the Labor Code for the TLVs, and determined which of those need to be reconsidered. You don't need to evaluate the basis for the TLVs, at this time, even though we provided that information for you in your materials for completeness. What you should consider is the weight of the evidence that has been developed since the time that the chemicals were listed, or at least since the time the TLVs were established. And as I

mentioned, that's a de novo review of the data today.

So next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So as I mentioned, what you need to do today is decide whether a chemical does or does not meet your own criteria for listing or whether you want to defer that decision to a later meeting. We have a number of chemicals we're reviewing today, and we -- you know, if you feel like there's information that you need that we haven't provided, we're happy to do that, or if you just need to think about it a little bit more, that's fine. So don't feel compelled to make a decision today.

And we will be presenting the other set of chemicals to you in a meeting early in 2014.

So any questions?

Yes, Dr. Pessah.

COMMITTEE MEMBER PESSAH: How do we consider conflicting information or information that really is contradictory in our deliberation or our reading of the information that's available to us.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, you should look at the whole body of information that you were provided. And some of it may conflict with other materials that you have. And that's why you discuss and

deliberate. You have to decide whether or not the weight of the evidence supports a listing or not.

Does that make sense?

And one of the ways you can do that is to use your -- the process that the Committee had developed to help you answer questions about how to approach data.

Any other questions?

All right. I think the next person up is Dr. Donald.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Thank you, Carol. My name is Jim Donald, I'm Chief of the Reproductive Toxicology and Epidemiology Section within OEHHA.

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DR. DONALD: As Carol has already thoroughly covered the charge with the Committee today is your usual charge to determine whether a chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. So consistent with that charge, we, as usual, attempted to identify and retrieve all of the relevant -- all of the data relevant to the reproductive and developmental toxicity of these chemicals. And we've provided that data to the Committee in the form of summary

tables, and also in the form of the original study reports and published papers whenever they were available to us.

And again, following our usual procedure, we made that material available to the public, so that if we missed anything the other interested parties were aware of, they could also provide those to the Committee.

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DR. DONALD: So our procedure for identifying those data was to have literature searches conducted covering the three major endpoints of reproductive toxicity, which are, of course, developmental, male reproductive and female reproductive toxicity.

We had those searches conducted by professional library staff through a contract with the Public Health Library at the University of California in Berkeley. And the search protocol that was followed by those staff is described in the hazard identification document we've provided to you as Appendix A.

Once the searches were completed, OEHHA staff reviewed the entire results of the searches and identified studies which appear to provide relevant data. And only those studies were provided to the Committee. Our staff will, as usual, present brief summaries of the data for each chemical. And due to the number of chemicals under consideration today, we will make the summaries very

brief. But, of course, we'll be happy to answer any questions you have on the data.

And for simplicity, we will present the chemicals -- we'll present the summaries on the chemicals in the same order as the chemicals appear in the HID.

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DR. DONALD: And the first presenter will be Dr. Francisco Moran.

DR. MORAN: Thank you. Good morning. I will present first the data available for tert-amyl methyl ether, abbreviated as TAME.

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DR. MORAN: A comprehensive literature research resulted in three references with data on the potential reproductive toxicity of TAME, one of which focuses on developmental toxicity resulting from prenatal exposure in two species of rodents; one multi-generational study, which investigated both reproductive and developmental toxicity; and one study of female reproductive toxicity.

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DR. MORAN: Developmental toxicity studies by Welsch et al. were conducted in 11-weeks old CD mice and Sprague-Dawley rats. Pregnant females were exposed by inhalation to filtered fresh air or TAME at 250, 1,500, or 3,500 ppm per six hours per day for 11 days in mice or 14

days in rats starting on gestational day six. Dams were sacrificed one day after last exposure and fetuses dissected for physical examination

All effects were observed at 3,500 ppm and they are summarized as follows:

There were reduced maternal body weight in mice and rats; reduction in fetal body weight in mice and rats; increased incidence of fetal death in mice, but not in rats; and, increased incidence of skeletal malformations in mice.

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DR. MORAN: In a two generation reproductive study by Tyl, 35 days old virgin Sprague-Dawley rats of both genders were treated by inhalation with 250, 1,500, or 3,000 ppm to filtered air for six hours a day per five days a week, during the pre-breeding exposure period, equal 10 weeks, and the post-mating holding period for males.

During mating, gestation and lactation of F1 and F2 litters, exposures were six hours a day for seven days a week. The endpoints considered were:

For dam toxicity, the survival, organ, and body weight, and feed consumption; and for the offsprings, the fetal survival, body weight, vaginal patency and preputial separation for the F1, and anogenital distance at birth

for F2. Reproductive organs from animals suspected of reduced fertility were subjected to a histopathological evaluation.

The results are summarized as follows:

Reduced body weight of dams during lactation at 3,000 ppm; increased percentage of abnormal sperm of 3,000 ppm for F0; reduced body weight in F1 and F2 at 1,500 ppm; decreased survival of F2 at 3,000 ppm; reduced estrous cycle length at 1,500 ppm; and, increased gestational length at 1,500 ppms.

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DR. MORAN: In a study of female reproductive toxicity by Berger and Horner, that consists of an in vivo treatment of females with an in vitro fertilization assessment, female Sprague-Dawley rats were exposed to 0 or 0.3 percent TAME in drinking water for two weeks prior to oocyte harvest. Exposed females were induced to ovulate and the ovocytes collected and incubated with diluted sperm from untreated males for 20 hours.

The results were a reduced percentage of oocytes fertilized and nonsignificant decrease of penetrated sperm per oocyte.

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DR. MORAN: That concludes this presentation.

CHAIRPERSON GOLD: So the organization today that

we decided upon is to have staff presentations for each individual chemical, and then invite public commentary and then there will be Committee commentary.

So, at this time, we invite any public comments on this chemical.

Cynthia, have you been informed of any?

MS. OSHITA: (Shakes head.)

CHAIRPERSON GOLD: Anyone want to make any?

Hearing, seeing none.

So it's now time to turn it over to the Committee for discussion, and I've asked the Committee just to give sort of a summary of their impression of all of the studies, because a great deal of the detail has been provided by the staff. But if you feel that you need the detail to explain your sort of position or feeling, that's fine.

So I'll turn it over to Dr. VandeVoort.

COMMITTEE MEMBER VANDEVOORT: Thank you. So I went through and read these studies. And I think in the first study, by Welsch et al. in 2003 that was performed in mice, the CD-1 mice, I guess I'm a little concerned about the skeletal effects, because they also saw some of these effects in the control groups, not all, but some.

And in the misaligned sternebrae was also present in the control group as well. And the effects in the

study I'm just really wondering if they're associated more with systemic toxicity of the dam rather than actual specific toxicity in development.

On the other hand, when you get to the rat model, I think the kinds of effects that they're seeing probably, I think, are more directed, and I think more significant in terms of the offspring and in the Tyl study in 2003.

So I'm sort of -- sort of a mixed feeling, but I think there's so little evidence about developmental toxicity in this compound, I guess I'm wondering how much weight do you need for weight of the evidence when you only have two studies that really look at development?

And the third study performed by Berger and Horner, where they're looking only at fertilization, I'm very concerned that this slight reduction in fertilization without any real other component isn't very compelling for me. So I'd like to hear discussion from other Panel members about -- you know, we basically have one study here showing some possible developmental effects in the rat.

CHAIRPERSON GOLD: Okay. Thank you. So I'm going to open it up to the Panel for comments now, and again reminding you that what eventually you have to vote on is the clearly shown criterion. So weighing what you know about various papers, you'll choose and select your

vote.

So Dr. Woodruff has a comment.

COMMITTEE MEMBER WOODRUFF: Yeah. I wanted to -- well, I have two comments. My first comment is that this question has come up twice now in our -- during the start of the meeting about the weight of evidence. And so I have -- I had that question too when I was reading through these studies, and I have gone back to look at the -- at least the current definition that is from 1993 for known to the state to cause reproductive toxicity. And actually I just ask a question, are these based on somewhat on what some guidelines that EPA has for cancer?

Because I would just say that there -- it does allow data on a single species from a well conducted developmental or reproductive -- reproduction study may be sufficient to classify an agent as a reproductive toxicant.

DR. DONALD: The guidelines to which you're referring that were adopted by the Committee in '93 were largely developed by OEHHA, under the Committee's guidance, and were very much based on U.S. EPA's guidelines for reproductive and developmental toxicity risk assessment, not their cancer guidelines.

COMMITTEE MEMBER WOODRUFF: Right. So my conclusion is if we -- if the study is reasonably well

conducted and it's -- and it only has to be on a single species. I think you mentioned that that's in the study is a rat. So that was -- my thought was -- not my thought. My conclusion is that that is -- it is possible for us to reach a decision based on a well conducted study that finds evidence of reproduction or developmental effects. Though, of course, we have more confidence if there's more studies, so...

CHAIRPERSON GOLD: Right. I think the weight of the evidence argument also as you read through it says, if you find it more than one species or in more than one study than that strengthens the weight of the evidence, but if you have one really well conducted study, then that may be sufficient, I think is the wording.

Dr. Baskin.

COMMITTEE MEMBER BASKIN: Yes. Larry Baskin. So I think this may be a recurrent theme when we look at a number of the other chemicals, because if you have an N of 2, two papers and one paper didn't find any toxicity and another paper did, but if it's a well done study and you believe the methods are credible and the outcome is worrisome, then that's all the evidence we have. And then it makes me wonder why weren't there other studies to refute it if there was a question that that study wasn't done well.

So I think we're stuck with this evidence we have and making a decision based on that. And I think that's going to come up with a number of the other chemicals.

CHAIRPERSON GOLD: Thank you.

Dr. Rocca, do you have a comment?

COMMITTEE MEMBER ROCCA: Yes. Meredith Rocca.

It appears to me that both of these studies were certainly well run. But what we're seeing, certainly in the first one, is very severe maternal toxicity. And I think that many of the findings could be based upon that. As Dr. VandeVoort said, we're looking more at systemic toxicity in the mouse.

In the rat study, this is a very interesting study designed in which animals are treated for three different generations. And what they're seeing is nothing consistent among those generations, except that there is overt parental toxicity in the first two generations. They have reduced weight. They're ataxic. They're not eating as much. And the paper goes into a discussion of what happens if animals are feed restricted to explain some of the decreases perhaps in F2 survival.

The other endpoint, such as reduced estrous cycle length is only by 0.3 days. And the percent of abnormal sperm is also one of those that is a very low number. All of those are well within the historical control, and I

consider them to be within the normal area of variability. Therefore, I would conclude that we do not have certain evidence based upon these studies.

CHAIRPERSON GOLD: Thank you.

Dr. VandeVoort, do you want to comment anymore about the quality of the studies that would help in making judgments, both I think for you and the Panel as a whole?

COMMITTEE MEMBER VANDEVOORT: Well, I agree with the comment just made and the comments made by the other Panel members regarding the quality. I think it was a very -- they were well designed studies. They had doses that ranged from, you know, the appropriate control zero dose up to very high levels, where clearly maternal toxicity was being affected. And so -- and those -- I went back through the guidelines that we were given about the quality of studies and what they should include. And so in that regard, I think they were high quality studies.

But I also agree that in the mouse I think it certainly appears to be maternal toxicity, systemic toxicity here. And in these other studies, I agree, the effects that were seen could be random chance. You know, that there wasn't anything really consistent through the entire treatment group and the generations. And so I'm -- and that's why I'm asking, you know, even there may be some effect in the rat, it is not clear in this study and

it's a well done study.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah. I want to discuss a little bit more about this issue that has come up several times, and it comes up in these tables or in the summaries of the information. And that is the issue of effects on the pregnant animal and the implications for developmental toxicity.

So if I'm thinking of a human, and we have had this experience working with air pollution studies and prenatal exposures to air pollution, and we see a relationship between prenatal exposures to air pollution and adverse pregnancy outcomes, for example, pre-term birth delivery and low birth weight, but we aren't necessarily sure of the mechanism of action of which it occurs. One may be direct effects on fetal development or placental adherence et cetera or it could be effects maternally mediated.

So I think -- I went back, because I've been thinking about this issue a little bit more because I went back into the guidelines. And I just -- there is a lot of focus on this either systemic or maternal toxicity, but I'm not -- I haven't heard a really compelling reason why if it affects the pregnant animal, why that would not be a developmental effect?

CHAIRPERSON GOLD: Is that something the staff wants to address, because it's come up before?

DR. DONALD: Yeah. This is, of course, a perennial question in developmental toxicology. Bearing in mind that the Committee is charged to observe generally accepted scientific principles, one consideration is what is the generally accepted principle? And one thing that might be considered reflective of that is the position that U.S. EPA has taken in their guidelines that were largely the basis for the Committee's guidelines.

And EPA's position is that if developmental toxicity occurs in the absence of maternal toxicity, then it's unquestionably developmental toxicity. But the more common situation is that developmental toxicity co-occurs with some degree of maternal toxicity. And they have taken the position that if developmental toxicity co-occurs with minimal maternal toxicity, then it should be interpreted as developmental toxicity.

They take the position that if there is excessive maternal toxicity, that it's difficult to interpret whether or not developmental toxicity has occurred. And somewhat unhelpfully, they have not defined what the difference between minimal and excessive maternal toxicity is.

So there is obviously a role for scientific

judgment in this instance, but it is generally recognized that just because there is some degree of maternal toxicity, that is not in itself a basis for discounting developmental toxicity.

COMMITTEE MEMBER WOODRUFF: Right, because if I think about -- if I have a pregnant woman and she's at UCSF and she has gestational diabetes, right, I'm concerned about how that affects the fetus. And that is also -- or prenatal -- pre-eclampsia, which can affect her as well as the fetus.

So I guess I'm not -- I think we -- I do not want to discount maternal toxicity as not a contributing factor to developmental toxicity, because clearly the health of the pregnant animal or human can adversely influence the fetus.

DR. DONALD: Yes. And another overlapping area of concern is the relationship between mechanisms in the dam. I think most people would accept EPA's concern about excessive maternal toxicity is reflective of concern that if a dam is severely impacted by the chemical, then that -- there maybe some sort of cascade of effects onto the developing fetus that may not be appropriate to interpret as developmental toxicity. In the most extreme case, if a pregnant animal loses all the fetuses -- if all the fetuses died, and there's no indication of maternal

toxicity in the maternal animal whatsoever, it's pretty clear that's developmental toxicity.

On the other hand, if the dam is moribund or dies, the fetuses are going to die too. The developmental outcome is identical, but the cause of that outcome is quite different. So I think what Dr. -- one aspect that Dr. Woodruff is raising is if you can identify mechanisms in the dam, effects in the dam that are directly resulting in developmental toxicity effects on the female reproductive system, then that may not be a basis for discounting developmental toxicity.

If you have extreme systemic toxicity in the dam and are seeing developmental toxicity associated with that, then it becomes a much more difficult decision as to whether you're going to identify that as a developmental effect.

CHAIRPERSON GOLD: Thank you. Could you also saying something about the impact of reduced maternal weight and how that might affect developmental toxicity or how we should look at that?

DR. DONALD: That's an area that we have looked into. And as with many aspects of reproduction and development, there is no absolutely clear cut answer. Our own review of that area indicates that reduction in maternal body weight gain during pregnancy is not

necessarily associated with developmental -- adverse developmental outcomes.

You can see a reduction -- it depends. It varies with species, but reductions of 15, 20 perhaps 25 percent appear generally not to be associated with adverse developmental outcome. But that's not hard and fast. It depends on the developmental effect. It depends on, as I said, on the species. Again, it's -- there's a -- it's essentially a matter of scientific judgment. The generally accepted principle is that just because there's some decrease in maternal body weight gain during pregnancy, that does doesn't mean that the developmental effects should be discounted.

In fact, U.S. EPA's definition of minimal maternal toxicity encompasses not only a reduction in body weight gain during pregnancy, but actually encompasses a reduction in body weight overall during pregnancy.

CHAIRPERSON GOLD: Thanks. I just want to say one thing, then I'll go to you. So I think what -- if I could summarize. It's seems pretty clear about how to make judgments at the two extremes when there's no maternal toxicity, but there is a fetal effect, and when there is significant maternal toxicity, so that everybody dies, for example. So we're dealing with the gray area in between.

And that's why this last piece of information is helpful, so -- but I think judgments have to be made by the Panel as to, you know, what degree of toxicity is likely -- and the possible mechanism to have an effect -- an adverse effect on the fetus, and what very may well not be enough in the maternal toxicity, if we can call it that, to have an effect. So we're in the gray area where we're -- I think the decision making is a little more difficult.

DR. DONALD: Yes, I think that's a very fair summary.

CHAIRPERSON GOLD: Okay. So Dr. Pessah.

COMMITTEE MEMBER PESSAH: So in terms of providing some judgment, there are three issues that really need to be addressed in my mind. One is the concentration, which is 3,000 ppm, which, from my perspective, is relatively high.

The second issue, I don't know, but what was the maternal weight gain loss, the impairment, and was it only during lactation? Because basically in the table we were presented, it mentioned lactation not during gestation.

And the third, were there any other maternal signs that would indicate that there's some probable mechanism or any other evidence that this compound has a mechanism at these levels?

CHAIRPERSON GOLD: Dr. VandeVoort, would you care to answer?

COMMITTEE MEMBER VANDEVOORT: Yeah. I'm going to have to look up about the exact change in maternal weight gain, because I've read too many papers in the past couple of weeks to possibly recall that. I really apologize.

As far as the other effects, 3,000 parts per million seems very high, especially when you consider it was inhaled at that dose for six hours a day, five days a week, and, you know, it was also in the F1 and F2 litters were also exposed. Here in the table, it says during mating, gestation, and lactation of F1 and F2 litters exposures were six hours a day, seven days per week. And so this actually went up. And so it's a huge level of exposure.

The effects that were seen in the offspring are mainly in the 3,000 parts per million group. And it's mainly this decreased body weight during lactation, and then also the -- I think it was in the female group that there was -- the females only in 1,500.

But again, nothing that would suggest some sort of specific mechanism or a specific effect. And the fact that the dam body weight was reduced in the groups where the offspring body weight was reduced, I think it gives me more of questions of is it a specific developmental

effect?

COMMITTEE MEMBER WOODRUFF: But in the -- not the Tyl study, the Welsch study, there are malformations, right? Oh, it's not on. There it is. Sorry.

COMMITTEE MEMBER VANDEVOORT: Are you asking me? Yes.

COMMITTEE MEMBER WOODRUFF: We'll, I'm looking at it, the paper.

COMMITTEE MEMBER VANDEVOORT: But if you look at these skeletal malformations, some of them also appeared in the control group. And I don't work with the CD-1 mouse model, and I don't know how often these skeletal malformations can show up in this model. But what kind of concerns is me is that when you see something that also appears in the control, how much weight can you put on that in the treated groups?

CHAIRPERSON GOLD: Just to deal with that, I mean, that's actually why you have a control group, because you want to know if it's significantly greater in the treated groups at different dosages.

COMMITTEE MEMBER VANDEVOORT: Right.

CHAIRPERSON GOLD: And I interpreted their statistical significance to mean compared to the control.

COMMITTEE MEMBER VANDEVOORT: Now, in that mouse group, they did -- you know, they say that there's a

cleft -- 18 percent of litters at 1,500 parts per million had cleft palate, but it was non-significant, which has to mean that there was cleft -- you know, there's cleft palate in the controls as well. And so this really makes it difficult to interpret the study and what is the underlying rate of these things in the CD-1 mouse model versus the -- you know, the treatment groups?

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: You're looking at -- I'm just -- this is on Table 2?

CHAIRPERSON GOLD: Is this the Welsch study that we're talking about?

COMMITTEE MEMBER VANDEVOORT: Yes.

COMMITTEE MEMBER WOODRUFF: Oh, you're talking about -- yes.

COMMITTEE MEMBER VANDEVOORT: I thought you wanted to discuss the Welsch study?

COMMITTEE MEMBER WOODRUFF: Yeah, that's right. I was looking at Table 2 with the one that you were talking about with the clefts and the malformations. I mean, but this is the one that also has -- where's --

CHAIRPERSON GOLD: Can I just say while you're looking at that, that I was looking at the Tyl study with regard to the weight question. And the figure there, I believe it's Figure 2, for maternal and paternal, it looks

like about 50 -- about 50 grams almost at every time point. And then for the F1 generation, it looks to be greater, like, I'm estimating, but about 100 grams. So that's the magnitude of the difference. Somebody asked that.

So Dr. Woodruff, did you have something else you wanted to say?

COMMITTEE MEMBER WOODRUFF: No.

CHAIRPERSON GOLD: No?

COMMITTEE MEMBER WOODRUFF: No, no.

CHAIRPERSON GOLD: Are we still on the skeletal malformations question -- on the malformations question?

COMMITTEE MEMBER WOODRUFF: Well, I just have to say I'm like looking in this paper for the rats that's why I got confused, so -- because I see the table with the mice, but you mentioned the rat model, right?

COMMITTEE MEMBER VANDEVOORT: Yes. The Tyl study is the rat model.

COMMITTEE MEMBER WOODRUFF: I'm sorry. Okay, yes.

CHAIRPERSON GOLD: Dr. Pessah, did you have something to say?

COMMITTEE MEMBER PESSAH: Just the one thing that everybody is certainly -- because it's not necessarily developmental, but it could influence development based on

our knowledge is, if you take a look at the liver to body weight ratio.

COMMITTEE MEMBER WOODRUFF: Which paper?

COMMITTEE MEMBER PESSAH: This is the Welsch 2003 in the mice. Obviously, something is going on. So there's a drop in maternal body weight of 27 percent. This is again at the high dose. That's statistically significant at P 0.01. And there's an increased liver weight at both the 1,500 and the 3,500 ppm.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER ROCCA: It's a very common phenomenon in rats that you will have an increase in liver weight if your drug is metabolized via the liver. There will be an increase in P450s and liver weight. So just the increase itself is not considered a matter of toxicity. The fact that it increased and their body weight still went down, you almost have to subtract a little more of the body weight, but the liver weight itself is not a toxic concern to me.

COMMITTEE MEMBER PESSAH: So the induction of liver enzymes, and especially cytochrome P450, are not a general concern for neurodevelopment?

COMMITTEE MEMBER ROCCA: No. This is an adaptive change to help them metabolize the drug that they're given. And, in fact, you'll frequently see that the toxic

effects reduce over time in animals that are treated for a long time with something, because this is an adaptive change.

COMMITTEE MEMBER PESSAH: But certainly for therapeutic drugs, but with environmental exposure, such as polychlorinated diphenyl ethers and PCBs, hydroxylation is well known to be an activating step not a detoxification step.

