MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

WEDNESDAY, MARCH 19, 2014

10:30 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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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.

Aydin Nazmi, Ph.D.

Isaac Pessah, Ph.D.

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

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. Francisco Moran, Reproductive Toxicology and Epidemiology Section

Ms. Cynthia Oshita, Proposition 65 Implementation

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

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

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

ALSO PRESENT:

Dr. Arthur Lawyer, Technology Sciences Group

Mr. Dennis J. Naas, Eastman Chemical Company

Mr. Tim Shestek, American Chemistry Council

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

DIRECTOR ALEXEEFF: We're going to go ahead and get started here. I'm George Alexeeff, Director of the Office of Environmental Health Hazard Assessment. And first, I just want to start just to remind you that we have the exit doors here, in case there's a need to evacuate the room in case there's a fire drill or any other reason.

So if there's a fire alarm, you know, take your valuables with you. Do not use the elevator. Staff will assist you if need to. We exit down the stairways outside and to a relocation site across the street. Also, drinking fountains and restrooms are out the door and to my left, your right, past the glass sculptures there.

Okay. So I would like to go ahead and introduce the Committee. First, I want to welcome you to the meeting of the Developmental and Reproductive Toxicant Identification Committee. And we are meeting today, March 19th, in the Sierra Room in Sacramento.

So on my left -- on my right is Dr. Ellen Gold, who is the Chair of the Committee. She is professor and Chair, Department of Public Health Sciences at UC Davis. And further to my right is Dr. Aydin Nazmi. And he is assistant professor of Food, Science, and Nutrition at Cal Poly, San Luis Obispo. Now, to my left is Dr. Meredith

Rocca. And she's the director of non-clinical toxicology at Janssen Alzheimer Immunotherapy Research and Development. And to her left is Dr. Isaac Pessah, who's professor and chair of the Department of Molecular Biosciences at UC Davis.

As you can tell, we are missing a few members of the Committee. They are on their way. Their train was delayed. And when they arrive, I will introduce them.

In the meantime, so we can go ahead and proceed, we'll be proceeding with some non -- essentially some non-discussion or decision items, just some informational items from staff. But I -- so I was wondering, Dr. Gold, first, if you wanted to make any comments in the beginning?

CHAIRPERSON GOLD: No, thank you. I don't really have any comments, except to welcome everyone here for a good discussion today, and a fuller discussion when the rest of the Committee arrives. But we'll turn it over to the staff now, I think.

DIRECTOR ALEXEEFF: Yes. We'll begin with Carol Monahan-Cummings.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. Just as a reminder to myself and others that you almost have to swallow the microphones in order for them to work well enough for people to hear, particularly on the

webcast. So if you can get right up there, that would be good.

So I'm just going to give you a couple of updates on some litigation that we're still involved in, and then some of our regulatory actions that you might be interested in as well.

I've given an update on the Sierra Club versus Brown case every year for the last eight years. So right now, the only issue left in that case is the attorney's fees. And so the whole thing has been resolved and that was a case about listings under Prop 65 and the other committee, the CIC, members were sued in their capacity as members of the Committee, but they have been dismissed and the actions resolved except for the fees. So I'm hoping one of these days I can get this off of our agenda.

There's two active cases currently in the trial court. We don't have any court of appeal cases. We have an action by the American Chemistry Council against OEHHA for the brief listing of the chemical bisphenol A. It was listed for eight days?

CHIEF DEPUTY DIRECTOR HIRSCH: Eight days.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. Okay. So that action is challenging the basis for the listing of the chemical under the authoritative bodies listing mechanism. It wasn't a committee listing. And in that

case, we are in the very early stages, where we're doing a lot of motion practice. It will be really boring for people that aren't lawyers. So we don't have a firm trial date yet, but we do expect that that would be resolved within the next year or so.

We also have a case where OEHHA was sued by the Syngenta Crop Protection Company. And that has to do with the establishment of a safe harbor level for a pesticide called chlorothalonil. And the company is suing us because they believe that the number is too low.

So that again is in the early stages of litigation in the motion practice, and we are similarly hoping that it will be resolved within a year. We do anticipate that most likely both of these cases will go up on appeal depending on the decisions, but we'll -- I'll let you know that later.

So that's all the active litigation. Of course, we have pre-litigation things going on all the time, and so I'll let you know if additional cases get filed. And so I'm going to take a little break here before I go into regulations, is that all right, George, so you can introduce the members?

DIRECTOR ALEXEEFF: Certainly. So I'd like to introduce the two members. We have on my right, after Dr. Gold, is Dr. Laurence Baskin. He's the Chief of Pediatric

Urology and professor of urology and pediatrics and surgeon scientist at University of California at San Francisco. Welcome.

And to my far left is Dr. Tracey Woodruff. She is professor at Department of Obstetricians, Gynecology, and Reproductive Sciences at the University of California at San Francisco. So welcome. And just to let you know, we've been -- we started with staff reports, so we'll continue with staff reports before we get to any discussion or decision items. So we're doing -- Carol Monahan-Cummings is giving us our legal update right now.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Welcome.

So the other issues I wanted to mention to you that may have -- may be of interest to you as individuals or members of the Committee, and you're welcome to comment on these during the public comment periods. We are -- we have proposed a new regulation to be adopted into our regulations regarding Prop 65. And it has to do with listings under what we call the Labor Code mechanism, which we'll talk about again, because the chemicals that are in front of you today have to do with the Labor Code listings.

But we haven't, in the past, had a regulation that defined how we list chemicals under that particular mechanism, though we have some limited regulations on the

other three listing mechanisms. And we're not required to have them, but we decided that it -- for purposes of transparency and understanding for the public, that we would adopt a regulation.

We have the regulatory language, Statement of Reasons, and related documents on our website. And there is a formal regulatory hearing on that proposal this Friday, which will be webcast. And people on the webcast can make comments via email. That's in the morning from 10:00 to noon or so.

The second one I wanted to mention is we are in the pre-regulatory process for changes -- significant changes to the regulations that have to do with providing warnings to individuals that are being exposed to chemicals that you have listed, or that we have listed under other mechanisms. Pre-regulatory means that we haven't proposed it for formal adoption. This is -- this will be our second pre-regulatory workshop, which will be held on April 14th.