COMMITTEE MEMBER ROCCA: Yeah, but that's typically how it's seen in rat studies. And rats are particularly sensitive to this as opposed to other species.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: That's an interesting point about the induction of the cytochrome P450, because I think -- have you ever considered that as a potential adverse health effect, because I mean what you're saying -- what you're saying is that it has implications for metabolism of, for example, chemicals that then can increase perhaps toxicity?

I believe that EPA did something on this on TCE, didn't they, looking at induction of one of the metabolizing enzymes as part of their RFD? I think that...

COMMITTEE MEMBER VANDEVOORT: So, Dr. Pessah,

were you saying that -- this study did not find an increase in liver enzyme activity that you're talking about. You're just saying the liver weight changed.

COMMITTEE MEMBER PESSAH: Yeah.

COMMITTEE MEMBER VANDEVOORT: And so you were speculating about the potential for cytochrome C activity changing, correct? There's no evidence of that in this study.

COMMITTEE MEMBER PESSAH: Well, there are, what, 200 forms of the cytochrome P450. Did they look at all of them?

COMMITTEE MEMBER VANDEVOORT: No, I'm saying did they look at any of them in this study?

COMMITTEE MEMBER PESSAH: I don't think they did --

COMMITTEE MEMBER VANDEVOORT: No.

COMMITTEE MEMBER PESSAH: -- but that doesn't mean that it isn't --

COMMITTEE MEMBER VANDEVOORT: No. Well, I'm just saying that we can't speculate on mechanism without evidence. And so while I agree that sometimes changes in liver weights can be associated with changes in cytochrome P450, I just don't -- where is the evidence in the case of this chemical?

COMMITTEE MEMBER ROCCA: Do you know if they did

histopath on the livers in this study?

COMMITTEE MEMBER VANDEVOORT: No, they did not, but I'm going to -- I will recheck that.

COMMITTEE MEMBER WOODRUFF: I think what I was hearing was that -- you were asking about the liver weight gain, and somebody else said, well, there's a reason for that, but you're right there's no data to suggest whether that's the reason or not, so I mean --

CHAIRPERSON GOLD: Right. And I think we have to make judgments based on what is before us. We can't sort of guess what's going on.

COMMITTEE MEMBER WOODRUFF: Right.

CHAIRPERSON GOLD: But I also think that this discussion is useful, because it's going to apply to some of the other -- that's why I'm sort of encouraging the discussion, because I think it's going to apply to some of the other things that we're going to review.

So, at this point, does anybody have anything to add, additional comments, concerns, other than the ones we've already raised?

Any feelings about a readiness to vote?

Are people ready to vote?

I see a couple of nods.

COMMITTEE MEMBER WOODRUFF: Well, I have to say that the amount of information for a chemical that's so

widely used, it's kind of disappointing in terms of the number of studies we have. I mean, that has nothing to do with what we're going to vote on, I know, but that just was my reaction to looking at some of these -- all these chemicals.

CHAIRPERSON GOLD: Just as a sidebar, I often tell my students that, you know, making policy is often what you do in the face of imperfect knowledge. And I would say that's squarely where we are. So we would like lots of other information, but we have what we have. And so I'm asking the question are we ready to vote based on what we have?

I see nods. Nods.

Okay. Well, I've got a formal piece of paper, right?

Let me pull that, which I must read.

So Dr. Alexeeff was whispering in my ear that if you would like to give reasons for your vote, we can also record those. Not required, but if you desire that, that's fine.

Okay. So let me read what I'm obligated to read. And actually we have to vote on each separate endpoint, right, developmental toxicity, female reproductive toxicity, and male reproductive toxicity.

Okay. Ready?

All right. So the question is, has tert-amyl methyl ether been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity?

So those that believe yes, would you please raise your hand?

(No hands raised.)

COMMITTEE MEMBER WOODRUFF: Which one?

CHAIRPERSON GOLD: Developmental toxicity.

(No hands raised.)

CHAIRPERSON GOLD: I see no hands.

All right. So. Okay. The next one is, has tert-amyl methyl ether been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity?

Please raise your hand, if you believe that is the case?

(No hands raised.)

CHAIRPERSON GOLD: Has tert-amyl methyl ether been clearly shown, through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity?

Raise your hand if you say yes?

(No hands raised.)

CHAIRPERSON GOLD: I see none.

Okay. I mean technically I'm supposed to ask for yes and no votes on each one?

CHIEF COUNSEL MONAHAN-CUMMINGS: (Shakes head.)

CHAIRPERSON GOLD: It's not necessary?

Any abstentions, I should ask. So any abstentions on the developmental?

Abstentions on the female reproductive toxicity?

Abstentions on the male reproductive toxicity?

Okay. So the result then is that we have all six members voting no for the clearly shown criterion.

CHIEF COUNSEL MONAHAN-CUMMINGS: So the result will be that that chemical will be removed from the list, at this time, and kind of put back in our -- the general group of chemicals we keep an eye on.

CHAIRPERSON GOLD: Right. So one point to make is even though we are deciding not to retain it on the list now, if, at some point, the staff decides that we should -- there's new evidence or whatever, we can re-examine this, correct?

DR. DONALD: Correct.

CHAIRPERSON GOLD: Very good. I think the discussion was very helpful.

Okay. So we're onto the next presentation.

(Thereupon an overhead presentation was

presented as follows.)

CHAIRPERSON GOLD: So this is 2-chloropropionic acid. And Dr. Wu is going to give the presentation.

DR. WU: Yes. Good morning. This -- I will present the information on 2-chloropropionic acid.

A comprehensive literature search on 2-chloropropionic acid produced two references with developmental and reproductive toxicity search terms specifically discussing male reproductive damage.

--o0o--

DR. WU: In the studies identified as relevant by the literature search, 2-chloropropionic acid was administered as a neutral sodium salt known as 2-chloropropionate to the test subjects. The studies were conducted by Yount et al. and published in 1982. Both references were metabolic studies conducted in Wistar rats.

--o0o--

DR. WU: In the vitro study, the metabolic effects of 2-chloropropionic acid on lipid and carbohydrate oxidation, as well as some features of energy metabolism were examined in isolated testicular cells. Testicular cells from one adult rat, eight or more 24- to 27-day old rats, or 40 14-day old rats were incubated with 2-chloropropionic acid for 60 minutes. This study showed

the capacity of isolated testicular cells to produce ketone bodies.

--o0o--

DR. WU: In the in vivo study, Yount et al. compared the metabolic and toxic effects of 2-chloropropionic acid and another compound, both of which are activators of the pyruvate dehydrogenase complex. Weanling rats received approximately 4 millimole of 2-chloropropionic acid per kilogram per day at the beginning of the 12-week study to 2.5 millimole of 2-chloropropionic acid per kilogram per day at the end of the study.

This study showed 2-chloropropionic acid caused testicular abnormalities, such as testicular maturation arrest and degeneration of germ cells. Also, mean testes plus epididymis weight was significantly less in the 2-chloropropionic acid treated group compared with the respective mean weight in control animals.

That concludes the information on 2-chloropropionic acid.

CHAIRPERSON GOLD: Thank you, Dr. Wu.

Next, if we have any public comments on this particular chemical?

We didn't receive any. I'm not seeing anybody moving to the podium.

Okay. So, Dr. Baskin, I believe you're taking the lead on this discussion?

COMMITTEE MEMBER BASKIN: Thank you. So there are two articles from 1982. There's no articles in humans. This chemical evidently is used as an intermediary for the manufacture of pharmaceuticals and pesticides. And the industrial literature exposure to humans causes problems, such as burns, sore throat, shortness of breath, abdominal pain. That's the reported human issues. There's no scientific studies related to humans.

The two studies that Dr. Wu nicely summarized, one is an in vitro study, which showed no issues, and the other is an in vivo study that involves six rats. There's no evidence -- or there was no female reproductive data in the paper, so I don't think that can really be addressed. There were two developmental -- there was one developmental time point and one male reproductive time point in a well done study from 1982 in six rats looking at the offspring where they carefully looked histologically.

I do want to bring up a point about histology, which is germane to one of the other chemicals that we're going to look at, that when we do testicular histology in humans, as well as in rats, there's lots of ways to do it.

And just putting it in formalin is considered acceptable, but the next level is to do special type of histologic sections to look for germ cell degeneration and maturation, really subtle findings.

If you have controls, which this paper did, and if you just do formalin sections and you can show a change between the formalin section histology from your control which this paper nicely did showing maturation arrests and in generation of germ cells in all six of the treated rats, which to me adds up to 100 percent, then I would have some concern.

So based on one paper from 1982, in my mind, there was clear changes in all of the animals in respect to male reproductive abnormalities. And the corollary, if we look at developmental abnormalities, basically what we have changes grossly in the epididymus and in the weight of some of the reproductive organs, which in my mind is a developmental problem.

So it's hard to make a scientific decision on an N of one paper, but I feel it's a well done paper with nice histology in -- that's presented in the paper. And who -- somebody who actually looks at these slides, it was pretty clear to me that there was some problems with this chemical in this animal experiment.

Thank you.

CHAIRPERSON GOLD: Thank you. Anyone else on the Committee have comments or questions?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: Well, since I was asked to provide a toxicologist's perspective, has anybody looked into the dechlorination of 2-chloropropionic acid and then searched the literature to see if propionic acid itself is involved in any kind of reproductive. There are bacteria that oxidatively -- or basically they hydrolyze the chlorine off of the 2-chloropropionic acid.

COMMITTEE MEMBER BASKIN: I can't answer that question. And I wonder, when I read these papers, and there's no other literature, did this paper tell us that this chemical -- did the chemical industry decide this was never going to be used again because it's so dangerous or why isn't there a follow-up?

So the answer is I don't know.

CHAIRPERSON GOLD: Yes. Dr. Rocca.

COMMITTEE MEMBER ROCCA: I have a technical question that I hope someone on the staff can help me with, as to whether this is the appropriate model, and whether this is really within our purview. In this case, these were weanling rats. So these were immature animals that were exposed to a chemical for 12 weeks and effects were seen.

My understanding of what -- and we've discussed this in the past, is we're not supposed to be looking at postnatal exposures to immature animals to make our decisions on.

DR. DONALD: The distinction between prenatal and postnatal exposures is specific to identification of developmental toxicity. If you interpreted this as a male reproductive effect, that distinction would not be relevant.

DIRECTOR ALEXEEFF: Also, if I could just point out, I think what you'd have to think -- you know, you'd have to know is using -- based upon this model and the developmental sequences that are occurring in this model, how does that correlate with developmental sequences in the human model?

So many of the things that occur in the rat, in terms of development postnatally are actually occurring prenatally in the human. So you'd have to take that into account.

COMMITTEE MEMBER BASKIN: So those are excellent points. And I would reiterate that it would be nice if these animals were followed longer, for example, because did the testicular -- abnormal testicular histology go away? In other words, we don't know. We don't have any information there. But on the other hand, I think it's

very well accepted that in the rat and mouse model, you can give alleged toxicologic agents postnatally, and they would simulate what the human would get prenatally. So I don't have any problem from that perspective.

COMMITTEE MEMBER ROCCA: Question. Is that the case here, since in humans you certainly would not have any spermatogenesis going on prenatally. In fact, it would be much later. So I think this may be one of those cases where we are talking about something that might be more relative to postnatal exposure. But either way, if postnatal exposure is something that we can consider, then I think we have our answer here.

COMMITTEE MEMBER BASKIN: So completely agree with you. And there's not spermatogenesis per se, prenatally, but there is maturation of germ cells prenatally. And that's seen all the time, for example, in the human scenario of undescended testes where the testes are abnormal prenatally if they're not in the correct position. If you don't have them entering puberty at three to six months of age with testosterone surge, if you don't have normal testosterone in utero, you get abnormal changes in the germ cells as they mature.

So this is a rat study, and it should be taken as a rat study, but when 100 percent of the testes look pretty darn abnormal, I think that's the data we have, so

I'm concerned. If another person does a study and follows these rats out to adulthood and they're all normal, I would change my mind.

CHAIRPERSON GOLD: Can I just ask you that but not in the control animals, it wasn't 100 percent, correct?

COMMITTEE MEMBER BASKIN: No, the controls were normal.

CHAIRPERSON GOLD: Yeah. Okay.

COMMITTEE MEMBER BASKIN: So I think the effect is real.

COMMITTEE MEMBER VANDEVOORT: So, Dr. Baskin, can you clarify for me then, are we looking at this -- are you looking at this as a male reproductive toxin or as a developmental toxin?

COMMITTEE MEMBER BASKIN: I think both in the sense that the epididymis was smaller and the other -- and the weight of the testes was smaller. So based on the fact that the epididymis was smaller, that's somewhat developmental to me. And I think I'm on thinner ice on that one, but pretty solid ice on the reproductive issue.

CHAIRPERSON GOLD: Does anyone else on the Panel have comments or questions?

Anything the staff wants to add?

No.

Are we ready --

DR. LI: Good morning. My name is Ling-Hong Li. I'm a Staff Toxicologist, OEHHA. And I was post-doc at Dr. Bob Chapin's lab for a few years at NIEHS. And for me that was the place to learn histopathology of the testis. I think that just I wanted to provide several comments to assist the Committee to discuss issues to focus on the real scientific judgment.

I think you mentioned three issues. The one issue is the development. I think it needed to be clear, are you talking about the development of the germ cells or developmental toxicity of these compounds? If you think about how a chemical affects development of germ cells, then clearly, you can look at the two aspects. One is the establishment of spermatogenesis or the stages of developmental cycles of the germ cells.

For the first one, the establishment of the spermatogenesis, you need to use animals of different ages of continuous exposure, then look at the testes at different stages of the ages.

If you think about the development of germ cells, you can use juvenile animals, you know, prepubertal animals, or adult animals depends on what germ cell population you wanted to look at it. So I think that that needed to be clearer whether you are considering this

chemical for its male repro tox versus both male repro and developmental toxicity.

In my understanding of Proposition 65, when you talk about the developmental toxicity, you only consider the prenatal exposure. And this study has no prenatal exposure component. I want you to keep that in mind.

Number two is the age of the animals. What's the best age of the animals when you look at the male reproductive toxicity. The answer is any age. And because you are considering the male reproductive toxicity, you can actually use -- actually use a pre-conception exposure, exposure of the dam, the father, and look at the male repro sex tumor in F1, F2, F3, you know, what people call the transgenerational studies.

You can use the fetal testis, you see. You can use the neonatal testis. I used three days old testes, when I was at Bob Chapin's lab, I routinely used 14-day old animals. So you are looking at the effect on the testes, regardless of the age of the animals. I want to point that out.

There's no standard that say you have to use which animal or which age. It all depends on your hypothesis of your study. What is the question you want to address? What's the best age you want to use to look at the germ cell development or Sertoli cells.

The third comment I want to provide is about a fixation of the testicular tissue. And I believe that the issue will come up again. I wanted to point out formalin fixation a fixative neutral -- neutrally, you know, pH neutral formalin is still the most popular fixative used in histopathology.

For the testes, if you use the formalin fixation combined with the parafin section, it's a poor fixation, and not good enough to detect the subtle changes. Subtle changes means vocalization of Sertoli cells, and some changes in the epithelium -- seminiferous epithelium, but not cell death. Cell death is not subtle.

You can look at the cell death in the frozen section, in the anti-tissue sections you prepare from the testes, so -- as well as there are other chemicals that people discussed. I think I needed to be specific on the endpoints, whether you are looking at it, and to give a blanket conclusion one method, on everything is to me is not accurate, may not be appropriate. And for this one and look at the cell deaths, look at -- I also mentioned the germ cell maturation or maturation arrest.

What it means in this paper, I believe, is people have not seen advance in germ cell development not unlike during the age development, 14-day versus, you know, 40-day older animals.

In terms of exposure, 12-week exposure times seven that's 84 days. That's long enough for people to look at the whole spectrum of spermatogenesis from spermatogonia to mature sperm. So for majority of the studies on the subchronic studies, that exposure period is long enough.

And those are comments I hope are helpful to you.

CHAIRPERSON GOLD: Thank you very much.

Dr. Baskin, did you want to say anything additional about this?

Anyone else have any comments, questions?

George.

DIRECTOR ALEXEEFF: Yeah, I just want to clarify, because it -- because I had made a statement, and I just want to make sure that we're thinking of the same thing. So in terms of developmental toxicity, we have to think about the developmental sequence in humans, and how it relates to developmental sequence in the animal model. So, Dr. Li, when you were talking about prenatal exposure, I don't know if you wanted to say something -- because what we're -- the fact that they were postnatal exposures is important, but if that type of -- if that part of development occurs prenatally in humans, then that information could be relevant to human developmental toxicity.

So what I'm curious is, based on your knowledge of testicular development, is the type of development that was occurring in those animals at that age postnatally, how does that compare to human development of the testis in terms of age, in terms of pre or postnatal.

DR. LI: Sure. I think there are two issues here. One is the exposure period versus when you begin to look upon the biological consequence. You can have an exposure anytime before birth, but as long as the effect occurs whether it's a prenatal or postnatal, there is effect. To my understanding in Proposition 65, there's a clear cut, there's developmental effect.

On the other side between the developmental consequences, the time -- the tempo status or the pattern between the animals and the humans there's always differences. It depends on the endpoint.

For example, the testosterone production in animals versus in humans, in humans -- in animals it could be -- the low production of androgen occurs right after birth and within the first two hours. In humans, it could be two years. And it also depends on the enzymes and the other aspects of testicular development. It really depends on the endpoint you are looking upon. What I'm saying is that two things, one is the way exposure occurred. The other thing is the biological consequence.

So you cannot say that one biological event occurred in animals postnatally. It doesn't mean -- if one event occurred in animals postnatally doesn't mean it will always occur in humans postnatally.

So it's up to the expert to decide whether that biological consequence is prenatal or postnatal. It's a biological effect. What I say it was exposure. And they are two different things. To me, as a scientist, not as a, you know, Proposition 65 scientist, I mean general scientist, development is a continuous process. There's no prenatal. There's no postnatal. It's the same thing.

CHAIRPERSON GOLD: Thank you.

Perhaps, Dr. Baskin, if you would, just comment on whether the developmental aspects that they're looking at postnatally in this animal study, if any of those occur prenatally in humans? If you could clarify that for those of us who are not experts on this area.

Can you do that?

COMMITTEE MEMBER BASKIN: I could try.

CHAIRPERSON GOLD: I'm sorry to put you on the spot.

COMMITTEE MEMBER BASKIN: I mean, I'm looking at the histologic picture from this paper, Figure 1, on page, you know, 505, formalin fixed, which is not the ideal way to look at testes. And I see fibrosis and interstitium.

I'm not even looking closely. And I see just major changes. You know, so even I can see this, and I've looked at a lot of testes under the microscope. So there's no question in my mind that that's a reproductive repercussion with this being a rat model.

Developmentally, thin ice was probably a reasonable word. What is the evidence that there's developmental issues? I'd like to see more data. I would like to see examination of the whole animal. That's not reported in the study. This was very focused, but the little data I do have suggests that there could certainly be developmental effects if you have a small testes, which is not reproductive, and some of this might be semantics, but you need your testes for puberty, sexual function, testosterone, et cetera. So I'm being pretty global in my interpretation of what I'm calling developmental.

And also in the animals, there is a clear -- as Dr. Wu pointed out in her nice table, the ratio of the weight of the testes plus the epididymis the whole body weight was significantly smaller in the treated groups.

Is that developmental?

I think each one in the Panel needs to decide that or each one in the room. For me, it's close enough that I'm willing to call that a developmental problem with the small testes, as well as a reproductive problem. And

again when no data on female reproductive aspect given in either of the papers.

CHAIRPERSON GOLD: Thank you.

Dr. Rocca.

COMMITTEE MEMBER ROCCA: Yes. While you were talking, I was looking at what our charge is. And in our definitions of male reproductive toxicity, it does answer my previous question, if I'd looked it up, "...is defined to include effects on the adult, or where appropriate, the developing male organism". And then it goes on to say those things it includes impaired sperm and endocrine function and all those things.

So according to this, I think that this would be a case where you could say that this was included under male toxicity because it affected the developing male organism in those ways, either endocrine or sperm or both. So that answers that.

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Baskin or Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. So that was very helpful. I was just looking back at the study because the rats were exposed at less than one week old. And if I followed the discussion, a less than one week old rat is similar to fetal -- human -- like the last trimester of fetal development, right? So that would be

considered a developmental exposure.

COMMITTEE MEMBER BASKIN: For me it would.

COMMITTEE MEMBER WOODRUFF: Okay. Just clarifying that.

COMMITTEE MEMBER ROCCA: Which study?

COMMITTEE MEMBER WOODRUFF: The rats less than one week old were injected with -- oh, I'm sorry. That's the sodium chloride --

COMMITTEE MEMBER BASKIN: That's in vitro study.

COMMITTEE MEMBER WOODRUFF: The in vitro study. Oh, not the other -- the other one is the in vivo study. Where they also exposed at less than a week?

COMMITTEE MEMBER ROCCA: No. It just says they were weanlings, so I was --

COMMITTEE MEMBER WOODRUFF: Weanlings, sorry.

COMMITTEE MEMBER ROCCA: Weanlings, which is typically around 21 days of age. And in the Sprague-Dawley rat at least -- this is Wistar -- you would not expect sexual maturity, which is known as preputial separations until day 42. So these animals were definitely quite immature at weaning.

COMMITTEE MEMBER WOODRUFF: So -- I don't --

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: I actually just have a question. Is the exposure relevant to human exposure? I

mean, is it reasonable?

COMMITTEE MEMBER BASKIN: I'm not an expert on that, but it supposedly was in a range that was not, you know, poison. I mean, water is poisonous, right?

CHAIRPERSON GOLD: Other comments?

So, Dr. Baskin, you're coming down on the side of developmental and your feelings on male reproductive toxicity?

COMMITTEE MEMBER BASKIN: Yes. And I can't -- and I would abstain on female reproductivity. I don't think we have any data.

CHAIRPERSON GOLD: But you would include male reproductive tox?

COMMITTEE MEMBER BASKIN: Yes.

CHAIRPERSON GOLD: Okay. Any other comments, questions from the Panel, from the staff that they want to add?

Anybody?

All right. So we're ready to vote.

All right. So the first question, has 2-chloropropionic acid been clearly shown, through scientifically valid testing, according to generally accepted principles to cause developmental toxicity?

If you believe yes, please raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three, four. Correct, four?

If you do not believe it has been clearly shown to cause developmental toxicity, please raise your hand?

(Hand raised.)

CHAIRPERSON GOLD: And those abstaining from this vote?

(Hand raised)

CHAIRPERSON GOLD: Okay. The second question, has 2-chloropropionic acid been clearly shown, through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity. If you believe yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see no yeses.

Those voting no, raise your hand, maybe, just so for completeness?

(Hands raised)

CHAIRPERSON GOLD: One, two, three, four, five, six.

Okay. And so no abstentions.

And finally, has 2-chloropropionic acid been clearly shown, through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity?

Raise your hand if you believe yes?

(Hands raised.)

CHAIRPERSON GOLD: Three, four, five, six.

So that would mean no noes and no abstentions.

I can do that math.

Okay. So the result is for developmental toxicity, we do not have sufficient votes to retain it on the list, so it will be removed from the list for developmental toxicity.

You have no votes -- all of no votes for female reproductive toxicity, but we have six votes for male reproductive toxicity, so it will remain on the list for that reason, correct, Carol?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. It ends up being on the list for reproductive toxicity, but with the male endpoint.

CHAIRPERSON GOLD: Correct. Okay. Thank you for the correction.

All right. Does the recorder need a break?

CHAIRPERSON GOLD: So we'll try and do one more chemical and go to lunch.

Okay. So we're now moving on -- I hope I'm looking at the right agenda here, 2-ethylhexanoic acid, which --

DIRECTOR ALEXEEFF: Methylacetamide.

CHAIRPERSON GOLD: I'm sorry, I've got two different lists. I apologize.

So N,N'-Dimethylacetamide. And we're going to go first to the staff on this one. My apologies.

(Thereupon an overhead presentation was presented as follows.)

DR. GOLUB: My name is Mari Golub. I'm going to be presenting the information for N,N'-Dimethylacetamide or DMAC. Eighteen articles relevant to DMAC were obtained from the literature review. DMAC belongs to the amide group -- type solvent group and whose agents have similar toxicity. There are concerns for inhalation and dermal exposure to the amide solvent group in the workplace. Recent regulatory reviews have emphasized the DMAC developmental toxicity including malformations.

--o0o--

DR. GOLUB: DMAC developmental toxicity research extends back over several decades. Early in the sixties and seventies, the developmental toxicity of the amide solvents was discovered, including DMAC. Because of the concern for dermal exposure in the workplace, early studies were conducted by the dermal route and they also found developmental toxicity. Later work in the eighties and nineties studied oral and inhalation routes of exposure, using developmental toxicity study guidelines.

And there are two recent guideline type inhalation studies also. Altogether then, there are 10 developmental toxicity studies by different routes in rats and in rabbits.

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DR. GOLUB: The developmental toxicity endpoints in the early studies included embryolethality, delayed embryo development, and external malformation after DMAC injection. After the dermal application, decreased litter size and fetal weight were documented at term, along with skeletal deviations and some individual malformations.

Later, when oral guideline type studies were conducted, similar endpoints of fetal loss and lower fetal weights were seen; along with broader teratological findings, including anasarca, or whole body edema; skeletal defects and reduced ossification particularly involving the sternebrae; individual fetuses with cleft palate and microophthalmia; and, in particular, distinctive cardiovascular malformations.

The later inhalation studies during this time period found also fetal loss and reduced fetal weights, but major malformations were not seen.

However, in the recent inhalation guideline studies, cardiovascular malformations were recorded along with the anasarca, skeletal malformations, and skeletal

variations.

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DR. GOLUB: This is more detail on the cardiovascular malformations from a rat inhalation toxicology study by Okuda et al., who used concentration -- inhalation concentrations up to 600 ppm in rats. A decreased pregnancy weight gain was seen at 450 and 600 ppm, the two top doses. In reference to previous discussions, we did prepare more information on pregnancy weight gain.

Increased dam relative liver weight was seen at the three top doses, along with the hepatocyte swelling in the histopathology, but no elevation of liver enzymes. And also there was no clinical science report in any of the subjects in this experiment.

In the fetal exam, there was increased fetal loss at the highest dose and decreased fetal weights at the three highest doses.

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DR. GOLUB: This slide gives a little more information on the cardiovascular malformations. Ventricular septal defect was seen in 22 fetuses in eight litters at the highest dose, 600 ppm, seven fetuses in six litters at the next highest dose. The hash marks are a statistical significance from chi square test. One hash

mark P equals 0.05 two P equals 0.01.

Persistent truncus arteriosus was seen at the high dose, 12 fetuses in seven litters. And the second highest dose, two fetuses in the same litter. Malpositioned subclavian artery at the high dose, and also retroesophageal subclavian artery at the high dose.

The picture shows -- demonstrates the persistent truncus arteriosus malformation. And the control heart, shown on the left, the common arterial branch, or the truncus arteriosus has appropriately divided into the pulmonary artery and the aorta by the time of birth, on the right side. In the DMAC treated fetus, the truncus arteriosus did not so differentiate leading to a potentially fatal misdirection of circulation after birth.

The subclavian artery malformations, in the last two rows of the table, were also seen in the gavage studies conducted earlier. And these are similar cardiovascular malformations.

We did -- also, in reference to the previous discussion, we did look into the historical control data for these malformations.

--o0o--

DR. GOLUB: Less research is available on the male and female reproductive toxicity of DMAC. Mutagenicity testing of DMAC did not produce clear

findings of dominant lethal effects. Based on the findings of various unpublished chronic and subchronic toxicity studies regarding testes, a subchronic inhalation study in male rats was undertaken, and at -- in -- by Valentine et al. in 1997. It used pubescent mice, adult mice, and adult rats.

In pubescent mice, there was clear evidence of testicular atrophy. However, mortality was high at the same doses. The adult mice showed some signs of testicular toxicity at those doses, excluding the highest dose, at which -- and no lethality was seen. The adult rats did not demonstrate testicular toxicity at the same doses.

A later fertility study with exposure only in male breeders did not find reproductive effects. That's the Wang et al., 1998 study.

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DR. GOLUB: A one-generation inhalation study with both male and female breeders exposed also reported no fertility effects, although developmental toxicity was seen. This final study in hamsters looked specifically at DMAC administration right before implantation and reported pregnancy loss as well as ovarian damage.

In a delayed fertility trial, those hamsters were allowed to recover from the treatment and re-mated, and

there was no indication of decreased fertility.

That concludes the overview on developmental and reproductive toxicity of DMAC, dimethylacetamide.

CHAIRPERSON GOLD: Thank you very much.

At this time, are there any public comments?

And I'm not hearing or seeing any.

So Dr. Rocca, you were going to take this one.

COMMITTEE MEMBER ROCCA: Thank you. That was a very well done summary. Thank you very much for making my job a little easier here.

So I'll start first with the embryo fetal developmental toxicity. It was shown in rats by inhalation, oral route, and dermal route that there were losses, so there was a reduction in survival. And also in rat and rabbit, they also showed as well by all three routes that there were malformations. And as was said, these are serious malformations. These are not ones that are seen sporadically. And this is a grouping of malformations, which tells you that there's something that's going on developmentally with that system at that time. And so I find this compound to be both embryotoxic and teratogenic in all those species.

The male reproductive toxicity is not quite as clear, that there were a variety of fertility studies in which there was no effect. There was a dominant lethal

study in which there was no effect. There was some effects seen in seminiferous tubule atrophy in mice. And its severity was increased in pre-pubescent mice. However, there were no effects in rats or no sperm effects in any of the studies that they looked at.

However, histopathology is thought to be a much more sensitive endpoint for male toxicity than just mating studies. So based on that, I think we can say we probably have sufficient evidence to believe that we have a male reproductive toxicant.

Female reproductive toxicity I think is the more difficult one. In fertility studies in rats, there was no effect whatsoever. In the hamster study, there were effects, but those effects went away after the chemical was gone, so they were not a continuing lasting effect. And also in hamsters, this had to do with the implantation. And this could be rescued with hormone supplementation, which makes you think that it is a specific mechanism of action that would have to do with reproduction, but I'm not clear that hamster reproduction at the time of implantation is relevant to human. And I couldn't find out much data on that.

So the female fertility. As I said, we don't have much in the way of rats. For the hamster study, I also want to point out that was between one and two grams

per kilogram per day as an oral route. And this is not a chemical that would be expected to be absorbed orally. That it's usually used in industrial settings via inhalation or dermal. It is metabolized by P450s in the liver of the rat at least. And that would go along with the liver findings that we have.

CHAIRPERSON GOLD: Thank you very much. Anybody want to add anything on the Committee? I was wondering -- I hate to put you on the spot Dr. VandeVoort, but the comment that Dr. Rocca made about female fertility and toxicity in the mechanism involving hormone supplementation, do you have anything to say about that?

It's okay if you don't. I'm putting you on the spot.

COMMITTEE MEMBER VANDEVOORT: I really don't, no.

COMMITTEE MEMBER ROCCA: Yeah. What I was trying to determine is I know, in some species that the hormones from the corpora lutea are essential in maintaining pregnancy, and in other species, they are not. It is more from the placenta. And in the hamster it appears it's the corpora lutea, but I really couldn't find out any data to help me.

COMMITTEE MEMBER VANDEVOORT: I don't know what it is in the hamster. I -- certainly, in many other species, including humans, you have this transition, you

know, in the luteal placental shift that occurs very early in pregnancy. And I just don't know about the hamster.

CHAIRPERSON GOLD: Fair enough.

Any other questions, comments from the Committee?

Anything the staff wants to add or are we ready to vote?

Yes. Good.

Okay. So the first question is, has N,N'-Dimethylacetamide been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity. If you believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Three, four, five, six.

So no noes, and no abstentions.

Has N,N'-Dimethylacetamide been clearly shown through scientifically valid testing, according to generally accepted principles to causes female reproductive toxicity? All those who believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see no yeses.

How many think no that it has not been?

(Hands raised.)

CHAIRPERSON GOLD: It looks like we have four.

Abstentions?

(Hands raised.)

CHAIRPERSON GOLD: Two. Thank you.

Has N,N'-Dimethylacetamide been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? All those who believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Six.

So we have zero noes and zero abstentions.

So as a result of these votes, N,N'-Dimethylacetamide will remain on a list for the reasons of developmental and male toxicity -- reproductive toxicity.

Okay. Thank you.

Very good. The question is whether we should do one more or go to lunch or take a break.

CHAIRPERSON GOLD: Well, the Panel says go for it.

Well, the next one is 2-ethylhexanoic acid.

Why don't we see if we can do one more before lunch.

And Dr. Iyer is going to present this.

(Thereupon an overhead presentation was

Presented as follows.)

DR. IYER: Good morning. Today, we are going to be talking about presenting information on 2-ethylhexanoic acid.

My name is Poorni Iyer and I am a staff toxicologist 2-ethylhexanoic acid with OEHHA.

A comprehensive literature search resulted in 10 references on the potential reproductive toxicity of ethylhexanoic acid in mice and rats, and in experiments using embryo culture. In a large number of the references, the emphasis was on developmental toxicity.

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DR. IYER: So eight studies examined the effects of ethylhexanoic acid on development subsequent to prenatal exposure in the rat and the mouse in various strains and in the rabbit in one strain. Three studies examined the effects of ethylhexanoic acid using in vitro systems, such as embryo culture, cell culture, and FETAX.

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DR. IYER: The effects on the Wistar rats. Several studies examined the effects of ethylhexanoic acid on development. These include studies by Ritter et al. and Pennanen and 1992 and 1993. All these involved prenatal exposure on specific days of gestation and evaluation following C-section on gestation day 20, that

is, pregnant rats were killed on gestation day 20 and following C-section, implantation sites were counted and fetuses processed for teratogenic examination; or males and females were exposed prior to, during mating, during gestation, and during lactation with postnatal examination of pups. And sperm motility, density and morphology was evaluated from samples collected from the epididymis.

The findings. There was an increased percentage of dead and resolved fetuses, a decrease in fetal weight, a decrease in litter size, an increase in fetal malformations, such as hydronephrosis and the skeletal system appears to be the main target.

A delay in developmental landmarks, such as opening of eyes and eruption of teeth was noted, and reflexes, such as grip reflex and cliff avoidance was also noted.

It appears that administration on gestation day six increased the number of implantations and caused resorptions in about 80 percent of the pregnant animals. And less severe effects was seen with exposure on gestation day seven.

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DR. IYER: Looking at the effects on Fischer rats. A slight developmental toxicity manifested as a decrease in fetal weight, and decrease in ossification in

fetuses was noted. These effects were noted at the high dose level with some maternal toxicity, such as signs of -- clinical signs of toxicity and increased liver weights. They were also noted at the lower dose level as well.

In Sprague-Dawley rats, delayed parturition at gestation day 22 or later was noted, along with reduced pup weight, decreased progeny viability, and the malformations that were noted included Syndactyly, vestigial tail, fused ribs, extra presacral vertebrae, increased incidence of cervical ribs, and lumbar ribs.

Also, increase in encephalocele and tail defects in animals fed low and adequate zinc was noted, with the highest incidence being in the adequate zinc diet with the low zinc group. According to the authors, the findings support the hypothesis that ethylhexanoic acid may influence embryonic zinc metabolism, and thus trigger abnormal development.

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DR. IYER: Moving on to slides using NMRI mice and SWV mice and C57 black mice, in the NMRI mice exposed prenatally via intra peritoneal injection, a decrease in fetal weight was noted, and embryotoxic and teratogenic effects, such as exencephaly was also noted.

In the SWV mice and C57 black mice exposure was

through both subcutaneous, and there were groups that were exposed intra peritoneally. And there was an increase in percentage of dead or resorbed fetuses, and increase exencephaly was also noted.

SWV appears to be more sensitive a strain than C57 black for induction of exencephaly. And gestation days 8, 8.5 and 9 appeared to be the most sensitive time for induction of exencephaly. Other malformations noted ablepharon, or open eyes, hydronephrosis, and skeletal effects affecting the -- with effects affecting the axial skeleton and skull were also noted.

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DR. IYER: Okay. In the study using New Zealand white rabbits, prenatal exposure via oral gavage resulted in no teratogenic effects, some decrease in fetal body weight at high dose -- at the high dose level of 250 mg per kg per day was noted, but this was not statistically significant.

--o0o--

DR. IYER: Three studies examined the effects of ethylhexanoic acid using in vitro systems, such as embryo culture, cell culture and FETAX. Gestation day 10.5 embryos collected from control dams were cultured for 48 hours in serum from control or ethylhexanoic acid-treated male rats fed 4.5 or 25 micrograms zinc per gram in the

diet. And embryos cultured in either ethylhexanoic acid or low zinc sera exhibited delayed development. Addition of zinc to these -- to the sera eliminated the developmental toxicity effects.

Ethylhexanoic acid was enhanced by about 30 percent. The GnRH-stimulated production of LH by cultures of pituitary cells isolated from untreated 20-day old female rats. And ethylhexanoic acid had no effect on the basal production of the luteinizing hormone.

In the frog embryo teratogenesis assay, increase in malformations, such as microcephaly, abnormal gut coiling, eye edema, and skeletal kinking and general edema was noted.

And that concludes the information available for ethylhexanoic acid.

CHAIRPERSON GOLD: Thank you, Dr. Iyer.

So, at this time, if we have any public comments on 2-ethylhexanoic acid.

I have one.

So Dr. Will Farber -- Faber, sorry.

DR. FABER: Good morning still.

My name is Will Faber. I'm a reproductive and developmental toxicologist. I'm here today for 2-ethylhexanoic acid on behalf of the Oxo Process Panel at the American Chemistry Council.

The American Chemistry Council Oxo Process Panel has funded the research that was conducted in Dr. Carl Keen's laboratory that we believe demonstrates the mechanism of action by which 2-ethylhexanoic acid causes developmental toxicity, and that is through a maternally mediated mechanism.

2-ethylhexanoic acid causes an acute phase response in the maternal liver. That is one of the peptides that's induced is metallothionein. Metallothionein subsequently binds and sequesters zinc within the maternal liver. And this leads to a transient decrease in zinc, which is an essential nutrient for embryonic development. A transient decrease to the embryo, so you're really causing a zinc deficiency within the embryo, and that the developmental effects are secondary to that maternal toxicity.

The second point that I'd like to make is that the testicular toxicity observed in the Pennanen paper has -- is very difficult to interpret. And we have provided comments to the DART Panel on how we interpret that information. Simply put, they had extremely poor readings, values, parameters in their control population, which to us demonstrated that they did not -- they were not adequately trained. Their laboratory could not really measure those parameters in experimental animals.

So since then, we've been engaged in negotiations to do additional testing on 2-ethylhexanoic acid to examine those endpoints, but that testing has not started for various reasons.

So, in summary, thank you again, and I'm here to answer any questions you may have of me.

CHAIRPERSON GOLD: Thank you. Are there any questions from the Panel for Dr. Faber?

I don't see any. Thank you.

DR. FABER: Thank you.

CHAIRPERSON GOLD: Okay. So Dr. Woodruff, right?

COMMITTEE MEMBER WOODRUFF: Yes. Thank you.

So thank you. So thank you for the presentation. It was excellent. As you noted in the presentation, there is very few data on the reproductive and -- the reproductive endpoints related to males and females. So there was the one study that you mentioned looking at some effects on sperm, but it was, I think -- I believe it's just one study.

So I focused my evaluation on the effects on fetal development, and because I -- I went through this information in a couple of different ways. And I actually put them onto some printouts, so that it would make -- help me evaluate the information a little bit more systematically.

So first of all, I went through and actually evaluated based on some tools that we have to look at study quality, as well as those that have been developed by the National Toxicology Program to assess some of the aspects of study quality to get an idea about the various studies that have been done related to developmental toxicity.

So the things that I focused on in this evaluation and cross checked this with Hanna, who I mentioned, is -- and these are tools that are available on the NTP website is randomization, allocation, concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

I would note that the studies were generally of medium quality. They're high quality in the sense that they're experimental designs, so we have control, and we also have direct exposures. So that gives us a lot -- some more confidence in the results, but not all the studies were clearly -- while some of them were randomized, not all of them were randomized, some of them -- it wasn't really clear if they were blinding their evaluation or not, and some of them had incomplete outcome data.

Nonetheless, when I looked at the -- I actually -- we actually put the data into a spreadsheet to

look at the outcomes that were in the OEHHA document, focusing on malformations exencephaly -- I can't -- exencephaly, malformations, variations. And then some of the specific malformations including external presacral vertebrae, lumbar ribs, and cervical ribs. And I have this spreadsheet, if people would like to see it, but we put down the number of controls, the number in the treatment, the samples, the outcomes, the incidence in both the control group and the treatment group, the doses in each of the studies. And then I -- we used this information to actually calculate an odds ratio, which is relatively simple, and I have a document to show how we did that, and then graphed all the outcomes, so that we could see them altogether to look and see how they might -- and again, I can show everyone this handout -- to look at both the incidence of anomalies, as well as the incidence of fetal weight, cause those were the main outcomes that were evaluated in the studies.

And so I would say the -- just to go back, the study quality overall I would say was medium, but the other factors that I considered when evaluating the strength of the evidence for the outcomes was the direction of the outcomes, the consistency of the outcomes, and the -- somewhat the heterogeneity.

So the results, as were mentioned, cover rats --

mostly rats, some rabbits, a few mice -- mouse studies. And then there was a -- oh, and also the dose response, and there were also frogs.

So for the birth weight, most of the findings, when you put it on a similar scale in terms of mean, difference, and effect size were mostly consistently, I would say, null. For the outcomes for fetal abnormalities, all the studies -- almost all of the findings were positive, almost all of the findings were statistically significant. Most of them had a dose response with the exception -- the one finding that was null, as was mentioned in both of the presentations, was the study in the New Zealand rabbits.

So from that, I concluded that the strength of evidence was sufficient in terms of developmental toxicity given a medium quality on the -- in terms of risk of bias and high quality -- or consistency in findings, as well as some evidence of dose response across multiple species.

CHAIRPERSON GOLD: Thank you. You don't want to say anything about male or female reproductive toxicity?

COMMITTEE MEMBER WOODRUFF: Well, I would say that I -- there were some findings on that, but they were pretty limited. So I didn't feel comfortable to recommend -- well, I would not suggest that they, from the evidence, were male or reproductive -- male or female

reproductive toxicants.

CHAIRPERSON GOLD: Thank you.

Any comments or questions from the Panel for Dr. Woodruff or in general?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: I'm very interested in seeing your scoring system. And, yes, I do want to see all of this.

COMMITTEE MEMBER WOODRUFF: I guess I can hand it to you.

COMMITTEE MEMBER ROCCA: Because I hope I can use them in the future, not at the moment.

COMMITTEE MEMBER WOODRUFF: Oh, I have a paper.

COMMITTEE MEMBER ROCCA: How did you weight the study in which they used IP as the route, because that's a very problematic route?

COMMITTEE MEMBER WOODRUFF: Yeah. We generally considered -- I like pulling up the papers -- pulling up the information. Oh, here. There were different routes of exposure from across the different studies. I mean, if you look at the findings. Again, like I said, I can hand this to you, they don't appear to -- oh, I wanted to make one more comment before I answer your route-of question, is that we did mark which -- what exposure level. There was maternal toxicity and there was findings of effects on

developmental toxicity below maternal -- the -- what the papers reported as effects on maternal toxicity.

And then I'm -- I would say that we -- if we have information to suggest that the route of exposure matters, then we incorporate it, but I didn't see anything that suggested that.

CHAIRPERSON GOLD: While you're looking, I'm going to ask counsel about the material she's prepared.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, here's what I would suggest is that it's fine if you want to share that with the rest of the Committee. What we would need to do is get a copy, so that we can make one for our record and then provide copies to members of the audience that are interested.

And if you all feel like you need to take some time to look at that, maybe what we ought to do is let everybody do that, take the break, don't discuss it amongst yourselves necessarily, but then you'll have a chance to think about that and look at it before you have a further discussion.

CHAIRPERSON GOLD: Right. So we could take it with us and each individually look at it over lunch, but not discuss it among ourselves, and make sure that copies are available for staff and for the audience.

CHIEF COUNSEL MONAHAN-CUMMINGS: (Nods head.)

CHAIRPERSON GOLD: Dr. Woodruff, are you okay with that?

Do you ave adequate copies for that?

COMMITTEE MEMBER WOODRUFF: I'm fine with that.

CHIEF COUNSEL MONAHAN-CUMMINGS: We can make copies where needed. If you just give us one, we'll make sure that we have some.

CHAIRPERSON GOLD: Okay. Well, while you're looking -- sorry, was there anything else?

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: I was just wondering what were some of the odds ratios that you came up with for developmental?

COMMITTEE MEMBER WOODRUFF: Oh, yes.