If you take a look at the proposed regulations, they're pretty extensive for us, and they would make some really significant changes. We think positive changes in terms of giving people more information about the exposures that they have, and also increasing the information that we have available on our website for

individuals that want more information than we can actually get included on the warnings. And as I said, your input would be most welcome.

The last one I wanted to mention is completed, and that was our regulation that defined the qualifications for this Committee and for the CIC Committee. And you'll be happy to know that you all qualify to be on this Committee.

We made sure, before we adopted the regulation. So -- and I think you've had an opportunity to see that. If you haven't already, it's on our website as well.

Currently, that is over at the Office of Administrative Law for their final approval, which we anticipate will come within the next couple weeks.

So does anybody have any questions on that or other stuff?

Okay. I guess next is Cindy.

MS. OSHITA: Good morning. I'm going to just give you a quick update on the administrative listings that have happened since you last met in November. We have added two chemicals to the Prop 65 chemical list. Both were added in January. It was the emissions for high temperature unrefined rapeseed oil and trichloroethylene. Both were added as known to cause cancer.

We've completed our review of the comments that

we received on methyl isobutyl ketone. And we expect to proceed with its listing next week.

There are a couple of other chemicals that are still under consideration for administrative listing that we mentioned at the last meeting. That includes beta-myrcene and pulegone. We received one comment on pulegone that we are currently reviewing, an extension to the comment period for beta-myrcene was granted, and it will close on March 24th.

We've also since issued Notices of Intent to List for atrazine, propazine, simazine, and their chlorometabolites, DACT, DEA, and DIA. Those are being considered for listing for reproductive toxicity.

And then we have also issued notices for nitrite in combination with amines or amides, megestrol acetate. Three drugs, pentosan polysulfate sodium, pioglitazone, and triamterene. And then also n,n-dimethyl-p-toluidine. These are all being considered for listing for cancer. We received no comments on megestrol acetate, and so we will proceed with its listing next week as well.

And we await the close of the various other comment periods. And if we receive any comments, they will be reviewed before we proceed with any listing decisions.

Thank you.

CHAIRPERSON GOLD: Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: What authority were they listed -- under what authority were they listed?

MS. OSHITA: Under the -- most of them under the authoritative bodies mechanism. Do you mean which --

COMMITTEE MEMBER WOODRUFF: Which authoritative bodies, I was just curious?

MS. OSHITA: Oh, okay. For the triazine pesticides, they are being listed by -- under the U.S. EPA. The nitrite by IARC. The megestrol acetate is a formally required, so that would be the FDA. The three drugs that I mentioned are via the Labor Code. And then the n,n-dimethyl-p-toluidine is by NTP.

CHAIRPERSON GOLD: Okay. Barring any other comments or questions, I think we can now resume our normal agenda, which we had planned to start 45 minutes ago, but Amtrak sort of interfered with that.

So the plan is to go through six chemicals, three glycidyl ethers and three ketones. And we will do it very much the same way we did it back in November. There will be some introductory comments I believe about why we are doing this and the process. And then we will have staff presentations for each of the chemicals. We'll go chemical by chemical with staff presentations, public comments, and then Committee discussion and Committee

vote. So we'll complete that for each of the six before we go on to the next one.

So I think I'll turn it back to Carol.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Hello again. I just wanted to give you a brief background on the chemicals that are before you. I know we just had a meeting recently. But given that you do a few other things besides be on this Committee, I just want to remind you why we're here.

I think the slides are in front of you. These chemicals that you're going to be considering today were added to the Prop 65 list a number of years ago. And it -- they were based on some provisions of Prop 65 that incorporate the federal Hazard Communication Standard. So I'm going to just give you a little background on that, and then we'll talk about the next steps for some of the chemicals that are being considered, and answer whatever questions you might have.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So for these chemicals, we're -- the reason that we have to look at them again is because we need to change the basis for

listing the chemicals or remove them from the list, because they no longer meet the listing requirements for administrative listings under the Labor Code. And so we have referred some of those to you for review of the basis for listing.

There was a basis for listing for six other chemicals that we've considered for -- under a different authoritative body or formally required listings. I don't know if you remember our introduction to the Committee some time ago, where we did talk about the four different listing processes. We have administrative authority to list chemicals under the authoritative bodies process, where this Committee and the CIC have identified certain -- we should probably go to the next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: -- certain bodies, including United States agencies and international agencies that identified chemicals that are known to cause cancer or reproductive toxicity. We have another procedure for identifying chemicals via what's called the formally required listing mechanism. Formally required means that there's already a warning that's required by a State or federal agency.

And so we just tag along on that. Generally speaking, we have, in the past, listed mostly drugs under

this mechanism, but we can list them based on any requirement for warnings. And so we are -- have -- as you can see here, we've got three chemicals that we changed the basis for listing from the Labor Code to formally required, because they're already required to have a very specific warning for reproductive toxicity that's required by federal OSHA.

And that's a different provision of the OSHA regulations than the ones that we're going to talk about today. The authoritative bodies process we've listed -- or changed the basis for listing of three chemicals, based on some findings of the Environmental Protection Agency.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the chemicals you're going to consider today are on the left-hand side of -- at least my left on this chart. I'm not going to try and pronounce them, but you have six that are in front of you today. And then we have three more that we're going to propose to you at our future meeting, which I think is currently scheduled for May.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Each of these chemicals, the nine that we have remaining have stated on

the list, because we are waiting for your decision as to whether or not they should remain on the list based on your own criteria, which is whether or not the chemicals have been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity.

So that's a de novo review basically by this committee. And so you don't have to rely on what the other listing mechanisms -- or the other authorities have said. You make your own decision regarding whether these chemicals should remain on the list.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: You can skip that one.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So just some general background. As I mentioned, these chemicals were added to the list of chemicals known to cause reproductive toxicity based on, what we call, the Labor Code listing mechanism, which is a provision of Prop 65 that incorporates a very small subset of the regulations that are in the California Labor Code. And the proposition requires these chemicals to be listed, if they're identified through that mechanism.