So every -- it ranged down to there -- the low end was -- there was one that was below one. Everything else was above one, but the log's odds went up to 1,000 -- I think the highest was around a couple hundred, but most of them were around -- I have to look in this. Most of them were around two to three, I would say, generally.

CHAIRPERSON GOLD: With confidence limits that didn't include one, I presume, or --

COMMITTEE MEMBER WOODRUFF: Right. Almost all of

them were above one, yes.

CHAIRPERSON GOLD: Okay. So we're still waiting for an answer to Dr. Rocca's question, is that correct?

COMMITTEE MEMBER WOODRUFF: Oh, right. I'm still -- I did answer it.

COMMITTEE MEMBER ROCCA: I think we can defer that till after we've looked at the data and talk about it later, if you don't have that right now.

CHAIRPERSON GOLD: Okay. Sounds like maybe we're at a breaking point for lunch that is.

I think we're doing really well.

So should we plan on being back at 1:00 o'clock? Is that good for everybody, 1:00 o'clock?

And we will resume with this compound.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. So it's, as I mentioned, best not to discuss it among yourselves. In the event that you do, you're going to need to talk about what you talked about again when you get back to the public meeting. The same thing for third parties, if they want to talk to you off-line, then you're going to probably need to talk about what you talked about when you get back.

CHAIRPERSON GOLD: And Dr. Woodruff will provide us with the copies that she has, and give one at least to the staff, so that they can make copies as needed for

staff and public.

Okay, 1:00 o'clock we'll see you back here.

Thank you all.

(Off record: 12:11 PM)

(Thereupon a lunch break was taken.)

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

(On record: 1:04 PM)

DIRECTOR ALEXEEFF: Hello, everyone. Why don't we come back to order after lunch, and I'll turn it over to Dr. Gold.

CHAIRPERSON GOLD: Thank you. Welcome back, everybody.

So everybody should have received the materials that Dr. Woodruff prepared. And I think what the plan will be is maybe she can walk us through it quickly to -- pointing out any highlights that we didn't have from before. Then I think we'll ask for any public comments on what she has distributed, and then the Committee will discuss it. So that's sort of the order for this particular chemical and these materials.

So Dr. Woodruff, you want to --

COMMITTEE MEMBER WOODRUFF: Yeah, we're talking about the -- yes, yes. We're just --

CHAIRPERSON GOLD: We have the capability to display them, correct?

COMMITTEE MEMBER WOODRUFF: Right. Okay. Why don't we start with -- yeah, we can start with the table. That's fine.

We'll start with the ugliest thing first.

Is it up?

Oh. Okay. Okay. Great. So thanks -- thank you, OEHHA for doing the search. And I -- which I appreciated that you had it documented in the back. One comment aside, is that it would be useful to also have the search terms listed when you do the presentations, so we can see what's in there, and see if there are -- I did see some email traffic about an additional reference that was found. I don't know how it is was found, and so -- and my other recommendation about the search was to also check -- I don't know if you checked the papers and then looked to see if there were additional papers listed that you didn't capture in your search strategy, but I'm going to -- I went from the assumption that you captured all the papers that were relevant to the question of developmental toxicity.

And since, as I mentioned before, there were little to no papers -- little to no data related to the female and male reproductive out -- endpoints, I thought it would be helpful to look a little bit more beyond the table that was given to us in the handouts on the developmental endpoints. And so we -- this is a table which extracts some of the key data from the papers that are relevant to either -- these I think are all related to the malformations, so there's also some additional information related to birth weight, which is in the

graphics.

And just to -- this pretty much has similar information to what you -- what is in the OEHHA tables with a little bit more -- its laid out just slightly differently in terms of up -- until the part that is yellow in the headline -- in the headline -- in the first line in the header. It could be a headline. We have the things that are extracted from the paper.

So -- and then also this source on the left is just a reference for us. If we want to go back and look at the numbers from the paper, it tells you which table in the paper it came from, the route of administration which was -- questioned the control, the number in the treatment, the sample, the outcome, the incidence, which was sometimes provided in the paper, but can be calculated from the treatment -- the number who have the treatment and then the control, the doses, the units.

And then -- I can't move this -- but at the bottom of this document, you can use these to calculate an odds ratio, which was -- is useful because it's a little bit hard to interpret these numbers on a relative -- the incidence numbers on a relative scale. And the calculation of an odds ratio is very standard in epidemiology studies. And we use that same tool here. And you -- it also gives you the confidence limits.

Can you go to the -- yeah, I have no control over this, so...

And the equations are given on the bottom, so it's clear how we did the calculations. I think -- is there any more at the bottom? I can't remember.

Yes. And then this tells you what's the treatment group and the formulas.

CHAIRPERSON GOLD: Can I ask one question.

COMMITTEE MEMBER WOODRUFF: Yeah.

CHAIRPERSON GOLD: That would be me over here.

So the 95 percent confidence intervals. These are on the odds ratios?

COMMITTEE MEMBER WOODRUFF: Yeah, right up. See, they're right here.

CHAIRPERSON GOLD: So there are a couple of them that have minus signs in front of them.

COMMITTEE MEMBER WOODRUFF: Keep going up. Where do you see that?

CHAIRPERSON GOLD: At the very top actually. Maybe -- am I looking at the wrong table?

DIRECTOR ALEXEEFF: No, is it minus 0.95 or is that a typo?

COMMITTEE MEMBER WOODRUFF: Where are you looking?

CHAIRPERSON GOLD: The very first.

COMMITTEE MEMBER WOODRUFF: Oh, oh. I see there's -- that's just a typo.

CHAIRPERSON GOLD: And if you go down a couple where it's --

COMMITTEE MEMBER WOODRUFF: Sorry.

CHAIRPERSON GOLD: -- 1.61 is the odds ratio minus 2.09. So I have two issues with that, the minus sign and the fact that the lower confidence interval is higher than the point estimate.

COMMITTEE MEMBER WOODRUFF: Yeah. So let me just look at this. This paper was a little bit hard to deal with, because the numbers were funny. I'm just looking at -- this one was -- I have some notes to myself on this other -- yeah, this one we might look at a little bit differently, because there -- they have -- if you look at this one -- let's see Bui. If you look at the treatments, they don't have a control group here, so it's -- is that the right one? Yes.

So it's a little bit hard to -- that one is -- has a little bit more uncertainty in it because of the control issue, control group's issue.

CHAIRPERSON GOLD: Well, the line above it looked like --

COMMITTEE MEMBER WOODRUFF: And it basically crosses a line of no effect. So you can see that in this

chart. Where is Bui?

COMMITTEE MEMBER ROCCA: Can I ask a question?

COMMITTEE MEMBER WOODRUFF: Yeah.

COMMITTEE MEMBER ROCCA: Yeah. This is Meredith Rocca. I think there might be a methodological issue that maybe is giving some of these results that don't seem to jive here. And that's that the N on these is all by the implant or by the embryo in most of these, as opposed to on the litter.

COMMITTEE MEMBER WOODRUFF: Right.

COMMITTEE MEMBER ROCCA: And that's going to give you erroneous conclusions.

COMMITTEE MEMBER WOODRUFF: Well, you know, some of these are based on the information -- some of them are based on the litter, some of them are based on the number of implants, and some of them are based on the data that we have in the table. So some of these, also you'll note -- if you can go to the risk of bias table, picture.

I mean, part of the change with looking at these studies -- so the goal in this was to try and put these on a relative scale. Like, those aren't -- these aren't supposed to be exact odds ratios. The goal is to put them to like look and see if we can get an idea about the incidence relative to the controls -- the effects in the treated related to the controls, because, in some ways,

it's a little hard to look across all these studies and try and decide what the outcome is.

So one of the other things is that because we have a little bit of a problem with some of the studies in terms of incomplete outcome data, meaning that we don't always know exactly the number -- so the Bui I think was the one where we only had -- right, we only have doses for certain controls. This leads us to have to look at these by the numbers that are reported in the papers.

CHAIRPERSON GOLD: So when you said before no controls, what you mean is no current --

COMMITTEE MEMBER WOODRUFF: There's no zero -- there's no zero dose. There's a low dose and then there's a high dose -- or I don't know if that's a high, but additional dose in the Bui paper.

CHAIRPERSON GOLD: Anyway. I think a couple of the numbers maybe need to be checked.

COMMITTEE MEMBER WOODRUFF: Yeah. That's true.

CHAIRPERSON GOLD: So maybe before it gets fully entered in the record, can she double-check these and make sure that they're correct.

COMMITTEE MEMBER ROCCA: Can I make another suggestion?

CHAIRPERSON GOLD: Yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: If we want to

change -- I'm sorry. If you're going to change it, what we'd do is leave this one in the record and then show another one that's amended.

CHAIRPERSON GOLD: Okay. That's fine.

COMMITTEE MEMBER ROCCA: Yes, I was hoping to make a suggestion. I think this discussion is very relevant to the discussion on the epidemiology data presentation. And I was going to say perhaps we could combine those two as to what would be a more robust method of evaluating all the studies together and not go through these line by line right now.

CHAIRPERSON GOLD: That's fine. I mean, that's going to be a discussion, if we get to it today, later. So that's fine.

So is there anything else that you want to say before we ask --

COMMITTEE MEMBER WOODRUFF: No.

CHAIRPERSON GOLD: Okay. So Dr. Faber, in particular, if you wanted to comment on sort of these new handouts that we have.

DR. FABER: Thank you for the opportunity to comment. Could we bring up Table 1 again, please. The dose levels for the Ritter study are incorrect. The dose levels should be 1 or 2 ml per kilogram, which was actually 900 or 1,800 milligrams per kilogram --

COMMITTEE MEMBER WOODRUFF: Which one?

DR. FABER: Ritter, the first two entries. It's not 6.25 and 12.5 milligrams per kilogram. It's 900 and 1,800.

COMMITTEE MEMBER WOODRUFF: Table 1.

DR. FABER: I don't know if that affects your odds ratio calculations at all or not?

COMMITTEE MEMBER WOODRUFF: Yeah. The data is taken from Table 1, so you can see it in here.

CHAIRPERSON GOLD: I don't think it will change the odds ratios --

COMMITTEE MEMBER WOODRUFF: No.

CHAIRPERSON GOLD: -- but it might change the inferences because of the dosage levels.

DR. FABER: Right. Right.

The other point I was going to make is that this still doesn't address the point of maternal toxicity. And maternal toxicity in these studies is a very different quality. In fact, the Ritter paper and the two Pennanen papers were evaluated by the OECD SIDS Program, as well as by the REACH registration process within ECHA. And all of the member states within the EU have agreed that these three studies are extremely poor quality, because of their lack to collect maternal toxicity data, or the way that it was presented and reported.

So what I would like --

COMMITTEE MEMBER WOODRUFF: The Pennanen study --

DR. FABER: What I would request --

COMMITTEE MEMBER WOODRUFF: What are the other two?

DR. FABER: -- is that discussion occur around the maternal toxicity influence on these developmental parameters and specifically the work that was done in Dr. Carl Keen's lab, and the way that -- that's the Bui paper. And the way that it would have an impact upon these developmental outcomes.

Thank you.

COMMITTEE MEMBER WOODRUFF: I'm sorry, the three studies were Pennanen, not -- we didn't do an odds ratio for that -- Bui and what was the other one?

DR. FABER: No, no, no. The three studies that are very poor quality are Ritter, 1987, where Ed Ritter at Cincinnati did not collect information on maternal toxicity. In fact, when we tried to replicate that study in Carl's lab at UC Davis, we were not able to --

COMMITTEE MEMBER WOODRUFF: Right. Okay.

DR. FABER: -- primarily because the animals did not recover within 24 hours. They actually had narcosis for 24 hours.

The second two studies are the Pennanen papers,

studies out of Poland, and those are on your next page.

COMMITTEE MEMBER WOODRUFF: Right. We don't -- they're not in the graphics.

DR. FABER: So anyway, those are my comments as to it doesn't really address the maternal toxicity, and how it may have an effect on the developmental outcomes, and, in fact, the mechanism of action that Carl showed in his laboratory. And again, if you have any additional questions, I'm here to answer them.

Thank you.

CHAIRPERSON GOLD: Thank you. Any questions for Dr. Faber before he sits down?

Yes, Dr. Rocca.

COMMITTEE MEMBER ROCCA: Just a comment that you may be able to address. If a baby has a malformation or is stillborn because of it not getting enough of zinc because it didn't get it from its mother, does that really make any difference to whether or not it has a malformation?

So I think knowing the mechanism is important, but I think -- still think it's a developmental toxicant.

DR. FABER: Yes. And the reason it's important is because zinc deficiencies in the human population is almost unheard of. There's been certain instances in Sub-Saharan Africa in cases of severe malnutrition, where

in fact they become zinc deficient, and even then it's marginal.

So this is not an experience that you have in a human population for the most part.

COMMITTEE MEMBER WOODRUFF: Right. So the one paper that is related to the zinc is the Bui paper. And I will note that when we looked at this paper -- first of all, there was a relationship for those that were in the non-zinc -- that didn't have the -- that were not zinc treated. And also, this paper had some quality issues, because it didn't appear that it was -- the animals were randomized.

So I'm not asking you a question. I'm just making a statement.

DR. FABER: Do you want me to respond?

COMMITTEE MEMBER WOODRUFF: No.

CHAIRPERSON GOLD: Are you finished, Dr. Woodruff?

COMMITTEE MEMBER WOODRUFF: Um-hmm.

CHAIRPERSON GOLD: Then you may respond.

DR. FABER: The animals were randomized. It didn't appear within the publication, but it did appear within the report. Dr. Keen's lab is very well versed in how to conduct these studies, and they were randomized. That's a basic principle of conducting these type of

studies.

COMMITTEE MEMBER WOODRUFF: Right, but we have the published paper. And so when we're evaluating study quality, we can only look at what's in the published paper.

CHAIRPERSON GOLD: The point made. I think we get it. I think -- actually, it's a comment that applies to a number of the papers, that sometimes the details, whether it's randomization, or blinding, or looking at dose response, is missing. And it -- just because it's not there, doesn't mean they didn't do it, but we just -- we can only evaluate what's there, so we don't know if they did it.

COMMITTEE MEMBER WOODRUFF: All right. So in this situation, when we were evaluating, looking at those things like randomization and the Ritter paper was also -- did not report randomization in their paper. If they didn't report it, then you're right we aren't quite sure, but they still get some marking as potential for not randomizing. I'll just note that a lot of these -- or these are based on empirical data that comes from the clinical literature, in terms of looking at some of these experimental design features and how they might influence study outcome.

CHAIRPERSON GOLD: Okay. Dr. Pessah.

COMMITTEE MEMBER PESSAH: Just one short statement, in that you mentioned that zinc deficiency is rarely seen. It's not just the amount of zinc. It's the dynamics of zinc in various compartments. I just want to --

CHAIRPERSON GOLD: Are there any other public comments at this time about this compound?

So, Dr. Woodruff, would you like, since we did take a break, to sort of summarize your position on this particular -- ethylhexanoic acid?

COMMITTEE MEMBER WOODRUFF: Yes. Let's see. So, like ethylhexanoic acid. We went across -- like I said, evaluated each of the studies the same way in terms of assessing different elements that may influence an internal validity of the findings. I think we'd found that there was, while the experimental design is -- produces the most high quality evidence in terms of being able to better identify effects from an exposure to an environmental chemical, so that means the toxicology studies inherently are of better design than perhaps -- or of higher -- can have higher internal validity than an observational epidemiology study.

There were a number of factors that limited the quality of the study. Some of them have been noted, in terms of randomization. It was also unclear about whether

there was reporting on blinding. And the outcome data was not always consistently reported. Though many of the studies did report randomization, and they all reported on the outcome of interests, in this case, the maternal malformations and also the birth weight.

So in terms of looking at the effects, the other factors that influence how I evaluate the strength of the evidence for this -- the two outcomes I was focusing on were birth weight and malformations. I looked at the issues of were there dose response, in terms of the doses that were evaluated in the studies, what was the -- were there positive versus negative findings in the study.

So I started looking at the overall pattern of the effect on the -- of the relationship between the exposures and the effects that were evaluated. And then somewhat -- so much a little bit about the number of animals in the study.

And so in terms of the birth weight, there was -- really, the findings were relatively consistently did not find an association with exposure to this outcome. While there are some methodological issues related to some of the studies in the -- that were evaluated in terms of the tox studies, they all -- with the exception of one outcome, and we can discuss the relative merits of looking at different statistical metrics in terms of how to look

at whether there was an increase in the observed events.

But nonetheless, there was an increase in the observed events across many different endpoints, and the question about route of exposure is -- there were different routes of exposure used in the different studies. And there was also a dose response seen in a number of the different studies that were -- where this was evaluated.

There was some maternal toxicity noted in two of the studies out of the seven that I looked at, in terms of quantitative estimates. And those were at the high dose and not at the lower doses.

So my conclusion is that it has sufficient evidence based on that for developmental toxicity, and that there is insufficient to no evidence for the male and female reproductive toxicity.

CHAIRPERSON GOLD: Okay. Thank you.

Does anybody else on the Panel have any comments or questions?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: I think based upon the studies that we did have and the information we have, for example, in the Hendrickx paper, there was no effect of malformations in either rats or rabbits, and that's a lot of the data you have here, whereas in the Narotsky study

where it looks on here as if there is more of a chance, it's not on a per litter unit. And also, there was very severe maternal toxicity at both doses, making it really hard for me to interpret that information. So I would say, at this point, that I'm not clear that there really is enough here.

CHAIRPERSON GOLD: Thank you.

Other comments, questions?

I mean, one thing I would note is if we look at your bias table, that the Hendrickx one probably is the -- at least seems to have the least amount of bias, but it was the most negative study.

COMMITTEE MEMBER WOODRUFF: Well, let's just -- no, there were rats in that study, and there were rabbits in that study, so there were positive findings, not in every -- for the rats, positive findings for some of the rabbits, but not every -- at every dose.

So if you look at the --

CHAIRPERSON GOLD: So those are for malformations not for birth weight, you're talking about.

COMMITTEE MEMBER WOODRUFF: Right, I'm talking about malformations not birth weight.

CHAIRPERSON GOLD: Okay. So would you rank that as among the better of the conducted studies as near as you can tell from what's written?

COMMITTEE MEMBER WOODRUFF: Oh, yes.

I would definitely rank that one among the better ones. Though -- yeah.

COMMITTEE MEMBER ROCCA: I've got the paper open at the moment. And for both rats and rabbits it states there were no differences in the indices of external visceral or skeletal malformations.

COMMITTEE MEMBER WOODRUFF: Right. Are you reading their conclusions?

COMMITTEE MEMBER ROCCA: No, I'm reading their stats, where there were no differences.

COMMITTEE MEMBER WOODRUFF: This stats. Which table are you on?

COMMITTEE MEMBER ROCCA: I don't think they have it in the table for malformations, so it is within the text for malformations, but it is statistical.

COMMITTEE MEMBER WOODRUFF: Yeah, but -- so when I -- right. So we take the data from -- so we're looking at -- so here's Table 3 was where we have the data, and Table 7. So if they -- some of the things it's a little challenging sometimes to, in a lot of these papers, is people will write things in the text, but it won't necessarily be in the tables. So it's probably empirically better to take what's in the table.

So this data in here is just from the tables. I

don't -- the author's conclusions are -- unless it's reported.

CHAIRPERSON GOLD: So it's interesting in Table 3 that there's no comment on statistical significance or dose response or anything like that.

COMMITTEE MEMBER WOODRUFF: There is no comment, but that doesn't mean we can't also look at the data, right?

CHAIRPERSON GOLD: No. I'm looking at the data and wondering why they didn't do a dose response.

COMMITTEE MEMBER WOODRUFF: Well, some of these studies are old too, and it's not -- this is not -- I mean, just to be fair, this is not the typical way that toxicologists actually look at this data. This is a different way to look at the data. You know, it's more akin to how maybe an epidemiologist might look at the data. So this is definitely, you know, not -- what's the date of this paper?

CHAIRPERSON GOLD: Ninety-three.

COMMITTEE MEMBER WOODRUFF: Right. So, and it's -- you know, that's -- how long ago is that, 24 years?

CHAIRPERSON GOLD: But we knew, there's a trend test done.

COMMITTEE MEMBER WOODRUFF: I know. I'm not -- I

don't want to -- It's just that it's not --

CHAIRPERSON GOLD: Anyway. I've made my point. Any other comments from other people?

Okay. So are we ready to vote?

Ready? Going, going?

Okay. The first question. Has 2-ethylhexanoic acid been clearly shown, through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? If you believe yes, please raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: Okay. Noes?

(Hands raised.)

CHAIRPERSON GOLD: One, two -- two?

Abstentions?

(Hands raised.)

CHAIRPERSON GOLD: One, two.

Okay.

DIRECTOR ALEXEEFF: So I only counted five.

CHAIRPERSON GOLD: No, I counted six.

DIRECTOR ALEXEEFF: Oh, two, two, two.

CHAIRPERSON GOLD: Has 2-ethylhexanoic acid been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity? If you believe so, please raise

your hand for yes.

(No hands raised.)

CHAIRPERSON GOLD: Zero.

No?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three, four, five, six.

No abstentions.

Has 2-ethylhexanoic acid been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? If yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: Zero.

No?

(Hands raised.)

CHAIRPERSON GOLD: Three -- six.

No abstentions.

So according to these results, we would not list the 2-ethylhexanoic acid. We'd remove it from the list.

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

CHAIRPERSON GOLD: Okay. Very good. Thank you, everybody.

Next is ethyl-tert-ether -- butyl ether, sorry, ETBE. And I believe Dr. Baskin is taking the lead --

sorry, we're doing staff first. My apologies.

(Thereupon an overhead presentation was presented as follows.)

CHAIRPERSON GOLD: So this is Dr. Moran, correct?

DR. MORAN: Okay. Good afternoon. I will be presenting the data on ethyl-tert-butyl ether, abbreviated ETBE.

A comprehensive literature research resulted in six references with data on the potential reproductive toxicity of ETBE in laboratory animals. Among them were two toxicological studies with reproductive endpoints in rat and mice, two developmental studies in rat and rabbit, and one one-generation reproductive study in rats.

In addition to these, one study with no positive result for ETBE was unintentionally omitted in the summary table, and I will present at the end of this presentation.

--o0o--

DR. MORAN: A toxicological report by Medinsky et al. was conducted in males and females, five weeks old Fischer rat and CD-1 mice. Animals were treated by inhalation with ETBE at 0, 500, 1,750, or 5,000 ppm for six days -- six hours a day, five days a week for 13 weeks, and euthanized on the day after the last exposure.

The endpoints were body weight and relevant reproductive organs, pituitary, testes, epididymis,

prostate, seminal vesicles, ovaries, vagina, uterus were collected for a gross pathology and histopathology.

The results. For rats, there were an increased percentage of seminiferous tubules with spermatocyte degeneration and decreased spermatocytes in tubules at 1,550 and 5,000 ppm. There were no reported effects in female rats or in mice.

--o0o--

DR. MORAN: In a toxicological study in rats by de Peyster in 2009, adult males Fischer rats where treated for 14 days with ETBE by gavage at 600, 1,200 or 1,800 milligrams per day or controls. The endpoints were organ weight, and testes were -- organ weights, from testes accessory sex organs, and testis were fixed for histopathology. Plasma concentration of testosterone and estradiol were assessed radioimmunoassay.

In an in vitro study, by the same author, isolated Leydig cells from adult Sprague-Dawley rats were treated with 0, 50, or 100 millimolar of ETBE. The endpoint for this was testosterone release into the culture medium.

The results were, in general, no effects in any of the organs studied. The increased circulating estradiol at 1,200 and 1,800 milligrams per kilo per day in the Fischer rats, and low testosterone production at 50

and 100 nanomolar ETBE in the Sprague-Dawley rat isolated Leydig cells in vitro.

--o0o--

DR. MORAN: In a developmental study by Asano et al., pregnant rabbits were treated orally by catheter with ETBE at 0, 100, 300 or 1,000 milligrams per kilo per day daily from gestational day 6 to 27 in olive oil. Animals were euthanized on gestational day 28.

The endpoints were number of corpora lutea, embryo-fetal deaths, live fetuses and their placentas were observed for external malformation and gross abnormalities, live fetuses were weighed and observed macroscopically for organ abnormalities and skeletal malformations, body weight and food consumption were measured in parents.

Results are as follows:

There were no significant differences in the number of corpora lutea or implantations, and no differences in fetal external malformations, as neither any other significant differences were found.

--o0o--

DR. MORAN: In a one generation reproductive study by Fujii et al., males and females, five weeks old, Sprague-Dawley rats were treated orally with 0 olive oil vehicle or 100, 300, or 1,000 milligrams per kilo per day

ETBE. Animals were treated daily for 10 weeks, mated, and then the males treated for an additional 16 weeks and females for 17 weeks.

The endpoints were:

For the F0, body weight, food consumption, and number of implantation sites. Male were examined for sperm parameters.

In the F1, during lactation, daily examination for clinical science and mortality. And one animal per sex, per litter was selected to observe sexual developmental, preputial separation or vaginal opening, one testis and epididymis per male was fixed for histopathology examination.

Results were:

Gestation was significantly prolonged in the 1,000 milligrams per kilo per day group; no differences were found in any of the studied parameters for the F1 generation; no statistically significant differences in the indices of copulation, fertility, gestation or delivery; normal estrous cycles in all groups; and, no significant differences in the number of pups delivered.

--o0o--

DR. MORAN: In the developmental toxicity study by Gaoua of 2004, female Sprague -- sorry I didn't change it -- female Sprague-Dawley rats were treated by gavage

from day 5 to 19 after mating with ETBE at 0 control, 250, 500, or 1,000 milligrams per kilo per day. Animals were sacrificed at day 20 post mating.

The endpoints were:

Clinical signs and mortality, body weight and food consumption, weight of gravid uterus, number of corpora lutea, implantation sites, early and late resorptions, dead and live fetuses. The fetuses were weighed, sexed, soft tissue, and skeletal examination.

Results were the lower maternal body weight gain over the treatment period, and no treatment-related effects on gestational parameters or fetuses were found.

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DR. MORAN: Finally, this is the study that was omitted in the summary table of the HID that was already presented for TAME. This is a study of female reproductive toxicity by Berger and Horner that consisted of an in vivo treatment of females with an in vitro fertilization assessment. Female Sprague-Dawley rats were exposed to 0 or 0.3 ETBE in drinking water for two weeks prior to oocyte harvest. Exposed females were induced to ovulate and the ovocytes collected and incubated with diluted sperm from untreated males for 20 hours.

The results were no effect on percentage of oocytes fertilized, and no effect on number of penetrated

sperm per oocyte.

That concludes the presentation.

Thank you.

CHAIRPERSON GOLD: Thank you very much. So now we'll go to public comment. Dr. Faber I believe you have a comment.

DR. FABER: Once again, thank you for the opportunity. I'm here on behalf Lyondell Chemical Company.

ETBE is an unusual case in today's considerations, in that while the listing -- it's come up because of the change in the federal hazard communication, as I understand it. Another important point is that the 2013 ACGIH review of ETBE no longer considers it to be a male reproductive toxicant.

The original listing in 2001 in ACGIH was based upon the early Medinsky study that used an incorrect fixative to fix the tissues. And we considered this not to be a scientifically just valid testing according to generally accepted principles, and that is within the EPA test guidelines as well as the OECD test guidelines. Formalin fixative is not considered adequate, especially in the case of the rat.

That led to continued testing. As someone had brought up how come we don't see follow-up tests for these

chemicals? This is exactly what happened in this instance, in that studies with that rat strain as well as an additional rat strain that's commonly used in reproductive toxicity testing were compared. And when the correct fixative was used, there is no effect in either rat strain to any reproductive tissues.

Finally, there's an excellent review that's been prepared by Ann de Peyster of UC San Diego on all of the studies that impact reproductive and developmental toxicity for ETBE. She had access to all the published and unpublished studies when she prepared this review. And I believe it's been provided to all of you.

The conclusion of Dr. de Peyster's interpretation of the data I think is pertinent to the issue at hand, and I urge you to read and consider it.

Thank you again. And as always, I will answer any questions you might have.

CHAIRPERSON GOLD: Thank you. Are there any questions for Dr. Faber?

Dr. Baskin, or do you want --

Okay. You'll be sticking around.

DR. FABER: Yeah.

CHAIRPERSON GOLD: So after he summarizes, can he ask you a question?

DR. FABER: Certainly.

CHAIRPERSON GOLD: Okay. Anyone else have questions for Dr. Faber?

So I'll turn it over now to Dr. Baskin. I jumped the gun a little bit before.

COMMITTEE MEMBER BASKIN: Thank you, Dr. Moran. That was an excellent summary. And there's also an excellent summary from the public statement by Marcy Banton that's in our book, which summarizes Dr. Moran's summary, so to speak.

Bottom line, there are six animal studies if you're looking at primary research, rabbits, rats, and mice. And the one study which showed a potential toxic effect on the testes, as mentioned, was the Medinsky study from 1999. I actually don't have any issues with the fixation formalin, and we discussed that in the early case, but I do have issues in that there's no histology shown in the paper. So that's a little weak from my perspective. I want to see some data. Not enough data was presented for me to be definitively able to say that this was toxic for reproductive health.

And the doses where there was some toxicity shown in the table were the higher doses, not the lower doses. So that's really the only evidence that potentially, in my mind, could be significant and it's not enough evidence, in my mind, to be scientifically valid.

I do have a question, maybe you could answer -- I'm sorry, I forgot your name.

DR. FABER: Will.

COMMITTEE MEMBER BASKIN: Will.

CHAIRPERSON GOLD: Dr. Faber.

COMMITTEE MEMBER BASKIN: You did mention a paper where they repeated that. Did I have access to that paper or is that --

DR. FABER: That was actually a probe study that was done for the multi-generation study, and that was not -- unfortunately, not published, other than in Dr. De Peyster's report.

COMMITTEE MEMBER BASKIN: So negative data is not published, but in this case it would have been nice to have published it. I appreciate that, because we didn't have access to that.

COMMITTEE MEMBER WOODRUFF: Well, I don't comment --

CHAIRPERSON GOLD: Excuse me. Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: We can't really --

COMMITTEE MEMBER BASKIN: Can I just finish up my whole summary?

COMMITTEE MEMBER WOODRUFF: Oh, yeah. Go ahead.

COMMITTEE MEMBER BASKIN: Okay. All right. So that's the Medinsky study. Of the other studies, one

indirectly and two directly also looked at the testes, and the study by Dr. Fujii looked at the testes and saw no change. However, that study was done a little bit differently in that it was -- this chemical, ETBE, which is a fuel additive -- and I guess it's ubiquitous and it's very important evidently. I didn't know anything about it, but it's probably in all the gasoline that we use. There is a fair amount of human data you can get from industrial studies where they had volunteers drink it. I don't know they got them to drink it, but they drank it. And in two days all the metabolites were out of their body and they seemed to have survived. I'm not sure I would have been the one to have signed up for that study.

(Laughter.)

COMMITTEE MEMBER BASKIN: That was done in rats extensively too and the metabolites were also out of their system based on, you know, looking at urine in both -- and blood in both human and rats, but there's no scientific human data, other than you can get from industry, at least that I could find. And hence again, we're stuck with the animal studies.

So getting back to the Fujii paper, this is stuff that you would imagine would be inhaled if you were at the gasoline pump. It wouldn't be ingested, unless you're somewhere where you really need a drink, so to speak, but

I don't think that's pertinent.

So the study from -- the Fujii study where they did look at testes histology and showed no changes was actually gavage. So that was really somebody drinking it as opposed to inhaling it. So they're not exactly analogous, but nevertheless, they didn't show any changes in the testes. And the Berger study indirectly looked at spermatogenesis and showed no effect.

So summarizing. No evidence that I found of developmental issues. The female reproductive issues were not assessed, or they didn't find any when they indirectly looked. And in the male, there's one paper that I found quite frankly a little bit suspect.

CHAIRPERSON GOLD: Okay. Thank you. Now, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So did you -- these human studies, they didn't look at -- did they -- do you look for them? Were they not relevant to the endpoints we're talking about today? I'm just sort of curious.

CHAIRPERSON GOLD: So you're asking Dr. Faber or are you asking --

COMMITTEE MEMBER WOODRUFF: I'm asking Dr. Messan -- Moran.

DR. MORAN: Yeah. You're talking about the studies presented in the review by de Peyster?

COMMITTEE MEMBER WOODRUFF: Well, I guess I'm asking -- you raise that there are some human studies?

COMMITTEE MEMBER BASKIN: No, I did. Can I answer -- help answer that. So I'm a member of the DART commission. I'm asked to make a -- I'm asked to know whether this chemical is dangerous or not. So quite frankly I don't -- I want to know what this chemical is, so I take it upon myself to look up and see what this chemical is, find out if I'm inhaling it, drinking it, or it's in my water, or it's in my kid's water or my cat's water. And it turns out that this one is all over the place, I think. At least from what I can tell, it sounds pretty ubiquitous.

So when you go on-line, you get all kinds of stuff from industry, and you get all types of stuff from OSHA, and from -- New Jersey, in fact, seems to really have a lot of literature on this, which you probably know more about than I do, because if somebody inhales this and you end up at San Francisco General Hospital, the poison control has to be able to tell you what this chemical is and what to do.

And that's where I found the industrial data on drinking this stuff, where they got humans to drink it. If you do a Medline search on the chemical, you won't find it that way. Okay. So that's why it's not in the report

from our esteemed scientists who give us this data, but I think it's okay for me to figure out what I'm dealing with here.

COMMITTEE MEMBER WOODRUFF: Right. So my question is -- I mean, I see that there's chamber studies, exposure studies for ETBE, I just was wondering if they're look -- because they might not be looking at the -- I'm wondering if there's any human data that's relevant to the endpoints we're talking about today?

DR. MORAN: Just for consistency, we followed the procedure that's described in the Appendix A in association with the library, so we didn't do anything extra than -- we treat all the chemicals the same way. So what the library provide us is what we select from there the reproductive and developmental issue papers. And those were provided to you in the summary tables.

DR. DONALD: And if I could add to that, we would expect that if there were relevant data in humans, we would find it through our search strategy. We know it's not -- you know, that's not absolutely true. There certainly are times when we miss things. But perhaps Dr. Baskin could clarify if the studies that he's talking about actually looked to any reproductive or developmental endpoints.

COMMITTEE MEMBER BASKIN: They didn't. I mean, I

have the -- this first study by McGregor is published IN Toxicology, and it basically -- it was people drinking it and seeing where it -- what the metabolites were, and they didn't -- I mean, those are adults. So there's not going to be developmental stuff, so you wouldn't pick that up in your normal searches.

DR. DONALD: No, we would not expect our search strategy to identify studies like that.

COMMITTEE MEMBER BASKIN: And same with the other study by Amberg also in Toxicology.

COMMITTEE MEMBER PESSAH: Just out of pure curiosity, the PK study, I guess it was in the volunteers, did they give half-life, elimination of half-life? You said a couple of --

COMMITTEE MEMBER BASKIN: You're stretching my scientific knowledge, but I think I happen to actually print that out, 10.2 to 28.3 hours in humans, 2.6 and 4.9 hours in rats for half-life for urinary metabolites.

COMMITTEE MEMBER PESSAH: So somewhere between half a day and a day.

COMMITTEE MEMBER BASKIN: Yeah.

COMMITTEE MEMBER PESSAH: So how many times do people stop at a gas pump, because you want to go five half-lives, right?

COMMITTEE MEMBER BASKIN: Not as many as the rats

in the study from 1999 who had it six hours a day --

(Laughter.)

COMMITTEE MEMBER BASKIN: -- five days a week. And I'm assuming it was five days a week, because they weren't working on weekends, the humans. If they were working on weekends, it would have been seven days a week, so a lot.

DR. DONALD: What Dr. Woodruff may be thinking of is that in our -- the hazard identification materials that we generally provide, we do usually go into a bit more detail about pharmacokinetics, metabolism, and so forth. In preparing these materials, given the time constraints we had, we did not attempt to provide all of that information. But if the Committee feels it's important to have that information, as Carol pointed out, you have the option of deferring a decision and asking us to provide it and we will certainly do so.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I wasn't suggesting that was necessary. I just was curious, because I want to -- I mean, I get that there are human studies that have been done looking at exposures to ETBE, but just whether they were relevant to the questions we're asking here.

But I did, looking at these, have a question if there is -- the relationship between ETBE and MTBE? What

does ETBE metabolize into in the body?

DR. MORAN: Primarily to TBA that -- don't ask me to translate that. I don't remember the real name, but I remember the acronym for the main metabolite of ETBE. And I believe it's a common pathway for MTBE and ETBE. That's as far as I can remember now.

COMMITTEE MEMBER WOODRUFF: Right. So I guess just as a follow-up question is would studies of MTBE be relevant to ETBE, because they have a common pathway of metabolism?

DR. MORAN: Well, the way -- they always refer to MTBE effects on all the ETBE papers. But at the end, they behave quite different. It seems like MTBE is more clear-cut on the effects, as we can find in the ETBE studies.

COMMITTEE MEMBER WOODRUFF: Right. I guess -- okay. Let me -- so my question is, if they both metabolize into similar -- or the same products and that's the chemical that is problematic, would it be helpful to look at MTBE as a way to get more information about toxicity for ETBE? That's what I'm asking.

DR. MORAN: Jim Donald wants to say something about this.

COMMITTEE MEMBER WOODRUFF: I don't know if it is or not. I'm just asking.

DR. DONALD: Potentially. I don't think we know, at this point, if the metabolite is the active form of the chemical. If it was, and it was a common metabolite, then yes, studies in MTBE potentially would be informative.

CHAIRPERSON GOLD: Go ahead, George.

DIRECTOR ALEXEEFF: George Alexeeff. So MTBE was considered by this Panel years ago, and it was not listed.

CHAIRPERSON GOLD: Okay. Do we have any outstanding remaining comments, questions?

Do people feel like they have enough information to vote now or is this one that you want more information and want to defer?

Ready?

Yes?

Okay. So we're ready to take a vote.

Okay. First question, has ethyl-tert-butyl ether, ETBE, been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity?

If you believe yes, place raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see no yeses.

Just for completeness, how many of you believe no?

(Hands raised.)

CHAIRPERSON GOLD: That's four, five, six. So no abstentions.

The second question, has ethyl-tert-butyl ether been clearly shown, through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity, please signify a yes by raising your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see no hands.

If your response is no to this, would you raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: Six. So no abstentions.

And finally, has ethyl-tert-butyl ether been clearly shown through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity? Please signify yes, by raising your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see none.

Just to be complete, if you believe no is the answer to this, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Six. And therefore no

abstentions.

So according to this vote, ethyl-tert-butyl ether would no longer be listed.

CHIEF COUNSEL MONAHAN-CUMMINGS: (Nods head.)

CHAIRPERSON GOLD: Okay. Thank you. So the next item on the agenda -- let me find it. I'm sorry.

DR. DONALD: I'm going to present on p,p'-Oxybis(benzensulfonyl hydrazide).

CHAIRPERSON GOLD: Thank you.

DR. DONALD: And I expect to set a record for brevity. Since we identified no relevant studies for this chemical, we have no data to present.

CHAIRPERSON GOLD: I think that is a record. I don't know if anybody was timing it.

Do we have any public comments on this?

No public comments.

So I'm assigned to this one.

COMMITTEE MEMBER BASKIN: Can I ask a question on how a chemical gets listed if there's no data on it?

DR. DONALD: The mechanism for listing, as Carol explained, was that a threshold limit value had been established by the American Conference of Governmental Industrial Hygienists identifying developmental toxicity as a basis for the TLV. And that was the sole basis that we could consider under the statutory requirement for

listing.

However, the background documentation by ACGIH noted that there was no developmental toxicity data on this chemical, so it appears that they simply made an error.

CHAIRPERSON GOLD: Okay. So I'll hopefully be brief as well. So we have no animal studies on reproductive or developmental toxicity. We have no epidemiologic studies or reports. And so I believe we have no studies on which to make a decision. And so I don't believe that we can say whether there's any developmental toxicity or female or male reproductive toxicity.

That's my short version. Anybody have any questions or comments?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: So are you suggesting that we don't have enough information, and therefore we don't vote at all as opposed to -- are we --

CHAIRPERSON GOLD: Actually, I wasn't suggesting that.

All right. Dr. Pessah.

COMMITTEE MEMBER PESSAH: Do we know what it's used for? I mean, what are the applications? What are --

CHAIRPERSON GOLD: Dr. Donald, do you -- I'm sure

I have it. I just can't put my fingers on it right now. It says it's a blowing agent for sponge rubber and expanded plastics.

DR. DONALD: Yes. Since the use of the chemical is not directly relevant to the Committee's deliberations, we did very little background checking on that. That's all the information we have on it.

CHAIRPERSON GOLD: Actually, I think in the materials from the ACGIH, it says a little bit more about what it's used for. So if you're really interested, you can go to that.

Okay. Are we ready for a vote?

Yes.

So the question is, has p,p'-Oxybis(benzenesulfonyl hydrazide) been clearly shown through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity?

Please raise your hand if you think yes.

(No hands raised.)

CHAIRPERSON GOLD: Please raise you hand if you think no?

(Hands raised.)

CHAIRPERSON GOLD: So no abstentions.

Has p,p'-Oxybis(benzenesulfonyl hydrazide) been

clearly shown through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity?

If you believe yes, place raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see zero. If you believe no, place raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: I see six, so no abstentions.

And has p,p'-Oxybis(benzenesulfonyl hydrazide) been clearly shown through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity?

Yes -- signify yes by raising your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see no yeses.

No, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see six, so no abstentions.

So the decision is that this will no longer be listed. I think the vote took longer than the discussion actually.

Okay. Onward. So the next item is triglycidyl triazinetrione and to be presented by -- I'm sorry.

DIRECTOR ALEXEEFF: Dr. Iyer.

CHAIRPERSON GOLD: Dr. Iyer, I'm sorry. Thank you.

(Thereupon an overhead presentation was presented as follows.)

DR. IYER: Good afternoon. So I'm now going to be making a presentation on 1,3,5-Triglycidyl-s-triazinetrione, also known as try triglycidylisocyanurate or TGIC, which is an epoxy compound, and recent reviews from regulatory agencies -- from regulatory agencies included the one from the Australian government and one from the Nordic Expert Group in 2001.

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DR. IYER: The comprehensive search identified several chromosomal -- chromosome studies on male mice germinal epithelium on the spermatogonia and spermatocytes, as well as dominant lethal assays in mice and one toxicity and fertility study in the rat.

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DR. IYER: Focusing on the cytogenetic assays, evaluating chromosomal damage in male germinal epithelium, there were 10 studies in several strains of mice via varied routes of exposure, six oral and four inhalation.

Most of these had chromosomal -- demonstrated chromosomal damage with increase in frequencies of

chromosomal aberrations and chromatid gaps, breaks and sister chromatid exchanges. Three studies showed no chromosomal damage. And for some of these studies, the primary source was not available and the information provided is from the reviews.

Subsequent to submitting the material to the Committee, we did retrieve two original studies. And the reviews for those two studies appeared to be in keeping with what the actual -- you know, the review -- the material that the reviews provided matched the information in the original studies. And we have them in case you do want to take a look at them.

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DR. IYER: Moving onto the studies with the dominant lethal assay study design. In the next two slides, the information from four of these studies are being presented. These were done in several strains of mice, via varied routes of exposure. Essentially after exposure the mice were mated over a specific period and then females were killed and examined for live and dead fetal resorptions.

In this slide, the effects on embryonic deaths are presented, and the next slide the effects on male fertility will be presented.

In the Ciba-Geigy 1986 study that had oral

exposure, a significant increase in number of embryonic deaths compared to control for the first mating period, but not in the second and third mating periods was noted. In the Hazelton 1989b study, also with oral exposure, no significant effects at any dose on fertility, total number of implantations, frequency of dead implantations, proportion of females with either one or more or two or more dead implantations, or frequency of dead implants relative to total implants per female was noted.

In the Bushy Run 1992a study with inhalation exposure, some effects on male fertility was noted and will be described in detail in the next slide. Overall, the positive dominant lethal effect was observed at only one dose point in one of four experiments. No dominant lethal effects in other three studies with no effect on the number of resorptions per litter, total number of implants, number of viable implants, or percentage of post-implantation loss was noted.

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DR. IYER: In this slide, the four studies conducted per the dominant lethal assay, the effects on male fertility are being presented. And in the Ciba-Geigy 1986, a significant increase in the number of embryonic deaths, as mentioned previously, compared to the control was noted for the first mating period, but not the second

and third mating periods.

In the Hazelton 1989b, no significant effects at any dose and fertility was noted.

In the Bushy Run 1992a study, one inhalation -- this inhalation study showed reproductive toxicity, such as reduced male fertility that is a reduction in the number of sperm positive and pregnant females. This reduction was noted at the high dose for the first three mating weeks and at week six. At 10 mg/m^3, a reduction in fertility was noted for the third mating week.