One of the Labor Code provisions, the 6382(d), incorporates by reference the federal Hazard Communication Standard.

And so -- next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Until March of 2012, the Hazard Communication Standard referred to the ACGIH, which is the American Conference of Governmental Industrial Hygienists list of threshold limit values, and subpart (z) of the regulations as mandatory listing -- or mandatory ways to identify chemicals that cause reproductive toxicity or other adverse effects on humans.

And -- next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: In March 2012, OSHA changed their regulations pretty substantially. And so before 2012, we had a legal decision that went up to the court of appeal, the California Chamber of Commerce versus Brown, which made it very clear that we have to list chemicals under the Labor Code. And so we had been listing these chemicals based on the ACGIH TLVs, or subpart (z).

And given the changes to those regulations, we no longer are able to do that, because the regulations are no longer mandatory, and businesses are able to look at

more -- I guess they have more ability to classify the chemicals themselves, rather than have a base list at the federal level, so -- next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: I think I already mentioned the points on this slide, that the chemicals were already listed via the Labor Code. We've looked at them and their background, and we're not able to find another administrative listing process for them, so we've referred them to you for consideration. You don't need to look at the underlying TLVs or the basis for why ACGIH identified them as reproductive toxins, although we have included that material for you.

So what you're doing today is looking at these chemicals basically de novo in the same way as you would look at other chemicals that we bring to you.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So today in your consideration of these six chemicals, the -- your Committee will decide whether or not they meet your criteria for listing or you can defer them -- consideration of the chemicals to another meeting, if you feel like you don't have enough information or we don't have enough time.

And then we've got the three additional chemicals that we'll be presenting to you on May -- in May -- oh, two additional chemicals, because we're not going to be able to present chloroform apparently.

So we most likely will have another meeting of this Committee later in the year. So, you know, we used to in the past only have one meeting a year, and now we're having a number of them. But at least under our regulations, we are meeting our mandate, because we have to meet at least once a year, but they don't count forward unfortunately.

So any questions on that?

Okay. One -- I'm sorry. Go ahead.

COMMITTEE MEMBER PESSAH: I have a question. I just wondering when you come across a situation where a chemical doesn't -- or you feel it doesn't have enough information, you said you'd move it to a future meeting, but what if it's unlikely there will be additional information, does that influence our...

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think what we do is we just let you know what the existing information is on it, and if you feel like there's not enough, then you can advise us to take it off the list, until -- you know, we keep tracking them anyway just to make sure that something new doesn't come up.

DIRECTOR ALEXEEFF: This is George Alexeeff. I think what Carol was saying is that staff didn't have enough time to prepare the package of information for the Committee.

CHIEF COUNSEL MONAHAN-CUMMINGS: Oh, sorry. I just want to make a couple other quick comments that I always make for the Committee hearings. And that is that just to remind you, of course, that you have your own scientific standard for listing chemicals. It's not a legal standard. It's a scientific decision. You're scientists or doctors or professionals in the identification of these kinds of chemicals for these endpoints. And so you don't have to worry about making a legal decision.

Your decision, of course, has a legal effect, but it's not -- the standard isn't beyond a reasonable doubt or, you know, clear and convincing or whatever. It's your -- what it says in the statute is you have to determine whether it's been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer -- or not cancer, reproductive toxicity.

So you don't have to consider. Although, lots of time you get some testimony on it, whether or not the current doses that humans are receiving are significant

enough to worry about. You don't have to worry about whether or not the chemical actually causes human reproductive effects. You can list it based on only animal evidence, as long as you find that it would be generally applicable to humans. And you do have your own criteria that you have -- or your prior Committee members adopted for you, so you can look at that in terms of what scientific evidence you want to consider and how to apply that. So I think that's all I have unless you have questions.

Okay. And if questions come up as you go along, I'm certainly happy to answer them.

Thank you.

CHAIRPERSON GOLD: Thank you. Very helpful. So next on my agenda I have that Jim McDonald(sic) is going to make some introductory comments.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Good morning. Just before I being on this as a minor clarification to avoid probably confusion more in the audience than among the Committee, we actually announced last Friday that the three chemicals that will be considered by the Committee at your meeting in May. So it's hexafluoroacetone, phenylphosphine and chlorsulfuron.

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DR. DONALD: Okay. I won't reiterate what Carol has already so thoroughly covered. Of course, the Committee is going to be making its usual decision about whether the chemical has been clearly shown to cause reproductive toxicity. So to that end, we have provided relevant data to the Committee in the form of summary tables, but also in the form of the original study reports and published papers, when they were available. And in this case, all of the papers that we have summarized were provided to the Committee.

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DR. DONALD: We identified those publications through literature searches that covered the three major endpoints of reproductive toxicity, which are, of course, developmental toxicity, male reproductive toxicity, and female reproductive toxicity. Those searches were conducted by professional librarians through a contract with the Public Health Library at the University of California at Berkeley. And the search protocol that they followed is described in the hazard identification document that you have as Appendix A.

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DR. DONALD: As usual, we will make presentations -- brief presentations of the information on

each chemical. Since we still have six chemicals to get through today, we will keep the presentations quite short, but we will, of course, be happy to answer any questions you may have.

And the chemicals will be presented in the same order as they appear in the hazard identification document, which is first the three glycidyl ethers, followed by two ketones, and then finally alpha-methyl styrene.

So I will turn this now over to the Dr. Francisco Moran, who will make the presentations on each of the chemicals.

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DR. MORAN: Thank you. Good morning. I will present the summary information on the reproductive toxicology for three glycidyl ethers first. I will start by presenting the summary of the finding for n-butyl glycidyl ether.

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DR. MORAN: A comprehensive literature search resulted in three references with data on the potential reproductive toxicity for BGE in rats and mice.

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DR. MORAN: In a subchronic toxicity study in rats by Anderson et al. in 1957, ten male rats per group

exposed to BGE by inhalation at 0, 0.2 to 1.6 grams per cubic meter for seven hours a day for five days a week for ten weeks. The endpoints were organ weight and pathology at the end of the experiment.

Oh, I think I pressed too fast.