According to the authors, these effects correspond to effects on mature sperm, maturing spermatids, and Type B spermatogonia at 50 mg/m^3, and Type B spermatogonia at 10 mg/m^{3}per.

In the Bushy Run 1992b study, which is also -- had inhalation exposure, no effect on male fertility or number of resorptions per litter, total number of implants or number of viable implants or post-implantation loss was noted.

Overall, no effects on male fertility were noted in three of the studies, other than the first one that we just mentioned.

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DR. IYER: Moving onto the 13-week toxicity and fertility study in Sprague-Dawley rats. In this

non-peer-reviewed toxicity fertility study conducted in compliance with GLP, groups of 10 male rats were given diets containing 0, 10, 30 or 100 parts per million of TGIC, which corresponded to 0, 0.7, 2.1 or 7.3 milligram per kilogram body weight for 13 weeks.

Four groups of 20 female Sprague-Dawley rats received the same diet and were included in the -- which was included in the diet on week 10. After 64 days of treatment, each male was placed with two untreated females for mating.

On gestation day 19, females were divided into two groups for hysterectomy or delivery. On the day of sacrifice, the males were sampled for sperm concentration and viability spermatozoa. Decreases in the mean number of spermatozoa in treated groups were 5 percent, 13 percent, and 23 percent compared to controls, as reported by the Nordic Expert Group, and they confirmed that there was no statistically significant difference between the dose groups, by ANOVA, however the test for linear trend showed significance -- significance for dose-related decrease in sperm count.

The mean spermatozoa viability in treated groups was similar to that in the control group. And the decrease in the number of spermatozoa did not impact fertility outcomes or embryonic and fetal development. No

changes or effects were seen compared to controls in a number of parameters studied, which included pre- and post-implantation losses, number of life fetuses, fetal body weights, sex ratios, number of live born, viability on day four and day 21 postpartum, pup weight for day 1 to 21, external anomalies, malformations, or physical and reflex development of pups.

And that concludes the information for TGIC.

CHAIRPERSON GOLD: Thank you, Dr. Iyer. Are there any public comments at this time?

Okay. In that case, I will turn it over to Dr. Pessah.

COMMITTEE MEMBER PESSAH: Thank you, Dr. Iyer, for summarizing the information.

I'm going to take a little liberty to -- because I think the structure of this particular compound is a little different from the previous ones we have discussed. It contains three epoxides, which can be reactive toward nuclear material. And so I think that one of the things we should look at is the potential genotoxicity, because oftentimes that will inform on mechanism and possible effects that weren't necessarily clear in reproductive or development.

So essentially -- and we also need to keep track that there are two ways -- two materials that the animals

were exposed to, the actual substance, which varies between 90 and 98 percent purity and then the powder coating, which I think typically is more like 10 percent TGIC. And that's actually important, because some of the ways that the studies were undertaken. So in terms of both in vitro and in vivo genotoxicity, I'm going to start with in vitro first.

So in many of the rodent studies, there actually were positive results with respect to things like the lymphoma cell mutagenicity assays, the Ames test was weakly positive, so it wasn't a blazing mutagen. But relatively speaking, it was weak toward some of the salmonella cell lines. And there was a difference whether or not S9, which is metabolic activators were included or not included.

What was surprising to me is that in human fibroblast, it was actually negative. Whereas, in rat hepatocytes, looking at unscheduled DNA synthesis, it was positive. And so I think one of the conclusions was that concentrations as high as 400 milligrams per milliliter did not induce on scheduled DNA synthesis in human fibroblasts.

Chromosomal aberrations. These -- looking for structural chromosomal aberrations in human lymphocytes seemed to be somewhat positive at very high concentrations

at about 2,500 nanograms per milliliter. And this again this is the pure compound or the relatively pure material.

In terms of in vivo genotoxicity, nuclear anomaly tests results that TGIC is clastogenic, and that at high concentrations can cause chromosome breakage, but these are up at the neighborhood of 560 milligrams per kilogram per day over a two-day period.

Another measure of chromosomal damage, which is sister chromatid exchange studies, suggests there was a positive effect at 560 milligrams per kilogram, which was the highest dose. And this was, of course, administered by gavage. So this was not an inhalation exposure.

Chromosomal aberrations in mouse germ cells were tested in two ways by gavage. So there, the results of this study were negative. There was one study that showed at least one animal, which had significantly induced, but that was at one dose level, and a second study basically was negative.

Whole body exposure to technical grade TGIC was done in the Busy Run Research Center at Union Carbide. And males were exposed. There were no deaths, no adverse clinical signs. There was a real problem with that set of studies, in that they scored animals with only -- what they were looking for was sperm problems, and in particular they were looking at problems in spermatogonial

cells. And at 10 and 50, which was the low and intermediate dose -- I'm sorry, the intermediate and the high dose, which was essentially milligrams per cubic meter for six hours each day over a five-day period, a lot of the animals had very few spermatogonia. So basically, they ignored a lot of these, because they only scored those animals that more than 50 scorable cells. And so the results of this study I felt was inconclusive.

Let's see, I'm trying to go down here. There was yet another study by Safe Farm Laboratory. Again, this was, I think, a mouse study, a five-day inhalation. And in this case, there was 10 percent powder used. And it was suggested that the methodology complied with the standard OECD protocol. That study showed effects only in one dose -- I'm sorry. It used only one dose instead of the three required, so this study actually didn't follow those protocols. There were several issues that came up that apparently confounded the interpretation of those results.

Let's see, what else do I have?

So in terms of the Ciba CIT study, this was the 1996 study, the doses that were chosen essentially were oral dietary exposures of the pure compound for six weeks. The males were exposed at 0, 10, 30, and 100 ppm, which translates into 0.72, 2, and 7.3 mg/kg per day. And

again, this was the technical grade material not the powder.

So assuming the GLP was followed, this is a 90-day subchronic toxicity standard, and so they evaluated several endpoints, including pathology, clinical chemistry, mating and fertility outcomes. There were 10 males per group and 20 females per group. The doses were based on a range finding study. So they basically chose a dose range where they had incorporated the NOEL and higher doses.

So there was a modest dose-related decrease in mean spermatozoa concentration, about a 23 percent decrease at 100 ppm, or approximately 100 ppm. No effect was noted on viability or fertility in the males with a reduced sperm count.

Although the 100 ppm group had a 90 percent success rate for siring litters, one out of the 10 failed. Two out of 10 males at the 100 ppm group developed a reddish coloration in the mesenteric lymph nodes, and this was considered to be treatment related.

However, microscopic examination revealed that four out of 10 males had hemosiderosis, or iron overload, and/or congestion in these mesenteric lymph nodes. This was not found in control or the lower dose groups

Dilated pelvis, angular surfaces of the kidney

and grayish-white foci on the liver were not considered treatment related. And I didn't quite understand how that was, since I don't think they saw this at -- certainly, it was higher in prevalence than in the controls.

No other treatment-related effects were noticed in any of the many body parameters that they assayed -- many of the parameters that they assayed.

The female showed no mortality adverse clinical signs. On day 20 of pregnancy, a subgroup of pregnant females were hysterectomized to assess litter parameters. No changes or effects were seen compared to controls in the corpora luteum, the pre- and post-implantation losses or fetal death, the number of live fetus body weights or sex ratios.

So in all, there was really unremarkable findings from this reproductive steady. No effects on physical development, including hair growth, tooth eruption, eye and auditory canal openings, reflex development were seen in the offspring.

Some of the behavioral outcomes that they measured were surface righting, cliff avoidance, and air righting. These were all normal. Therefore, the only effects seen in all of these areas tested was a slight dose-related decrease in the mean number of spermatozoa. And this slight decrease didn't influence fertility.

So I think that's pretty much it.

CHAIRPERSON GOLD: Thank you. Are there any questions or comments from the Panel about this agent or for Dr. Pessah?

So can you sort of come up with a summary of your feeling regarding developmental toxicity, male or female productive toxicity.

COMMITTEE MEMBER PESSAH: Clearly, the possibility of male reproductive toxicity, I think the weight of evidence is equivocal. Female really isn't tested. Although, the last study did a reproductive study that went at least one generation out and didn't find any female reproductive toxicity. However, it should be noted that the structure is a weak alkylating agent and mutagen.

CHAIRPERSON GOLD: Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me, Dr. Gold. Did you ask for public comment on this one?

CHAIRPERSON GOLD: I thought we did that before Dr. Pessah and there was none.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. I must have missed it. Sorry

CHAIRPERSON GOLD: Did I forget?

COMMITTEE MEMBER PESSAH: No, you asked.

CHAIRPERSON GOLD: We can certainly have public comment now, if I forgot?

COMMITTEE MEMBER PESSAH: You didn't.

CHAIRPERSON GOLD: I thought I asked, but okay.

COMMITTEE MEMBER WOODRUFF: I thought you asked.

CHAIRPERSON GOLD: All right. Any -- maybe we need a break.

(Laughter.)

COMMITTEE MEMBER WOODRUFF: I have a question.

CHAIRPERSON GOLD: Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So if it is -- one of the definitions for a -- so you said it was a weak mutagen. So one of the definitions is a somatic or genetic germ cell mutation in the conceptus or genetic damage to the ovum. I'm looking at these different ones that related to mutagenic activity. Is that related to what you --

COMMITTEE MEMBER PESSAH: Right. So essentially, in in vitro and in some in vivo studies, there's some evidence that it can modify DNA and have different kinds of mutagenic effects. These effects are generally weak. Where I think this became questionable is that in the two human cells -- or cell lines that were used to see if, in fact, it would modify DNA or promote mutagenic effects, it proved negative. So the weight of evidence is in the rodent studies, in this case.

COMMITTEE MEMBER WOODRUFF: Which ones are the

human studies in this table?

COMMITTEE MEMBER PESSAH: They're not actually human studies. They're human cell studies.

COMMITTEE MEMBER WOODRUFF: Human cell studies.

COMMITTEE MEMBER PESSAH: Lymphocytes and -- I can point them out to you.

COMMITTEE MEMBER WOODRUFF: I see mice, mice, mice, mice. Hazelton study. Oh, I see.

COMMITTEE MEMBER ROCCA: I think the data may have been in one of the papers that was part of the review. I don't think it was one of the papers we were given.

COMMITTEE MEMBER WOODRUFF: So do we have the data on this or is it just in the review -- just this.

COMMITTEE MEMBER PESSAH: Yes

COMMITTEE MEMBER WOODRUFF: Hazelton, the one that is only 4.6 percent whatever this compound is, is that right?

COMMITTEE MEMBER PESSAH: No.

COMMITTEE MEMBER WOODRUFF: Not that one. Oh, here it is. This one. That one?

COMMITTEE MEMBER PESSAH: Those are on mice too. The human study isn't on the table. The human cells.

COMMITTEE MEMBER WOODRUFF: So the human study is not in this --

COMMITTEE MEMBER PESSAH: Are not on the table, yeah.

COMMITTEE MEMBER WOODRUFF: So how do we -- where are the human studies then?

COMMITTEE MEMBER PESSAH: In the report summary from the Australian report or evaluation of TGIC, which we received as a PDF.

COMMITTEE MEMBER WOODRUFF: Oh.

CHAIRPERSON GOLD: So that's the NINCAS document.

COMMITTEE MEMBER WOODRUFF: All right.

CHAIRPERSON GOLD: Which is basically a review, and includes the human in vitro studies.

COMMITTEE MEMBER PESSAH: Correct.

COMMITTEE MEMBER WOODRUFF: Right. So is it a review or is it actually a study? I guess I was confused.

COMMITTEE MEMBER PESSAH: It was an assessment of the literature in 1994, I think it was.

COMMITTEE MEMBER WOODRUFF: Right. I guess my confusion is, is that if it's a literature -- if it's a review, shouldn't we look at the primary underlying data or studies?

COMMITTEE MEMBER PESSAH: We should.

COMMITTEE MEMBER WOODRUFF: Right. So I guess --

CHAIRPERSON GOLD: Excuse me. My recollection -- I don't know if it pertains to this one -- is that some of

them were unpublished. And so --

COMMITTEE MEMBER WOODRUFF: Right. So how do we consider unpublished data on this Committee?

COMMITTEE MEMBER VANDEVOORT: I didn't hear what you said.

CHAIRPERSON GOLD: Some of them were unpublished. I don't know if it pertains to this specific in vitro human cell study. But some of them that were reviewed in that document were unpublished.

Dr. Donald, do you have a comment?

DR. DONALD: There were some studies that were -- where we could not retrieve the original study report. So where those were reported, they were reported on the basis of other bodies' reviews of those studies. Unfortunately, Dr. Iyer who worked on this stepped out for a moment. When she comes back, we can perhaps get more information from her.

COMMITTEE MEMBER WOODRUFF: There she is. Magic.

CHAIRPERSON GOLD: So there is a question for you, Dr. Iyer.

DR. IYER: Yes.

CHAIRPERSON GOLD: In terms of some of the unpublished studies, and in particular unpublished studies that might have used human cells, sort of what's the status of those? Did you review them?

DR. IYER: We looked at all the ones that have --

CHAIRPERSON GOLD: Microphone, please.

DR. IYER: We looked at all the ones that had the male germinal epithelium. And actually I was going to see if I had the reviews to bring. And I had them here. I thought it was outside.

But we just looked at the ones that had the male germinal epithelium and that's the ones that I summarized. The ones that you're talking about, lymphocytes didn't -- you know, it's important from a mutagenic aspect, but not necessarily from the reproductive system.

COMMITTEE MEMBER PESSAH: I thought it was important to include that information, because obviously if it's a DNA modifying agent in humans, it would have been more compelling for me anyways. The reference is number 37. And unfortunately, you didn't provide the references along with an in-cast -- it sort of ends without the references. Oh no, I'm sorry. The references are there. Number 37, at least I think -- yep. Hold on.

DR. IYER: I think it's the Safe Farm.

COMMITTEE MEMBER PESSAH: Yes, that's the Safe Farm.

DR. IYER: Thirty-seven, Ciba-Geigy 1985.

COMMITTEE MEMBER PESSAH: It is 37 Ciba-Geigy Limited, 1985, chromosome studies on human lymphocytes in

vitro. And that's a Ciba-Geigy publication.

DR. IYER: Yeah. We didn't look at the -- we didn't present the ones that had, you know, non-male germinal --

COMMITTEE MEMBER PESSAH: Got it.

COMMITTEE MEMBER WOODRUFF: So what's the rule about unpublished? Well, first of all, we haven't -- actually, we don't have the actual data, so we don't -- we can't review the study, is that right?

DR. ZEISE: Correct.

COMMITTEE MEMBER WOODRUFF: Okay. And it's not peer reviewed, is that right? It's not published. I just sort of wonder if we can make a lot of -- put a lot of weight on a study, where don't even -- haven't seen it? Or I don't know what -- what is the rule about considering studies that are unavailable to the Committee?

CHAIRPERSON GOLD: Does anybody know if there is such a rule?

Dr. Donald.

DR. DONALD: I'm not sure that there's a rule, per se. It's really at your discretion how much weight you place on any information. As I mentioned before, you know, if you feel that there is information available or potentially available that would be important to you and that you have not yet seen, you can defer a decision, and

we can attempt to identify and retrieve that information. So far, we've been unable to retrieve some of the studies that have been presented to you on the basis of other people's review of them.

But if there's information that is available, such as what we would generally present perhaps as supporting information and a more extensive hazard identification document. If you think that would have a significant impact on your decision, we can generate that information and present it to you at a future meeting.

CHAIRPERSON GOLD: Dr. Alexeeff.

DIRECTOR ALEXEEFF: Yeah. George Alexeeff. So regarding unpublished data, we do not exclude unpublished data, and -- but, you know, if we were to provide unpublished data, then that would be something the Committee would have to look at to see if it met, you know, the standard needed by this Committee.

And one of the reasons we do not exclude previewed data is because in the many study reports, particularly of pesticides or other chemicals, could be very useful in understanding the effects of the chemical, so...

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: Again, my intent for comparing the human data, which I don't have actual data

for, but it appeared in a document that was used for risk assessment, I guess it was, is that the rodent data suggests that it is a mutagen and that it can change sperm nuclear integrity. One has to take that with a grain of salt that it's in vitro. And whether human cells can be similarly modified, I think is an important point. The fact that I don't have the data, I can't defend the study.

COMMITTEE MEMBER WOODRUFF: Right. Yeah, I mean, I'm just saying that I agree with your point about looking at the human data, but I would -- I think we should -- I think we should rely on the data, whether it's published in a peer-reviewed manner or not. I mean, I agree with the point about availability of data, but I just think we can't really conclude, unless we actually see the study.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER ROCCA: Yeah. So I had a question about looking at this as goes to normal scientific processes. I know that's some place in our Prop 65 that we're supposed to look at things, and the quality of the data, and is this up to normal scientific scrutiny?

And my understanding of a chromosomal aberration assay, is it is a screening assay for carcinogenesis, and that it is not applied for reproductive endpoints. And I'm looking at the male toxicologist here.

COMMITTEE MEMBER WOODRUFF: I think -- wasn't the relevance that it was done in these germ cells? Is that what the -- right, is that what you were saying?

DR. IYER: Say that again.

COMMITTEE MEMBER WOODRUFF: That they were during germ cell lines.

DR. IYER: Yeah. We just looked at them, because they were done in germ cell lines, so we thought maybe that would give us some information, other than, you know, what was available, because we had a very limited amount on actual classic reproductive or, you know, developmental toxicity studies. So we figured, okay, at least this is telling us something about the, you know, germ.

COMMITTEE MEMBER WOODRUFF: Well, it is one of the criteria by which you can list something right here in your document, so...

DR. IYER: If you found, you know, effects, then that would definitely tell you something about the fact that this compound is affecting, you know, spermatogonia or spermatocytes. So it would you useful information, which is why we even presented the findings that we had.

CHAIRPERSON GOLD: So the question is would you like to defer a vote on this and ask the staff to try and obtain this material so you can review it at a subsequent meeting -- for a subsequent meeting and defer the vote?

Okay. Dr. Rocca says no. I'm going to ask Dr. Pessah.

COMMITTEE MEMBER PESSAH: Again, I was using it as a basis for comparison and relevance of these particular spermatocyte and spermatogonia findings, which were performed, I think, at extremely high concentrations. And also, the studies were flawed. So I just want to put it in perspective.

CHAIRPERSON GOLD: So that's a yes?

COMMITTEE MEMBER PESSAH: That's a no.

CHAIRPERSON GOLD: That's a no.

Dr. Woodruff, a yes or a no, would you like to defer this and --

COMMITTEE MEMBER WOODRUFF: I don't need to defer it, but I would ask what your opinion is about the germ cell mutagenicity that is in this -- these studies.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: Okay. So again, in the whole body exposure, this is the Busy Run Research Center study from Union Carbide. There was technical grade TGIC used. The exposures were 2.5, 10, and 50 milligram per cubic meter per hour per day for five days. There were no deaths and no adverse clinical signs. The chromosomal aberrations were scored on spermatogonial cells. And only animals at the 10 and 50, which are the two higher levels

with greater than 50 scorable cells were essentially counted.

And the problem in those studies is that very few of the animals had greater than 50 scorable cells. And so the quality of that information is somewhat inconclusive, because they're very small numbers that they're scoring. In the powder study, the amount of powder that the animals were exposed to was 100, 1,000, and 1,700 mg per cubic meter.

One of the problems with the powder where you have about 10 percent of the active principal -- and again, what I'm thinking is that they actually didn't use the powder alone without the TGIC. I think they just used filtered air. So you don't know what the powder is doing and what the TGIC is doing, but nevertheless -- so that wasn't clear to me, but I just assumed that there was no powder only control in that study.

But one of the things that they noted was -- and again I get this out of the Australian summary is that there were very large quantities of dust deposited in the cage and on the animal where there was grooming, and clearly there must have been some oral consumption of what was sprayed. And so the dose couldn't really be accurately determined.

So that's why I was a little bit skeptical about

those particular studies, which showed these problems in the spermatogonial cells.

The CIT study, Ciba study that was filed under TSCA, actually didn't show anything that was really compelling in terms of reproductive toxicity, and those again were relatively high doses. They had a modest reduction in spermatozoa at the highest exposure level at 100 ppm -- or at one of the doses. Sorry, not 100 -- no, it was 100 ppm, but that didn't influence their reproductive success, either in numbers or in --

COMMITTEE MEMBER WOODRUFF: Right. I think why I'm a little confused --

CHAIRPERSON GOLD: Microphone.

COMMITTEE MEMBER WOODRUFF: Oh, yeah, it's on -- confused is because when I'm looking at the presentation, they say there's 10 studies with these evaluating it and only three studies found no chromosomal damage. And it sounds -- I mean, I think it's a little hard to compare what you're saying to what the summary is from the staff.

COMMITTEE MEMBER PESSAH: Sorry?

COMMITTEE MEMBER WOODRUFF: Well, like you mentioned three studies. So in this one they say there's 10 studies here that have been looking these cytogenetic assays, looking at damage in male germinal epithelium spermatocytes, and three were negative. I'm assuming that

seven were positive, is that right?

DR. IYER: Well, there was increased frequencies of chromosomal aberrations in those other studies. And so I don't think he said anything different.

COMMITTEE MEMBER WOODRUFF: Oh. Okay, but you don't think that the -- okay. That's fine.

COMMITTEE MEMBER ROCCA: Question. Perhaps Dr. Pessah could also talk about the companion studies to the two Bushy Run studies, where they actually did the dominant lethal, and so actually dosed the animals and we do have real reproductive endpoints on those.

COMMITTEE MEMBER PESSAH: Yeah. Those were the ones that were sent out yesterday.

COMMITTEE MEMBER ROCCA: No. Those were the ones that -- so it's the Bushy Run 1992a and 1992b on 48 and 49. My interpretation of those two studies is that when they actually did do an assessment of fertility using the same doses, that there was no effect on fertility, and so there was no male reproductive toxicity.

COMMITTEE MEMBER PESSAH: So I think we're talking about two different studies here.

COMMITTEE MEMBER WOODRUFF: Where's the other one?

Oh, I see.

DR. IYER: Can I get the clicker?

If you look in the table that you have, the actual -- the HID, the studies that do have -- okay. So did you want clarification on this one or the dominant lethal?

COMMITTEE MEMBER ROCCA: The dominant lethals that are on page 48 and 49. And I wanted to hear Dr. Pessah's conclusion on those.

COMMITTEE MEMBER PESSAH: Now, I see which ones we're saying. So these were inhaled dust. And in the CD-1 mouse there was increased -- I'm sorry, decreased fertility in the first three weeks, and six weeks at high doses. I'm sorry, I just don't remember what these studies are trying to tell me.