The results for systemic toxicity they found that at the two higher doses there were -- there was an increased mortality and reduced weight gain, and increased lung and the liver -- and liver weight, statistically significant at 1.6 grams per cubic meter and bronchopneumonia in one rat at 0.4 and five rats at 0.8 grams per cubic meter.

For reproductive toxicity, there were atrophic testes in four of five surviving animals and one animal that died after 40 exposures at 1.6 grams per cubic meter; very small testes in one of ten at 1.6 grams per cubic meter; a slight patchy testes atrophy in one animal at 0.4 grams per cubic meter that also presented pneumonia; only one case with testes atrophy was reported that had no other organ pathology.

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DR. MORAN: In a dominant lethal study by Pullin and Legator in 1977 -- are we on the right -- yes -- ten male mice were exposed dermally to 0 or 1.5 grams per kilogram of BGE three times a week for eight weeks. Each

male was mated to three untreated females per week for two weeks. The endpoints were evaluated at 13 or 14 days from presumptive mating, since they were -- the vaginal plug was not checked. The endpoints were pregnancy rate, implantations, and fetal mortality. They found a lower pregnancy rate at one and two weeks after exposure with a P equal to 0.05, and greater fetal mortality and post-implantation loss.

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DR. MORAN: In another dominant lethal study by Whorton et al. in 1983, 36 to 44 -- there is a small correction here with what appeared in the HID from 42 to 44 animals -- male rats were exposed dermally to three doses of BGE three times per week Monday, Wednesday, and Friday, eight weeks -- for eight weeks and saline control. Each male was mated to three virgin females per week for three weeks.

The endpoints were a weekly body weight and testicular pathology after the final mating period for males, and in the females, pregnancy, implantation, and fetal death were evaluated at 13 or 14 days from presumptive mating. They found no significant dose-related testicular changes, low number of altered cells; greater fetal death rate at 1.6 grams per kilogram per day after one week of mating only.

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DR. MORAN: That concludes this chemical.

CHAIRPERSON GOLD: Okay. Thank you very much, Dr. Moran.

So we're now open for public comments on n-glycidyl ether -- n-butyl glycidyl ether, sorry.

DR. MORAN: N-butyl glycidyl ether.

CHAIRPERSON GOLD: Sorry.

Any public comments?

Okay. Hearing none -- sorry. So hearing no public comment, we'll turn to the Committee discussion. And I've asked Dr. Baskin to take the lead followed by Dr. Nazmi, and then we'll open up to the general Committee.

COMMITTEE MEMBER BASKIN: Good morning. This is a chemical that's used in epoxy resins, and evidently stabilizes chlorinated solvents. Dr. Moran's nice summary presentation points out that in the literature there's three studies, and none of these studies are really directed at reproductive toxicology. There were some serious systemic effects, but the focus of our evaluation relates to reproductive toxicology.

And I'd like to look at the Whorton study in 1983 first. This was a mice study. Dermal application. And the reason I think this study should be highlighted is that they actually, as a secondary analysis, clearly

looked at the testes. The testes were evaluated histologically. They were done in proper fashion. They were put in Bouin solution. There was fixation and bedding and direct analysis of really the cellular pathology. And there was really no positive findings.

So I think that it is of significance, because it's the most recent study and it actually was done in a scientifically valid way.

The 1977 study by Pullin was also a mice dermal exposure, and they didn't real do any gonadal histology. And although, as pointed out, there was clearly increased fetal mortality, there was no findings related to reproductive toxicology in the testes.

As an aside, I didn't see any evidence that the ovary was evaluated in any of these studies. The 1957 study, before I was born, rats were given an inhalation agent. And there are some positive gross findings as pointed out, which have some concern, but they're not really substantiated with any statistics or follow-up histology. And the gross findings that are of concerning is that there was an atrophic -- atrophic testes found or what is called slightly patchy testes atrophy. And I'm not 100 percent sure what that means.

So I personally don't think we have a huge amount of evidence here by present standards to be able to make a

solid statement.

CHAIRPERSON GOLD: Dr. Nazmi, would you like to follow up?

COMMITTEE MEMBER NAZMI: I have nothing to add. Thank you.

CHAIRPERSON GOLD: Okay. I'll turn to the rest of the Committee and ask if they have any questions or further points of discussion on this chemical?

Awfully quiet group this morning.

Nothing?

Okay. Are we ready to vote?

Yes?

All right. So I have -- yeah, so I have my voting protocol.

All right. So we have to vote on each of the three endpoints, so we'll take them one at a time, right? So has n-butyl glycidyl ether been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity?

All those voting yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see zero.

Has n-butyl glycidyl ether been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive

toxicity?

(No hands raised.)

CHAIRPERSON GOLD: Again, I see zero.

DIRECTOR ALEXEEFF: Could I just ask -- George Alexeeff. You may as well ask for no votes, just so we see, maybe for each endpoint.

CHAIRPERSON GOLD: All right. So let's go back to developmental. Sorry. Thank you.

How many are voting no that for developmental toxicity that n-butyl glycidyl ether has not -- has been clearly shown through scientifically valid testing to generally accepted principles to cause developmental toxicity? How many are voting no?

(Hands raised.)

CHAIRPERSON GOLD: I see three -- six.

And there's no abstentions, yes.

Okay. Now back to female reproductive toxicity. Has n-butyl glycidyl ether 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 zero.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see six.

No abstentions.

And finally has n-butyl glycidyl ether been clearly shown through scientifically testing, according to generally accepted principles to cause male reproductive toxicity. If you believe yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see none.

Those believing no?

(Hands raised.)

CHAIRPERSON GOLD: Three -- six.

And no abstentions.

So the result is for all three endpoints that a unanimous vote of no in terms of listing, in terms of showing that it causes developmental, female reproductive or male toxicity.

Okay. All right. Very good. Thank you.

So next we will go on. And, Dr. Moran, I see you're on for all of these, is that correct?

DR. MORAN: Yes.

CHAIRPERSON GOLD: So you'll do the staff presentation for diglycidyl ether.

DR. MORAN: Yes.

CHAIRPERSON GOLD: Thank you.

(Thereupon an overhead presentation was

presented as follows.)

DR. MORAN: Okay. Our next chemical as was introduced is diglycidyl ether.

A comprehensive literature search produced one reference regarding male reproductive toxicity of DGE in laboratory animals. The single reference found for DGE by Hine et al. in 1961 has several toxicological studies rats, rabbits, and dogs.

These studies were designed to assess:

Peripheral blood, bone marrow, body weight, and mortality; physical observation and histology for testes among other organs at necropsy were performed; specifically for males, weekly body weight, testicular pathology, and for females pregnancy, implantations, and fetal death.

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DR. MORAN: The rat study number one on this document, we have the results from treated rats to cutaneous exposure of DGE where five males per rat per dose group were treated at 0, 125, 250, or 500 milligrams per kilogram daily for five days a week for four weeks.

For systemic toxicity, the observed effects were:

In the 125 milligrams per kilogram group, there were two deaths by the second week and a third death by the third week of treatment; two deaths each at 250 and

500 milligrams per group -- per groups were, at this time point, the treatment stopped in this group.

And at all doses, they found: Weight loss, reduced leukocyte, necrosis of the skin, lymphoid tissue and kidney and hemorrhage of the adrenal medulla.

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DR. MORAN: For reproductive toxicity, they found focal necrosis of the testes at all doses. No specific findings for the different dose groups were provided, and the P values were not provided either.

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DR. MORAN: The study number two of cutaneous exposure, five males per rat per group were treated with doses of DGE and at 0, 15, 30, or 60 milligrams per kilogram daily for five days a week for four weeks. Changes in the method will be indicated by the red color font in the slide that is kind of faded, but it will continue through the presentation.

Systemic toxicity. They found that weight gain reported to be significantly retarded at 30 and 60 milligrams per kilogram, and where the data was not provided; no deaths; no visceral abnormalities. For reproductive toxicity, it was reported that there were no adverse effects on testes to body weight ratio

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DR. MORAN: In the third study, we have results from an inhalation study, where 30 male rats were exposed to diglycidyl ether at 3 ppm for four hours a day, five days a week for 29 days. Ten animals served as control, where only 15 treated and all control animals were evaluated after the final exposure. The basis for this selection was not stated.

In the systemic toxicity, they found five animals died during exposure, where pneumonia, bronchopneumonia, necrosis of the pancreas and the spleen were reported for some of them; reduced percentage body weight gain; reduced total leukocyte count, percentage of polymorphonuclear cells and number of nucleated cells femoral marrow.

The rest of the animals, ten, were held for a year with apparent normal range on the endpoints analyzed at that time.

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DR. MORAN: For reproductive toxicity, we have that one case of necrosis of the tubules of the testes was reported. The authors reported an apparent nonsignificant increase, about 10 percent in relative testes weight.

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DR. MORAN: The fourth study in this continues -- report is where they used 30 rats were exposed by inhalation to diglycidyl ether at 0 or 0.3 ppm for four

hours a day for five days a week for 90 days. Ten treated animals and five controls were killed after 20 exposures, 30 days, with only one case of pneumonia in the experimental group. No other differences were reported.

After 60 exposures in 90 days, ten more treated animals with no control were killed and the results are shown here.

For the systemic toxicity, we have one animal had acute peribronchiolitis. Not reported if it was one of the five showing reproductive toxicity that we'll present soon. No other systemic toxicity reported. For reproductive toxicity, five rats had poorly defined focal degeneration of the germinal epithelium.

The last ten treated animals and ten control animals of the experimental group were kept for a year, where it was reported three cases of bronchopneumonia, two of these in the control group with no differences in testes to body weight ratios.

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DR. MORAN: In the fifth study is a result from an inhalation exposure, where three male rabbits were treated with DGE at 0, 3, 6, 12, or 24 ppm for 24 hours.

For systemic toxicity we have the two rabbits in the 24 ppm, the high dose group, died with 30 and 35 percent of weight loss. One had confluent

bronchopneumonia and serous hepatitis and the other had focal atelectasis, peribronchiolitis, and focal hemorrhage in the kidneys and lungs. The third rabbit died two days later with 35 percent weight loss and was not necropsied. Rabbits exposed to lower levels showed no gross changes at necropsy and were not studied histologically.

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DR. MORAN: And for the reproductive toxicity, we have the first two animals that died at 24 ppm had greatly atrophied testes. No additional testicular effects were reported.

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DR. MORAN: The sixth study, where they have three males dogs were treated intravenously to DGE at 25 milligrams per kilo per week for three weeks and no controls were reported.

For systemic toxicity, we have low leukocyte count; two dogs died, one died seven days after the second injection, apparently of pneumonia. The other at six days after the third weekly injection.

For reproductive toxicity, we have that the animal that died at seven days after the second injection, presented hyaline degeneration of the testicular tubules.

No control group was described for this study, but three additional animals treated at 12.5 milligrams

weekly apparently following the same protocol did not show signs of toxicity.

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DR. MORAN: That concludes this presentation. Thank you.

CHAIRPERSON GOLD: Thank you. We would now invite public comments on diglycidyl ether?

We have not been notified of any.

Hearing none.

Okay. We will now ask the Committee for a discussion. And we've asked Dr. Woodruff to do the primary on this one.

COMMITTEE MEMBER WOODRUFF: Thank you. Thank you for the presentation. It was very thorough.

As you said, there's only one study, even though they did several different types of exposures in animals. In the experiment though, of course, I think you noted that this study is also older as the one that we just -- some of the ones that we just discussed. And a lot of the focus of these studies were on systemic toxicity, even though there was some focus on pregnancy outcomes -- didn't really hear that reported -- and also the primary focus was on male reproductive effects, of which there was mixed findings among the different animal groups that were evaluated.

So there was a cutaneous exposure, an inhalation exposure, and then inhalation and intravenous exposure. We had rats, male rats -- all male rats, a few rabbits, and a study of a few dogs. I would say these studies are generally very small, so it's very difficult to really draw any conclusions.

My conclusion is that, as you have said, that really there weren't very many -- there was a lot of findings on systemic toxicity and it's -- and there was, it seemed to me, findings focused on effects on pulmonary function. But as far as reproductive findings, those were either very not evaluated, or when they were evaluated did not appear -- primarily male reproductive effects did not appear to be significant.