COMMITTEE MEMBER ROCCA: Okay. So may I comment on it then?

COMMITTEE MEMBER PESSAH: Please.

COMMITTEE MEMBER ROCCA: When you look into the data for this, what you find out is those animals never mated. So it really wasn't a matter of that they weren't fertile. I'm guessing it was a matter of toxicity, so that less than 50 percent of them mated. If you look at the ones that mated, they were all perfectly fertile. There was no semen analysis done in this study. So when they're giving results about what spermatic part of the cycle it is, they were just inferring that from the timing

of when they mated.

They didn't actually look at any of the sperm. And so my conclusion is the animals didn't mate. Those that did mate were perfectly fertile. And as the effects wore off, then they did mate and they were fine.

CHAIRPERSON GOLD: Any other comments from the Panel?

By the way, were you looking at the 1992a when you were talking about that, Dr. Rocca?

COMMITTEE MEMBER ROCCA: I was.

CHAIRPERSON GOLD: Okay. Yeah, because my notes say basically no effect on resorptions, implantations, et cetera.

COMMITTEE MEMBER ROCCA: I actually graphed it.

CHAIRPERSON GOLD: Okay. Well --

COMMITTEE MEMBER ROCCA: But I can at least read you my notes. Sorry.

I can at least read you my notes that I did look at this carefully. And for the high dose group, the male mating index was about 50 percent for the first week, and then went up to seventy something, then was eighty something. And it didn't get into the ninety percent range until four weeks in.

And the same thing with the number of females that those males were paired with, so it wasn't a matter

that they were mating, but for some reason they weren't able to see sperm. They got the same exact results for these females. There was no copulatory plug, and there was no sperm. So my interpretation of this, which it also says in the NICNAS paper, is that it's not an effect on fertility, per se.

Does that make sense?

CHAIRPERSON GOLD: Are there further comments or questions?

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Gold, I wonder if this might be one where you want to defer?

CHAIRPERSON GOLD: I as just going to ask if people were ready to vote or if they'd prefer to defer.

So --

CHIEF COUNSEL MONAHAN-CUMMINGS: We could --

CHAIRPERSON GOLD: Pardon?

CHIEF COUNSEL MONAHAN-CUMMINGS: You know, we could provide more information, whatever you feel like you need.

CHAIRPERSON GOLD: Okay. So the question is, does anyone on the Panel feel like they would like more information, which I hope they would specify, and therefore we should defer the vote or are you ready for a vote?

So how many have -- want more information and

want to defer?

COMMITTEE MEMBER WOODRUFF: Yeah, I have a question. So did we get the Bushy Run -- those are the BRRC ones here?

COMMITTEE MEMBER PESSAH: Yes.

COMMITTEE MEMBER WOODRUFF: Okay.

DR. DONALD: Yes, you received the Bushy Run 1992a and b studies. But what seemed to cause a little confuse was they were provided to us as one PDF. So we actually provided it twice with different titles.

CHAIRPERSON GOLD: So does the Panel need more time and want to defer this or do -- are we ready to vote?

This side looks ready. Is this side ready?

I'm seeing yeses all around.

We're ready.

Okay. So has 1,3,5-triglycidyl-s-triazinetrione been clearly shown through scientifically valid testing to generally accepted principles to cause developmental toxicity. If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Abstentions?

(Hand raised.)

CHAIRPERSON GOLD: One.

Okay. Has 1,3,5-triglycidyl-s-triazinetrione been clearly shown through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity. If yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see none.

If no?

(Hands raised.)

CHAIRPERSON GOLD: Okay, six, and therefore no abstentions.

Has 1,3,5-triglycidyl-s-triazinetrione been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? If yes, please raise your hand.

(Hand raised.)

CHAIRPERSON GOLD: We have one.

If no, raise your hand.

(Hand raised.)

CHAIRPERSON GOLD: We have one.

Abstentions?

(Hands raised,)

CHAIRPERSON GOLD: We have four.

So according to my tally, this will -- this

compound will no longer be listed.

CHIEF COUNSEL MONAHAN-CUMMINGS: (Nods head.)

CHAIRPERSON GOLD: Okay. Perhaps we should take a break?

DIRECTOR ALEXEEFF: Yeah, that's good.

CHAIRPERSON GOLD: Should we, what 10 minutes? Reconvene in 10 minutes?

DIRECTOR ALEXEEFF: Yeah, that sounds good.

CHAIRPERSON GOLD: Yes, 10 minutes enough?

DIRECTOR ALEXEEFF: Yes.

CHAIRPERSON GOLD: Yeah. Then at 2:55, we will reconvene.

Thank you.

(Off record: 2:44 PM)

(Thereupon a recess was taken.)

(On record: 2:58 PM)

CHAIRPERSON GOLD: Okay. If we can reconvene.

So the next agent on the list for us to discuss, and actually I believe the final agent, is 4-vinyl-cyclohexene. And we're going to do vinyl cyclohexene dioxide at the same time, one being a metabolite of the other.

And Dr. Wu is going to do the presentation.

(Thereupon an overhead presentation was presented as follows.)

DR. WU: Thank you. 4-vinyl-cyclohexene and vinyl-cyclohexene dioxide are the next two chemicals I will present. These chemicals are related compounds.

Vinyl-cyclohexene -- and vinyl -- vinyl-cyclohexene is the parent compound of the metabolite vinyl-cyclohexene dioxide. Cytochrome P450 enzymes metabolize vinyl-cyclohexene hereafter referred to as VCH to vinyl-cyclohexene dioxide, hereafter referred to as VCD.

Although, the liver is the major site of bioactivation of VCH, cytochrome P450 enzymes are also present in the ovary. Thus, the ovary may contribute to its own toxicity by promoting bioactivation of VCH to the toxic metabolite VCD. In the late 1980s, the National Toxicology Program described the effects of VCH and VCD in mice and rats. The NTP studies assessed carcinogenicity of VCH and VCD. But before the conclusion of those studies, ovarian atrophy was a noted effect of exposure. These observations prompted further study of VCH and VCD by other researchers.

--o0o--

DR. WU: A comprehensive literature search on VCH produced few references on male reproductive and developmental toxicity, and numerous references on female reproductive toxicity.

--o0o--

DR. WU: Four references were identified, which pertain to male reproductive and developmental toxicity of VCH. Of those references, two references reported positive findings on male reproductive endpoints. A reproductive assessment by continuous breeding study in mice demonstrated reduce spermatid heads per milligram of testicular tissue as a result of oral exposure to VCH. No effects on mating and fertility indices or pregnancy outcome endpoints were reported. Also, no developmental toxicities were reported.

The numerous references on female reproductive toxicity were not conducive to providing a concise summary table of the references identified in the HID. However, the DART IC received a recent review of female reproductive toxicity of VCH published in a peer reviewed scientific journal as well as all of the individual references on VCH and female reproductive toxicity.

These references pertaining to female reproductive toxicity were studies conducted in mice and rats that largely demonstrated the ovotoxicity of VCH. There is extensive data on the ovarian toxicity of VCH, because VCH is a model compound for inducing loss of small pre-antral follicles by apoptosis. Other identified references discussed the bioactivation and metabolism of

VCH into VCD. Those metabolic studies demonstrated species differences in the metabolism of VCH in that mice are more capable than rats of metabolizing VCH to VCD.

--o0o--

DR. WU: That concludes the information on VCH.

Vinyl-cyclohexene dioxide is used commercially as well as being a metabolite of VCH. A comprehensive literature search on VCD produced one reference on male reproductive toxicity and a large volume of references on female reproductive toxicity.

--o0o--

DR. WU: One reference was identified which pertained to VCD and male reproductive toxicity. That study showed male mice treated with VCD had reduced testicular weight and testicular degeneration compared with controls.

A larger volume of references were found on the female reproductive toxicity of VCD compared with VCH. The numerous references on female reproductive toxicity of VCD were not conducive to providing a concise summary table in the references identified in the HID. However, the DART IC received a recent review of female reproductive toxicity of VCD published in a peer-reviewed scientific journal, as well as all of the individual references on VCD and female reproductive toxicity.

The references pertaining to female reproductive toxicity were studies conducted in mice and rats that largely demonstrated the ovotoxicity of VCD in both species. Studies conducted largely in the 1990s demonstrated that VCD was the ovotoxic chemical when VCH was administered. Administrations of the monoepoxide metabolites of VCH did not reduce ovarian follicle populations, which led to the conclusion that the dioxide metabolite was causing the ovotoxicity in small follicles.

There is extensive data on the ovarian toxicity of VCD, because VCD is a model compound for inducing loss of small pre-antral follicles via apoptosis. Rodents treated with VCD are well suited as models of human perimenopause and menopause because they exhibit a gradual decline in ovarian follicles, and thus are a better than ovariectomized rodent models which exhibit am abrupt decline in all ovarian follicles.

In general, the body of literature identified by the literature search covered the topics of VCD as a model chemical for menopause and old-age related conditions, such as decreased bone mineral density, atherosclerotic lesions, and neurodegeneration. There are also mechanistic studies detailing how VCD affects different sell signaling pathways and hormonal profile. That concludes the summary of the literature.

CHAIRPERSON GOLD: Thank you, Dr. Wu.

Are there any public comments on either of these compounds?

Hearing, seeing none.

We have asked Dr. Baskin to deal with the male side of this, and Dr. Rocca to deal with the female side, and they have --

COMMITTEE MEMBER ROCCA: (Shakes head.)

CHAIRPERSON GOLD: No? Sorry, Dr. VandeVoort. I beg your pardon.

COMMITTEE MEMBER ROCCA: Good try.

(Laughter.)

CHAIRPERSON GOLD: See, I thought I had it all together. I hope I didn't alarm you there. I'm sorry. I apologize.

(Laughter.)

CHAIRPERSON GOLD: Okay. Well, and -- the feeling it seemed was that we should go with the female first.

So Dr. VandeVoort.

COMMITTEE MEMBER VANDEVOORT: Okay. This is a really interesting compound, and it's actually an example that I use when I teach reproductive toxicology, because a lot is known about this compound. And in the review that we were given by Hoyer and Sipes on VCH, there's a nice --

if you look at Figure 1, it shows that there is this balance between VCH being activated by cytochrome P450, and going through this phase of the monoepoxide and being driven to VCD. And then it's actually the microsomal epoxide hydrolases that deactivate VCD.

And interestingly enough, they found effects in mice and not in rats. And for a while, this was really puzzling, because the effects that they were finding were on a very specific range of follicle size. And it was either in the primary, you know, pre-antral follicles. And so the small follicles were being affected, and it was increasing apoptosis in those follicles.

And what they ended up finding out through a whole series of papers and studies is that it's actually -- whether or not there's an effect in the mouse or the rat depends on -- not only on how much VCD is being produced by activation of VCH, but interestingly the rate at which the epoxide hydrolase is able to deactivate it as well. And it appears that the rat is able to do a better job than the mouse is. And thus, you don't get the negative effects on the ovotoxicity in the rat that you do in the mouse.

And so I guess the -- I was sort of curious after reading all of this, and having some questions about, well, which way is a human going to go? Because I think

we have the -- we have one species of rodent where you have a really marked effect, and another species where there's no effect on long-term fertility.

And so I dug a little deeper. And there's just really no data on humans in this compound. And so what I ended up finding was a couple of studies where they were -- and one of them is by Sipes that also was a co-author on this review, where they used human hepatic microsomes to determine whether or not they could metabolize VCH into either of the monoepoxides. And indeed, human microsomes are quite capable of that. And so they tend to prefer -- the microsomes prefer the 1,2-monoepoxide as opposed to the 7,8 form. But certainly they had very robust activity in that regard.

And I guess, for me, that was sort of the overriding evidence that I needed to feel that there is a real potential to affect these small follicles. And, of course, the effect is devastating in terms of long-term fertility for animals that are exposed to this.

You know, it's premature ovarian failure, and loss of fertility. So without going into every one of the studies, I mean, I just think this is -- the evidence is so well known and so well published that it acts on these small follicles, and even the mechanisms through -- and it gets into this in the second review that we were given

about the c-kit, c-kit ligand interactions. And it affects the ability to autophosphorylate the c-kit. And so it's very well researched, and I feel quite confident in recommending that it is definitely a female toxicant.

CHAIRPERSON GOLD: Thanks very much.

So before we go on to the male, does the Panel have any questions or comments for Dr. VandeVoort on the female side?

Okay. Dr. Baskin, the male side.

COMMITTEE MEMBER BASKIN: Am I covering development too?

CHAIRPERSON GOLD: Okay.

COMMITTEE MEMBER BASKIN: There was no data on development.

(Laughter.)

COMMITTEE MEMBER ROCCA: Well covered.

COMMITTEE MEMBER BASKIN: I thought that would be quick.

So there's three studies that pertain to the male. And it's not such an impressive scientific story with lots of mechanism and clear issues. And of the three studies in male, really the one that may be the most pertinent is this Grizzle study from 1994. And there are some statistically significant changes, for example, in sperm count. There's no histology in this paper. Sperm

count is important, but the statistical significance may not be clinically relevant.

For example, 13 million to 11 million, I'm not sure if that means anything. It's kind of like, in all the clinical studies we do, if the sodium is 140, but in the study it's 138 and it's statistically significant, it doesn't really mean anything in my mind. So I think the data is actually a little bit thin on the male side. The Bevan study showed no change in really weight. And the mouse study showed no changes at all.

So it's really that one study with, I think, statistically significant changes in sperm count, but no histologic changes, because that wasn't actually done, and no weight changes.

That's all I have.

CHAIRPERSON GOLD: Okay. Thank you.

So does anyone on the Panel have questions or comments for Dr. Baskin?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: I have one technical question for you. In that study that was significant, that there was reduced weights of the reproductive organs, and it also says reduced weight of seminal vesicles. Is there perchance just an issue of concentration being different?

I don't know how that -- so my question is will that affect somehow the counts, and they're pretty variable I know?

COMMITTEE MEMBER BASKIN: The answer is yes. And I think you know more about this than I probably do. So the answer is yes. So I want to see -- I would have liked to have seen some more data that was a little more definitive than just a statistically significant number without the histology describing, you know, maturation degeneration, arrest, or, you know, fibrosis in the interstitial space, change in Leydig cells, that type of thing. And they didn't show evidence of that, because they didn't measure it. They measured plenty of other stuff related to the female side, which was actually quite provocative.

CHAIRPERSON GOLD: Okay. Thank you.

Any further comments, questions for either Dr. VandeVoort or Dr. Baskin?

Are we ready to vote?

Okay. So we're going to vote on the two compounds separately. I have two separate voting things.

Can we vote on them together?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think it's fine if you want to vote together, unless there -- I mean -- no, okay. They're listed separately, so I guess

we need to do them separately.

CHAIRPERSON GOLD: Okay. So we will vote on them separately.

DIRECTOR ALEXEEFF: I just had a question. Dr. Baskin, was there any additional data on the epoxide worth mentioning in the male? There seemed to be some different studies.

COMMITTEE MEMBER BASKIN: Can you clarify. There's VCH and there's VCD. And the three studies in the VCH were the ones I was alluding to. And in respect to the VCD, Hoyer looked at both compounds and there was no effect of the -- in VCH. And he looked at the same compound in VCD, and there was nothing that changed any of the data.

DIRECTOR ALEXEEFF: Thank you.

CHAIRPERSON GOLD: Okay. Now, are we ready to vote?

Okay. So the first question is has 4-vinyl-cyclohexene been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see zero.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: So no abstentions.

The second question, has 4-vinyl-cyclohexene been clearly shown through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity? If you believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: We have six.

Okay. So no noes and no abstentions.

Has 4-vinyl-cyclohexene been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity. If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: If you're abstaining --

DIRECTOR ALEXEEFF: How many on no?

CHAIRPERSON GOLD: Yeah. Can I see the hands for no again.

(Hands raised.)

CHAIRPERSON GOLD: Okay. So I think we'll call it six.

Okay. So for 4-vinyl-cyclohexene this will remain listed for female reproductive toxicity.

Next, has vinyl cyclohexene dioxide been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: None.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Three, four, five -- I think that was six.

No abstentions.

Has vinyl cyclohexene dioxide been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity. If believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Six. So that's no noes and no abstentions.

And has vinyl cyclohexene dioxide been clearly shown through scientifically testing, according to generally accepted principles to cause male reproductive toxicity? If yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: If no, please raise your hand.
(Hands raised.)
CHAIRPERSON GOLD: Six.
No abstentions.
And therefore, this will remain listed for female reproductive toxicity.
So thank you, everyone for your work and your thoughtfulness about this.
DIRECTOR ALEXEEFF: Can I make a comment?
CHAIRPERSON GOLD: Yes.
DIRECTOR ALEXEEFF: Thank you. I just wanted to comment on a comment that Dr. VandeVoort meant -- made. And that has to do with the issue of trying to interpret the animal data which it sounds like it did in its applicability to humans. So actually there's been a court case on this. And I think Carol can opine on this, if I'm not correct. But basically from -- even -- if it's been shown in animals, non-human species, then that is sufficient for listing whether or not you think or you don't think it causes it in humans. So that's just something I just wanted to make. So although it's great to have a full understanding, it's not a requirement at all.
CHAIRPERSON GOLD: Okay. So we'll go to the next item on the agenda, which is a discussion of how to

present epidemiologic data, and how to summarize it really for purposes of the Committee to review. And in this context, I -- did you want to say something, Carol? After I get done.

CHIEF COUNSEL MONAHAN-CUMMINGS: We can't hear you.

CHAIRPERSON GOLD: You can't hear me. Oh, okay. I'm sorry.

So in the context of how to summarize, in a tabular form, epidemiologic studies for the future, I put together a draft table, which I sent to OEHHA staff, in which they have circulated to the Committee. And I believe it was posted, but I'm not sure. But we didn't invite public comment because we were just going to have a discussion about this. This is just a draft. I would -- we were hoping to get input from the entire Panel on revisions or changes, additions, whatever.

However, we did receive some public comment, which has been circulated to the Committee as well. And also I think in the context of today's discussion, we've seen some additional suggestions that might come from Dr. Woodruff did, for example.

And so really what we want to do is open up the discussion. The reason it wasn't for public commentary is we weren't planning on taking a vote. We just want to

have a discussion about this. And as I say, this is a draft which will probably get revised now. And hopefully, we will eventually reach some sort of consensus on what it ought to look like. The public comment we did receive was based on an environmental consulting group that has done some work on -- and has developed a white paper, in fact, on how to present weight of the evidence material, and made suggestions about what the tables ought to contain. And expressed the fear that if we didn't design the tables correctly that we might exclude some studies or we might exclude some data, and thus have the potential to misrepresent the situation.

So I think it is worth considering those comments that we received, but I'd also like to hear discussion from the Panel. So I'm really going to be quiet and take notes. I mean, I may respond to things, but this was just a starting point, a draft, and we'll make revisions.

So, Dr. Baskin, looks like you have something to say.

COMMITTEE MEMBER BASKIN: Not surprising. I think it's a great idea, but I still think we should have the source data. I want to see a table when something is statistically significant. For example, in the last paper, it would show a pair is statistically significant, but potentially clinically or environmentally relevant.

So those are two things that the experts -- and I'm an expert in a few things, not many things, but all of us are experts in certain things. So I think source data is critical especially for histologic pictures and how experiments are designed. And so without the papers I think we're really in trouble. That would be my major comment.

CHAIRPERSON GOLD: I'd just ask you to clarify. When you say source data, do you mean you want to see paper or do you want --

COMMITTEE MEMBER BASKIN: I want to see the original papers.

CHAIRPERSON GOLD: Oh, yeah. So let me clarify. I don't think this is to replace that.

COMMITTEE MEMBER BASKIN: Okay. And I'm assuming it wasn't, but I think we still need to look at the papers.

CHAIRPERSON GOLD: No, absolutely. I actually think what we did today is a good model, where you have tables that summarized the papers, but you also had the papers. And we would envision it would always be that way in the future.

And then the second thing was sort of the context or clinical significance of anything that's statistically significant.

COMMITTEE MEMBER BASKIN: Right. So in other words, if somebody is going to ferret through these and extract information, it might be all well and dandy, but how you extract that information is very important.

The next point which will hopefully be relevant in the future is a lot of journals are, you know, rating the papers, so to, speak you know, JAMA, you know Nature, you know up-to-date for clinical medicine, you know, what level of evidence is this to start with?

So some of that will be done for us, so to speak. You know, this is a case report or this is a prospective, you know, well done study. And then as our literature matures, I'm assuming that will be included inherently.

CHAIRPERSON GOLD: So are you suggesting that we should actually be rating them or?

COMMITTEE MEMBER BASKIN: No, it's -- I think we should do what we're still doing. I mean, ultimately, other people will do that for us, but we still have to take that, but use our own expertise.

CHAIRPERSON GOLD: Yeah. I would just make the comment, I remember a couple of years ago, something that I was reviewing, I kind of ranked the papers according to the -- what their -- I thought their quality was and presented the findings according to quality. And that might be an approach that we could think about taking.

Other comments?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. Thank you. I think it's an excellent idea to have the information from the tables laid -- information from the papers extracted in a way that's similar across all the papers. It will be easier for us to see the relevant aspects of the studies as well as the study design. And I think this is a -- so this is a great start.

I would say that there's a lot of experience on how to do this in the clinical medicine field, particularly with Cochrane Reviews as well as GRADE. And so there's some lessons there, though those are clinical -- most of those are -- those are almost all exclusively randomized control clinical trials, and don't necessarily address the kind of studies we would see here, which are observational human studies.

So there is work that's going on at the National Toxicology Program, and some work that we have been involved with, to look at tools for extracting relevant information from human observational studies in a systematic manner that is also consistent with the experience that -- the empirically based experience from the clinical medicine field.

So I think that it would be worth having --

looking at some of those tools to help guide these kinds of tables development, and the kind of -- like, there's -- because this provides some of the summary information, but it doesn't probably have all the information you're going to want to extract from the studies in order to look at the various aspects related to quality nor -- and what the studies find.

So, for example, while you have the reference and the study design, and the outcome, and some of the factors in here, some of the things like looking at study quality is going to be a separate exercise and probably has to be done in a different way, consistent with how this is done in either the clinical literature, but also looking at what's being developed through NTP or the work that we're doing in the systematic reviews at UCSF.

So I have some specific comments.

CHAIRPERSON GOLD: Can I just ask, are you suggesting then that we -- because over here we just said a minute ago that we wouldn't --

COMMITTEE MEMBER WOODRUFF: I don't think we should rate an overall quality score. Though I think there are tools now to evaluate both internal validity, in terms of risk of bias elements. And I do think that that would be a very valuable way to look at different methodological features which have been shown, at least

empirically, to influence study findings. So, yes, I do think we should do that. Though I would say that a new -- one numerical score has been moved away from in the clinical field, so I wouldn't say to do that.

CHAIRPERSON GOLD: Okay.

COMMITTEE MEMBER WOODRUFF: I was thinking there was somebody who's working on a -- anyway. So if we have specific suggestions, should we just send them to you? How does that work?

CHAIRPERSON GOLD: Yeah. So that was my next question is how to proceed? Because I mean we could have people send them to me and I could compile them, but we don't want to be doing anything behind closed doors. So if you want us to send them to staff and they'll compile them, we can do that.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, this is not -- I mean, this is kind of a procedural element for your group. And so it's not as much of a concern about, you know, collecting information and coming up with another version of something. So it kind of -- whatever your preference would be, we're happy to collect information, and kind of put it together and provide it to you maybe at the next meeting, or just prior to the next meeting or something. So it's kind of where your comfort level is.

CHAIRPERSON GOLD: Well, I'm comfortable with having the staff accumulate it for us.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: And I also wonder if there's anybody in the public that might want to talk about it too, or submit comments, you know, later as well.

CHAIRPERSON GOLD: Okay. Well, I can open it up for public comment now, but if we could designate a staff person to receive comments, so that we know who to send them to.

Who are you pointing at?

DIRECTOR ALEXEEFF: Cynthia Oshita.

CHAIRPERSON GOLD: Okay. All right. And the point being to send comments to Cynthia who will compile them, and then sometime before the next meeting, circulate them to us. And I guess if there's another iteration -- maybe have -- do that enough in advance so that if people want to do one more stab at it to edit a little bit, we could send those, so that we'd have -- okay.

So maybe I will ask at this time, if there are any public comments beyond what the Committee has recommended for revisions to this table?

DR. LAWYER: Is this on?

Yeah.

Dr. Arthur Lawyer. TSG, Davis, California.

Only a public comment on public comments. There's not very many of us in this audience, but I could think of quite a few people that would want to make comments on it, and it could be useful input into the system. So I know it was made public that this was an agenda item, but I don't think it went out specifically requesting public comments. So it probably would be good for OEHHA to say that something is being developed and ask for public comments beyond just --

CHAIRPERSON GOLD: Okay. We'll talk about the mechanism. Thank you for the thought, yeah. We can talk about that.

And Dr. Alexeeff.

DIRECTOR ALEXEEFF: As we're trying to work this table out, I mean the previous table that Dr. Rocca came up with I thought was very helpful, and us, in terms of organizing our information as we look through the studies. And I think I was looking at the next group of chemicals in the future meeting as to whether or not any of them will actually have epidemiologic data. It looks like one -- at least one will. I'm not sure about the other ones, but -- so we may actually -- we could try to put it into practice, and see, you know, what's there, what's not there, what's missing, or is it easy to actually identify

the information that fits those criteria and that kind of thing.

CHAIRPERSON GOLD: Yeah. Lauren.

DR. ZEISE: Yeah. This is a follow up on George's comments, so we're already compiling information for the next meeting. And we've started compiling it in much the same way as you have here. So if there are -- I'm wondering if the way to proceed would be that for that chemical that will be coming in front of the Committee, we kind of continue along those lines, unless we have a really clear idea about how we might add a column or make a change to this table today, but then also then as a separate discussion at the meeting, we'll have had the opportunity to look at data organized that way. And also, we'll have had some additional thoughts. Maybe we could have another comment with a public comment period.

CHAIRPERSON GOLD: So I believe we're trying to schedule the next meeting for the spring, right?

DR. ZEISE: (Nods head.)

CHAIRPERSON GOLD: So I wonder if we could give the panel a deadline to get comments to Cynthia about this table, I don't know, by January 1st let's say. I'm just throwing that out. If you don't feel like that's good, then -- so that you will have the next iteration of the table. And maybe we won't have time for everybody to

review it, you know, but we'll try it out, as you suggest, with the next chemical that has some epidemiologic data for the spring meeting, and see how it works. And then have a discussion item on the agenda for that meeting about the table. Did it work? Do we need to tweak it some more? How does that sound?

DIRECTOR ALEXEEFF: Yeah. Probably I wouldn't suggest January 1st, but maybe January 15th then. And then, you know, I think we'll see if it -- I'll talk -- maybe it will make sense for us to just post this. Has this already been posted, this table been posted?

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't think it's actually been posted, or was it? Oh, I'm sorry. Maybe -- the table has been posted. We didn't specifically ask for comment on that.

DIRECTOR ALEXEEFF: Right. So we could just ask if there's any comments, people can submit it by the 15th to us as well. And that way, we can just look at it, because we have had, you know, a number of issues raised from members of the public about, you know, procedural things that don't actually -- aren't about a specific chemical. And so there seems to be an interest in that, if there is something that is missing or could be clarified or something.

CHAIRPERSON GOLD: I'll get to Dr. Sandy. One

second. So this January 15th deadline would apply to the Panel, but also to public comment. So to answer the point back there, if we post it and invite public comment and ask them to have all their comments in by January 15th, then Cynthia can compile it and come up with a new table that we will try out.

Dr. Sandy, first.

DR. SANDY: Yes. I would like to suggest we move that up, that deadline, because January 15th is too short a time after that before we need to release the document for your next meeting. So perhaps December 20th or -- I don't have a calendar in front of me, but --

CHAIRPERSON GOLD: Dr. Zeise, you have a comment.

DR. ZEISE: Yes, it's just related to this one as well. Again, we've already started compiling the information. It's pretty time consuming. So if there are small changes, addition of a column, I think we could accommodate that. But if we find we're not able -- let's say that we have a number of suggestions to do something very different, perhaps what we could do is present you the information in the way that we're compiling it now, maybe with a couple of changes. And then at that meeting, you can come up with a new table, but it might be that we won't have enough time to fully make changes to the table we're already working on.

Go ahead, George.

DIRECTOR ALEXEEFF: That's what I was suggesting with regards to we're already trying to use this table, and then we'll see if it works, and then we'll have comments. So I think there could be the table that we -- the tables we come up with, and then there will also be comments. And so there will be a discussion at the next meeting about how it all kind of played out.

And as Dr. Zeise says, we can make some small changes, but just so that we can get the information to the Panel, if there's some very interesting, but time-consuming suggestions, then that could be discussed maybe at the next meeting.

CHAIRPERSON GOLD: Dr. VandeVoort.

COMMITTEE MEMBER VANDEVOORT: Thank you. I'm kind of comparing this table with the table that we've been working with this time. And one of the things that I'm kind of wondering about, and maybe I'm kind of missing something here, is there's a column in our current table that talks about what endpoints were assessed. And in this proposed table, I'm not seeing where that information would be.

CHAIRPERSON GOLD: Outcomes of interest.

COMMITTEE MEMBER VANDEVOORT: But then what if it wasn't interesting? What if you have a null finding, and

so --

CHAIRPERSON GOLD: Well, no, outcomes of interest -- so maybe the terminology needs to be fixed. But it just says that's what the hypothesis or objective was focusing on, whether it turned out significant or not.

COMMITTEE MEMBER VANDEVOORT: Okay. Because I think that's really important, because sometimes --

CHAIRPERSON GOLD: You could take out the "of interest" if you like, if that -- but I really think when people state their objectives or their hypotheses, they say this is the outcome we're interested in. This is the exposure and this is the outcome.

COMMITTEE MEMBER VANDEVOORT: I think knowing what they may -- as long as that table has -- that column has the actual endpoints that were measured or what that data was, because otherwise, in the current table that we're using, sometimes you can go back. You can look at what they measured, and if there wasn't any significant effect in a particular area, you know that there wasn't an effect, as opposed to you just don't know if they were even looking for that.

CHAIRPERSON GOLD: So we can easily change the title of that column to endpoints measured.

COMMITTEE MEMBER VANDEVOORT: Okay.

CHAIRPERSON GOLD: Dr. Kaufman.

DR. KAUFMAN: I can just clarify that. Dr. Farla Kaufman, staff toxicologist. Currently, that column reflects all of the outcomes examined.

COMMITTEE MEMBER VANDEVOORT: Okay.

CHAIRPERSON GOLD: Okay. So I'm -- Dr. Baskin.

COMMITTEE MEMBER BASKIN: I like the way you guys do your tables. They're outstanding. It allows me to look and say, hmm, there's a statistically significant issue here or a finding. Then I can go to the paper and judge for myself, whether I think it's real or not. I think that's what my job is, so that should still be in there in some form.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah. I like the tables too. I thought they were really extremely helpful. I think we should -- I think it would be very helpful to have -- what I like about this, the one for the epi is that it has the odds ratio with relative -- or the relative risk with the confidence intervals.

I think we have to be careful about -- I don't think we should just put things that are statistically significant in the table, because that's often -- that can be driven by the sample size and the power of the study. And also, I would encourage eventually to look at approaches. And this was recommended recently in the

National Academy of Sciences report on arsenic for EPA to start to look to methods for meta-analysis. I know those are all on epi studies, but I believe -- I think you know that the National Academy is also doing a whole evaluation on how to evaluate -- how EPA should evaluate noncancer endpoints. So I believe that will be -- provide some other useful information for our Committee.

CHAIRPERSON GOLD: So I want to get back to this point about changes in deadlines and things like that. If we suggest that anybody who has -- including the public, has any -- is there a specified amount of time that we have to have for public comment?

Is it six weeks or what is it?

CHIEF COUNSEL MONAHAN-CUMMINGS: No. We have to put items on the agenda at least 10 days prior to a meeting, but there's not a set amount for something like this that's a procedural issue.

CHAIRPERSON GOLD: For getting public comments, there's no set amount of time?

CHIEF COUNSEL MONAHAN-CUMMINGS: Uh-huh.

CHAIRPERSON GOLD: So if we asked the Committee and the public, because this will be posted, to get any revisions suggested to you by December 15th. And then we'll just use that as the draft number 2 for the meeting in the spring. And then we'll discuss in the spring --

we'll have an agenda item about how the revised table worked, how does that sound?

DR. ZEISE: Okay.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER WOODRUFF: That works for me.

CHAIRPERSON GOLD: Excuse me?

COMMITTEE MEMBER WOODRUFF: I like that schedule.

CHAIRPERSON GOLD: Okay. Dr. Rocca.

COMMITTEE MEMBER ROCCA: One other comment I wanted to make upon the current tables. I thought they were very useful as well, but I wasn't quite clear on the organization. What would be helpful to me is to have all the same study types organized in a row. I don't know, because it's not by date. It's not alphabetically. I don't know how they're organized.

But, for example, all of the ones that looked at chromosomal aberrations all together, all the ones that looked at dominant lethal all together. It makes it a lot years to compare the study designs and doses. So if that's possible, I would appreciate that.

CHAIRPERSON GOLD: Can I just say before I go to Dr. Woodruff, I had a similar question, I couldn't tell if it was by date or alphabetical, but I think the one potential problem with doing it by outcome of interest is if you have a paper that has multiple comes, where do you

put it?

COMMITTEE MEMBER ROCCA: I'm not so concerned about the outcome as the experimental design. So if we have embryo-fetal studies that are done a certain way, we would want to group those differently from the chromosomal aberrations or from the male toxicities, not necessarily based upon the results, but based upon the design of the study, and more what they're looking for.

CHAIRPERSON GOLD: If that's feasible.

So Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah, I had two comments. One is I agree about looking at this by endpoint, because this seems to be organized by study. And so what you would end up having is you'd have all -- whatever -- the chromosomal aberration studies, and so you might be repeating studies under different endpoints, but it would be a lot easier if we had the endpoints all grouped together.

So one study -- and this was true for a lot of the studies that we looked at today. One study has multiple endpoints. And really what we care is looking at the endpoints across different studies, even if we're repeating the studies in different places. So I think that would be -- I think if you do the data extraction a little bit like NTP is doing it, that that will come

out -- will be organized in that fashion. I know you're looking at me like I'm --

CHAIRPERSON GOLD: Well, what I might suggest is broad groupings like developmental toxicity, female and male reproductive.

COMMITTEE MEMBER WOODRUFF: Well, even that would be helpful. And so you might have a study that's repeated within each of those -- the author person, the source, but it would be a lot easier -- but that's okay, right, because for us we're looking at -- we're really interesting in looking at it within a group. I think if you -- and then, you know, there's these -- the way that some of these -- okay, and I keep going back to NTP, but they have a data extraction tool, so if you extract -- and we have been developing something too, you extract the data in the same way across the studies, it will be easier to group them like this.

CHAIRPERSON GOLD: Dr. Zeise, you have a comment.

DR. ZEISE: So these are really good suggestions and we'll try to implement them with the next set that are coming.

COMMITTEE MEMBER WOODRUFF: Well, I know and I didn't mean the next time necessarily.

DR. ZEISE: But maybe what we could also do is take comments on our animal tables as well, along with the

epidemiology tables and have a discussion at the next meeting about both the organization of data for the epi, as well as for the animal studies.

Meanwhile, we'll try to see with -- because again for the next meeting, there's many studies, a number of chemicals again, and so we've already done a lot of work pulling together the data. So things that can be changed easily, we'll go ahead and do that. And meanwhile, we'll have a robust discussion of both at the next meeting. Does that work for people?

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: So as we saw today, there are some compounds that have extensive peer-reviewed literature and mechanism, which really makes it easy to evaluate those studies. Other compounds where it's almost 100 percent, if not 100 percent, proprietary in-house kind of, do we evaluate those differently?

I guess that's always been a question in my mind. If you're going to rate epidemiological studies, how do you rate animal studies, depending on where they're published or not published or not even peer reviewed? So that's a discussion point.

CHAIRPERSON GOLD: Yeah.

COMMITTEE MEMBER ROCCA: Yeah, we were talking about that a little bit earlier, that peer-reviewed papers

you would normally expect to be of good quality. They might not have all of the nitty-gritty data that a full GLP study will have. And a lot of times, they won't have the robustness that a GLP study has. So I don't know if people are aware of what good laboratory practices are, but when we keep saying a GLP study, there are federal regulations that say how these studies most be run, and there are inspectors who go and check all those things.

And so just the fact that it's not peer reviewed in a journal, and frequently won't be, because this isn't data that the manufacturer wants and/or it's negative data that nobody wants to publish, doesn't necessarily mean that it's not good data. It is different to evaluate it though, because you really have to go through all those pages and figure it out for yourself. But I think the quality of either of those could potentially be very good or very bad.

CHAIRPERSON GOLD: I happen to be a personal proponent of publishing negative studies, because I think they're as important as the positive ones. But I know not everybody believes that.

So any other comments about this or should we go to the next agenda item?

Do we have a plan? Are you comfortable with the plan?

Excellent.

So I believe we have staff updates next.

I thank the Committee for its input on this.

MS. OSHITA: Okay. Good afternoon. I'm just very quickly going to update you on the administrative listings that OEHHA has been working on since you last met earlier this year. OEHHA has added -- administratively added nine chemicals to the Prop 65 list. Two were added for reproductive toxicity, and seven were added as causing cancer. And the additions to the list as well as their effective dates are shown on this slide right here.

You'll note on the slide that bisphenol A was subsequently delisted on April 19th 2013. And Carol will discuss a little bit further the status of bisphenol A further in her litigation update.

But there are also several other chemicals that are under consideration for administrative listing, which includes trichloroethylene, methyl isobutyl ketone as causing reproductive toxicity. And then also beta-myrcene, pulegone, and the emissions of high temperature unrefined rapeseed oil as causing cancer.

With the exception of the rapeseed oil, we've received comments on each of the chemicals, and they're under review. The comment period for the emissions of high temperature, unrefined rapeseed oil is still open,

and will close on December 16th 2013.

Then in terms of the safe harbor levels, since you last met, we've adopted several maximum allowable dose levels.

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MS. OSHITA: The chemicals and their respective levels are shown here on this slide right here. And that's the update.

CHAIRPERSON GOLD: Thank you.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Did you say that you're considering TCE, is that right?

MS. OSHITA: Yes, administratively.

COMMITTEE MEMBER WOODRUFF: Is it not listed?

DR. ZEISE: Trichloroethylene is listed as a carcinogen under the Prop 65, but it's not listed for developmental outcomes -- or sorry, reproductive toxicity.

COMMITTEE MEMBER WOODRUFF: Got it.

CHAIRPERSON GOLD: Do we have other staff items?

CHIEF COUNSEL MONAHAN-CUMMINGS: Hi. This is Carol again.

I just wanted to give you a quick update on some of our litigation and regulatory work. Cindy mentioned that we had briefly listed BPA as a developmental toxicant under Prop 65. We had done that based on a report from

the National Toxicology Program that identified it as a developmental toxin. We were sued by the American Chemistry Council, and ordered by a court to delist the chemical until the case is resolved.

Subsequent to that, the National(sic) Resources Defense Council intervened in the case as a co-defendant. And so right now, we are in the process -- very early processes of the trial court level motion practice. We don't expect anything to really resolve at the trial level until sometime perhaps late next year. And then we would anticipate that one side or the other will probably appeal the matter.

And so at the present time, BPA is not listed. We do have alternatives for listing that chemical, but we haven't proceeded with those yet.

In terms of other litigation, we have a case right now that's pending. Syngenta sued our office last year regarding a safe harbor level we had changed for the chemical chlorothalonil. That's actually a carcinogen not a reproductive toxicant, but that case is still pending. Kind of in the same posture as the other one, we're in the trial court. Motions are pending and it's not clear when that case will be resolved or whether it will be appealed.

I think I mentioned to you several times previously that in 2007, we were sued by the Sierra Club

and some labor organizations. Actually, it was the Governor, the Agency and OEHHA were sued for not timely making listing decisions under Prop 65 under three of our four listing mechanisms.

And we recently settled that case, and -- except for the attorney's fees part is still pending. But in any event, the changes that affect this Committee and DART listings have to do with the time frames for listing. Decisions on certain chemicals are set out in the agreements. Some of our decisions have to be made in the next two or three months, some of them sometime next year, and other ones not till 2015. But we have ongoing responsibilities to make listing decisions in a pretty tight time frame for us.

And so you are on our list of people that we let know when we're making listing decisions and adopting other regulations, like safe harbors. And so if you have any questions on those, please let us know, but you may see more activity in those areas.

We also agreed to shorten some time periods for public comments. And that includes on materials that are prepared for this Committee. We shortened the public comment period for HIDs to 45 days. It used to be 60 days. And we eliminated a informal comment period for authoritative body listings. And those were both done

under the agreement as methods for trying to speed up the process for making decisions on listing or not listing chemicals.

We also agreed to do a couple of regulatory actions. One of them that affects this Committee is that we are in the process of adopting more specific regulations about the qualifications of the members of this Committee and the CIC. You'll be happy to know that you all qualify under the proposed regulations, and we checked that before we proposed them.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: But anyway, essentially what we were trying to do is give some clarity to the existing regulations, because they were not entirely clear on what level of expertise different folks needed to have, and how you might measure that. And so we expect those regulations to be completed and adopted in the next few months.

We also are -- we have to at least start the process for adopting a regulation for Labor Code listings. We heard a lot about the Labor Code today. And we don't currently have any regulations for those listings. We have floated some ideas from time to time. And we do expect to propose a regulation formally within the next three or four months. And you're absolutely welcome to

comment on any of those regulatory actions.

We also have a project that you may or may not hear about, where we're planning to adopt more specific regulations concerning warnings for chemicals that are listed under Prop 65 that would actually give more information to consumers about the types of endpoints for the chemicals, ways to avoid exposure where they can, actual -- the names of the chemicals they're being exposed to, things like that, that aren't currently required that we think would really improve the effectiveness of the warnings.

And so that will be an open public process. And again, you're welcome to participate. And we'll -- I believe that you're on -- you're all on our listserv, and you get those notices. If not, let us know and we'll make sure.

Any questions?

Thank you.

CHAIRPERSON GOLD: Thank you. Any questions for Carol -- counsel?

Okay. So the last thing is a summary of our actions today, which is Dr. Alexeeff.

DIRECTOR ALEXEEFF: Well, I want to thank the public for tuning in and being present here for this meeting. And I want to thank the Committee for all the

hard work. We were not sure how much of this agenda we'd actually accomplish today, but we seem to have accomplished it all. So that's great. That's wonderful.

And I think in part it has to do -- well, with obviously the materials I guess were very helpful, and the hard work on the members, in terms of preparing for this meeting. It was very clear how well prepared all the members were. And maybe the organization that we put in the tabular form and such was also very helpful, just to find the information.

So in terms of identifying chemicals that cause reproductive toxicity, nine chemicals were reconsidered today. And the chemicals that were actually -- that will be remaining on the list are the following: So N,N'-dimethylacetamide was clearly shown to be scientifically valid testing according to principles to cause both developmental toxicity and male reproductive toxicity. So that will remain on the list for those two endpoints in particular.

And then 2-chloropropionic acid was clearly shown through scientifically valid testing according to generally accepted principles to cause male reproductive toxicity, yes. So it will remain on the list for that particular endpoint.

And then 4-vinyl-cyclohexene was clearly shown

through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity. And it's sister compound vinyl cyclohexene dioxide was also shown, through scientifically valid method -- testing, according to generally accepted principles, to cause female reproductive toxicity.

So the chemicals that were considered, but not found to meet the criteria for remaining on the list were tert-amyl methyl ether, 2-ethylhexanoic acid, ethyl-tert-butyl ether, p,p'-Oxybis(benzenesulfonyl hydrazide), and 1,3,5-triglycidyl-s-triazinetrione. So those chemicals will be removed from the list.

And then there was also a discussion about the agenda item regarding how to tabulate epidemiologic data for the hazard identification materials. So we have a deadline of -- we will be posting this table -- or it's already posted, but we'll make it clear that we're asking for public comment on how we organize this data as well as the data we've organized for today's meeting and for the animal data.

And we'll request that people -- that the Committee members as well as members of the public submit comments by December 15th. December 15th.

So I think that completes the Committee actions for the day.

CHAIRPERSON GOLD: Thank you.

Unless anyone has any further items, I'd like to thank the staff for their, as always, very thorough review of the literature, providing us materials even at the last minute, and also to the Committee for their hard and thoughtful work. It's obvious that through the discussions I think we had very important discussions about considerations that were very helpful in our deliberations. And obviously, you'd all spent a great deal of time and effort and thought. And so I want to say thank you for that. And I think with that, we can adjourn, and I wish you all a good evening.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 3:58 p.m.)

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

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

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, Developmental and Reproductive Toxicant Identification Committee was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and 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 6th day of December, 2013.

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