CHAIRPERSON GOLD: Thank you.

Dr. Baskin, do you have any further comments?

COMMITTEE MEMBER BASKIN: I agree with Dr. Woodruff's summary, and would just reiterate that the primary design of the study was to look at the outcome in the blood. And there were -- this is clearly a chemical that you probably don't want to take. It killed a lot of the animals.

But for reproductive toxicology, there was some, what I would say, concerning descriptors, degeneration of testes tubules, hyaline degeneration. I mean, that's

common terms that are used. But again, as a secondary data analysis, there was no statistics, and there were no imaging to really be able to definitively say that this is a primary problem.

CHAIRPERSON GOLD: Okay. Thank you.

So I'll now open up the discussion to the rest of the Committee. Is there any further discussion on diglycidyl ether?

Seeing none.

Are we ready to vote?

Yes.

Okay. Has diglycidyl ether 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 none.

If you believe no, please raise your hand?

(Hands raised.)

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

No abstentions.

Has diglycidyl ether 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 none.

If you believe no, please raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: I see six. And no abstentions.

Finally, has diglycidyl ether 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: I see none.

If you believe no, please raised your hand?

(Hands raised.)

CHAIRPERSON GOLD: I see six, and no abstentions.

Therefore, we are unanimous in stating that we do not believe that through scientifically valid testing, diglycidyl ether has been shown to cause developmental toxicity or male or female reproductive toxicity.

Okay. Thank you.

All right. Our next chemical for Dr. Moran is phenyl glycidyl ether.

DR. MORAN: Yes. Thank you. A comprehensive literature search resulted in two references with data on

the potential reproductive toxicity of PGE in rats and dogs.

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DR. MORAN: The first study by Terrill et al. in 1977 is a toxicological study, where six male rats per group were exposed by inhalation to phenyl glycidyl ether at 0 or 29 ppm for four hours a day, five days a week for two weeks.

The endpoints assessed were: Daily weight and physically examination; at the end of testing, half of the rats were sacrificed for histopathology; the rest of the animals were sacrificed and examined histologically after two weeks.

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DR. MORAN: In the second study by Terrill et -- oh, sorry. In the systemic -- the results. Twenty-five. Sorry.

For systemic toxicity we have that depressed weight gain where the P value was not provided. And reproductive toxicity results, we have the atrophic changes in various organs, including testes, was described, where the P values are not provided either.

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DR. MORAN: In the second study, by Terrill et al. in '77, 32 male and female rats per group were exposed

by inhalation to phenyl glycidyl ether at 1, 5, and 12 ppm for six hours a day for five days a week for 90 days.

The endpoints were daily physical inspection, weighed twice a week; sections of testes, prostate, ovary, uterus, mammary gland, among other tissues were fixed and examined by histology.

And they found no adverse effects on systemic toxicity, and no significant changes in histological examination of relevant reproductive tissues.

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DR. MORAN: In the first study by Terrill in '77, the same protocol as previous study in rats, but in this study six male dogs were exposed by inhalation to phenyl glycidyl ether at 1, 5, 12 ppm for six hours a day for five days a week for 90 days. In this study also were no adverse effects on systemic toxicity and no significant changes in histological examinations of relevant reproductive tissues.

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DR. MORAN: In this report -- in this report, there are two studies: A two-generation of rat reproduction and dominant lethal, teratogenic study by Terrill et al. in 1982. The dominant lethal study was flagged in HID as considered invalid by the U.S. EPA. In the first study, eight males per group were exposed to PGE

by inhalation at 0, 2, 6, and 11 ppm for six hours a day for 19 consecutive days. Three untreated females were used for mating for six weeks.

Depending on the number of pregnant females -- females per male, one-third to a half of the females had autopsy GD 18, gestational day 18; two-thirds allowed to deliver and F1 raised to weaning. Then, 20 males and 40 females per group per week, plus any abnormal pups were raised to 12 weeks. From these, eight males were mated to 24 females per group per week, mate normal and abnormal also.

Finally, the F2 raise to five weeks and killed for examination, discard F1 parents, and preserve abnormal F1 and F2 for examination.

The endpoints were: Fertility parameters; on gestational day 18 gross examination of uterine content and fetuses in some, one-third to one-half of the pregnant rats as explained, corpora lutea, implantation and resorptions; gross pathology on rest of the females at gestational day 23, if they did not conceive, and F1 males and females of 12 weeks post weaning; histopathology on testes of the F0 males.

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DR. MORAN: The results are for systemic toxicity, there were no increase in mortality on the F0.

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DR. MORAN: In the dominant -- yeah, 30. For the dominant lethal study by Terrill in '82 for the reproductive toxicity, there were no increase in resorptions; no differences in number and survival of pups; lower number of pregnant females in week 1 and 11 with P of 0.05; low fertility indices in F1 and F2a in all groups including controls; no evidence of dominant lethal response.

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DR. MORAN: This second study by Terrill et al. '82, 25 females rat per group -- are we on this slide?

Yes.

Twenty-five females per group were exposed by inhalation to PGE at 0, 1, 5, 12 ppm for six hours a day from gestational day four to gestational day 15.

The endpoints assessed at autopsy on gestational day 20: Fetal body weight and length; number of implantations; live fetuses and resorptions; fetuses were fixed for examination of skeletal and soft tissue examination.

The results are summarized as no changes in clinical science or body weight of dams compared to controls.

And for the offspring we have: No changes in

number of implantations, fetuses and resorptions; and fetuses had similar length and weight, and all appeared normal upon gross examination.

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DR. MORAN: That concludes the phenyl glycidyl ether presentation.

CHAIRPERSON GOLD: Thank you very much. So we now are open for public comments on phenyl glycidyl ether.

Any comments from the public?

Hearing none.

We'll turn to Committee discussion, and Dr. Nazmi is going to start us off.

COMMITTEE MEMBER NAZMI: Thank you. Thanks, Dr. Moran for that very thorough overview.

I'd like to being with the Terrill 1982 study. And, of course, there's one serious and I'd say intractable problem with this study and that was the fact that it was invalidated -- at least a part of it was invalidated by the U.S. EPA. And, in my opinion, that brings into question the entire study. But even the other proportion that was not considered and invalidated, due to the falsification of the data by the laboratory, did not indicate any developmental or toxic -- reproductive toxicological effects.

The other study from 1977, there was one finding.

They indicated referring to atrophic changes in the testes. Although, no further details were provided, as you mentioned, so it's very difficult to interpret. Besides that, no other systemic -- no other reproductive toxic findings were reported, and essentially no systemic toxicity findings either.

So in light of that, I'd say we can conclude that there are relatively weak indication of any default mental or reproductive toxicant effects.

CHAIRPERSON GOLD: Thank you.

Dr. Rocca, anything further to add?

COMMITTEE MEMBER ROCCA: I must say that I agree, since all the reproductive endpoints were invalidated for the second study, even though there was no reproductive toxicity. We really can't judge that accurately.

And the first set of studies, which were the subchronic studies, I also think show no signs of reproductive toxicity.

CHAIRPERSON GOLD: Thank you.

Any further comments by the rest of the Committee regarding phenyl glycidyl ether?

Are we ready to vote?

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Gold, did you ask for public comments?

CHAIRPERSON GOLD: I did.

CHIEF COUNSEL MONAHAN-CUMMINGS: She did?

CHAIRPERSON GOLD: I did.

CHIEF COUNSEL MONAHAN-CUMMINGS: Oh, I'm so sorry. I missed it.

DIRECTOR ALEXEEFF: No public comments.

CHAIRPERSON GOLD: Right, I asked?

DIRECTOR ALEXEEFF: Yes.

CHAIRPERSON GOLD: Okay. But it's always good to check me. Thank you.

Okay. So for the vote. Has phenyl glycidyl ether 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: I see six.

And no abstentions.

Has phenyl glycidyl ether 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 zero.

If you believe no, please raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: Six, and no abstentions.

And finally, has phenyl glycidyl ether been clearly shown through scientifically valid testing, accord to generally accepted principles to cause male reproductive toxicity? If you believe yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see zero.

If you believe no, please raise you hand?

(Hands raised.)

CHAIRPERSON GOLD: Thank you. Six, and no abstentions.

And so we're unanimous again that phenyl glycidyl ether has not been shown to produce developmental, female reproductive or male reproductive toxicity.

Very good.

So, Dr. Moran, we will call on you again to do the summary of the first ketone, methyl n-butyl ketone.

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DR. MORAN: Thank you. So Mike.

So we'll start with methyl n-butyl ketone, MnBK,

where a comprehensive literature search resulted in three references with data on the potential reproductive toxicity of methyl n-butyl ketone in rats.

In a developmental neurotoxicity study by Peters et al. in 1981, 25 female rats per group were exposed by inhalation to MBK at 0, 500, 1,000 or 2,000 ppm for six hours a day from gestational day zero to gestational day 20.

The endpoints were: Daily maternal weight; pregnancy outcome at birth, post-natal day two behavior observation, post-natal developmental indices at weeks four, eight, 12 and month 18 to 20 gross and histopathology and behavioral test battery.

Ages tested were newborn, weanling, puberty, adult, and geriatric.

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DR. MORAN: For developmental -- in the study we have for parental results decreased maternal weight gain at 1,000 ppm, about 10 percent, and 2,000 ppm at about 14 percent of decreased maternal weight gain. Clinical signs at 2,000 ppm, hair loss, incoordination statistics were not given.

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DR. MORAN: For the offspring they found that decreased litter size -- Sorry. For the offsprings they

found decreased litter size and birth weight at 2,000 ppm; decreased postnatal and adult weight in males at 1,000 and 2,000 ppm; grip strength, maze latency, activity at 1,000 and 2,000 ppm, male and/or female at least at one age of the -- age considered; pentobarbital increased sleeping time at 2,000 males at puberty; decrease testes weight in weanlings; and ovarian cysts at 18 months.

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DR. MORAN: In this adult neurotoxicity study by Katz et al. 1980, five male rats were exposed by inhalation at 0 and 700 ppm for 72 hours a week for 81 days, two times 20 hours and two times 16 hours exposure periods per week.

The endpoints were body weight, clinical chemistry, gross and histopathology of various organs including the testes and neurotoxicity.

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DR. MORAN: All treated rats were killed at the time they developed hindlimb weakness: 34 exposure for the three rats and 42 exposures for two rats.

Systemic toxicity they have found that markedly reduced weight gain, decreased white cell counts at 31 exposures.

For reproductive toxicity we have decreased absolute and relative testes weights, atrophy of testes

germinal epithelium described where the data was not presented.

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DR. MORAN: Forty.

In this neurotoxicity study in male rats by Krasavage et al. in 1980, five animals per group were exposed by gavage at 0 and 660 milligrams per kilogram for five days a week for 90 days. The endpoints were body weight; for histopathology the testes and epididymides were fixed in 10 percent buffered formalin, embedded in paraffin and sectioned, stained with hematoxylin-eosin.

The neurotoxicity endpoint used to assess neuropathy was severe hindlimb weakness or paralysis exhibited by dragging a least one hind foot.

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DR. MORAN: The results are summarized here. We have reduced body weight gain, and for reproductive toxicity they described atrophy of the testicular germinal epithelium over 55-day period.

That concludes this chemical presentation.

Thank you.

CHAIRPERSON GOLD: Thank you very much.

So are there any public comments regarding methyl n-butyl ketone?

Hearing none.

I believe we're ready to move to the discussion by the Committee. And I've again ask Dr. Baskin to take the lead on this one.

COMMITTEE MEMBER BASKIN: Thank you. Outstanding summary. There's three papers that were in the literature. I'd like to turn your attention to the 1980 paper by Krasavage. And as presented elegantly by Dr. Moran, there is some concerning findings that were quantitated by histology in the paper showing testicular germinal epithelium. And there's two figures. One is a control and one is an experimental figure. And they look bad, at least the experimental one does.

The problem is is that there's no statistics. I don't really get a handle on how many animals. In fact, there's no way to know, at least in my reading. And we know that there were five animals per group, so it's hard to be able to hang your hat on that. Although, it is concerning when you see a picture like that. But without really any substantiating statistics, I'm having a hard time trying to, you know, move forward with any type of, you know, reliable science that I think we need to have. That's the 1980 paper.

There was some clear neurotoxicity that was shown, again not with fantastic statistics but with a picture of an animal whose not walking very well.

The 1991 -- or, I'm sorry, 1981 paper by Peters, there's -- the data really is -- it's an inhalation experiment. The data is not reported accurately to make any determination, and as pointed out, except that possibly the weight of the testes decreased.

And the 1980 paper by Katz, again looking at neurotoxicity, there's no histology shown and no statistics for the testes. Although, they report also decreased testicular weight and atrophy of testicular germinal epithelium. But I think without the statistics, it's again hard pressed to really make any definitive statement.

Thank you.

CHAIRPERSON GOLD: Thank you. Dr. Pessah, additional comments.

COMMITTEE MEMBER PESSAH: Yes. So I'm going to focus on the evidence for neurotoxicity. I don't have any additional comments about the reproductive toxicity. Dr. Baskin did a thorough job as did the presenter.

One of the concerns that I have is that this particular compound is metabolized through hexanedione, the 2,5. And that has been shown to be an neurotoxic agent at relatively reasonable exposure levels, both in terms of producing a peripheral neuropathy, as well as a few studies that have indicated that it's a central

neurotoxicant.

The peripheral neuropathy, depending on dose and time of exposure can be severe, but is reversible. The central effects are probably less reversible. And so based on several papers in the literature, and the implication of 2,5-hexanedione in the metabolism of MBK, I would say that there's sufficient evidence to suggest that it's a problem.

CHAIRPERSON GOLD: Just to clarify, a problem from a neurotoxicological --

COMMITTEE MEMBER PESSAH: Yes.

CHAIRPERSON GOLD: So -- but if we have to vote on reproductive toxicity and developmental toxicity, do you have any comments relevant to that?

COMMITTEE MEMBER PESSAH: That's a little tougher. There is some indication that neonatal behavior is affected, but I think the data is a little less strong on that. There's not a lot of data on that, that I've seen anyways.

COMMITTEE MEMBER WOODRUFF: Can I ask a question.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Did you -- this first study by Peters this is a developmental neurotox study. Does that -- is that part of the things that you were talking about in terms of your -- I mean, even though it's

a -- it could be a neurotoxicant, could that implicate it for developmental neurotoxicity, because I was looking at the food maze behavior results, did you -- I just wondered if you had a comment on those?

COMMITTEE MEMBER BASKIN: I think we need some clarification on what we mean by neurotoxicity versus developmental toxicity, because I kind of equate them. I mean, if you can't walk on your hind legs, you have developmental problems, and I don't know if --

COMMITTEE MEMBER WOODRUFF: Well, I think that --

COMMITTEE MEMBER BASKIN: You know, how -- I mean, I would like some clarification on that or how we're supposed to deal with that?

COMMITTEE MEMBER WOODRUFF: Well, I mean one option is that I would be concerned if something was a neurotoxicant that it would also be a developmental neurotoxicant. So meaning that if you had the exposures during development, it would impair neurological development.

CHAIRPERSON GOLD: I think the question before us is do we have evidence that when it's given during pregnancy, is it a developmental neurotoxicant? So I'd invite the Committee to comment on that.

Dr. Rocca.

COMMITTEE MEMBER ROCCA: Yes, it was indeed given

to the females during the entire pregnancy period. There was severe maternal weight loss at the 1,000 and 2,000 parts per million. And unfortunately, all the 500 part per million group had to be terminated because of technical issues.

One of the things that's missing from this paper, which surprises me from the NIEHS, but this is 1981, is that they did not use body weight as a covariate for any of their statistics. That we know that the mothers had severe weight loss. And in the high dose, they lost 14 percent, and that's despite pair feeding of one of the control groups. So they had -- there were very sick animals. And we know from lots of other data that many of these other things that you would see, in terms of activity and grip strength and all those sorts of things are highly correlated with body weight.

And since we don't have any body weight as a covariate, I don't find that there's anything here that we can say is a toxin in that paper.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah, I -- it looks -- what is the definition of severe weight loss for you? Because I'm looking at the numbers, and -- I mean, they have some weight loss in 1,000 ppm, but at day -- gestational day 20, it looks like 10 percent in the 1,000

ppm, and for the 2,000 ppm it's down to 13. Is that severe to you?

COMMITTEE MEMBER ROCCA: Yes, for pregnant animals it is.

COMMITTEE MEMBER WOODRUFF: But that would be considered a reproductive effect then, right, if we have weight loss during pregnancy? I think it's a listed as one of the --

COMMITTEE MEMBER ROCCA: No. In this case, this is systemic toxicity of the mother, and I would not consider that to be reproductive toxicant.

COMMITTEE MEMBER WOODRUFF: Um-hmm. But in our list of sufficient evidence in experimental animals, consideration of maternal and systemic toxicity is in here.

I mean, I guess I think that if you have weight loss during pregnancy -- I know this has come up before -- that if a chemical is causing weight loss during pregnancy, I as a -- you know, looking at humans, that would be concerning to me. So I wouldn't -- I think if that's a concern for this chemical, then we should consider that as an endpoint.

DR. DONALD: Just to clarify, in case there any confusion, the reported result was not weight loss. It was a reduction in weight gain during pregnancy. And even

weight loss during pregnancy is recognized by regulatory guidelines is not necessarily a basis for discounting developmental effects. The degree of reduction in maternal weight gain, of course, is a factor that you have to, you know, individually take into account. Whether or not it's considered severe is probably open to debate.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: Two things here. I think we've lost sight of the fact that there is known mechanisms that cause neuronal damage by the parent, and most likely by the metabolite, the major metabolite, of this compound.

Second, the behavioral studies they did were very blunt instruments. I bet if -- I would predict that if they had done finer behavioral studies, they would have seen what would be clearly outcomes that were developmental outcomes.

CHAIRPERSON GOLD: Referring to the offspring.

COMMITTEE MEMBER PESSAH: In the offspring, yes.

CHAIRPERSON GOLD: Right.

Other comments?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: I mean, so one of the issues, they didn't do the studies, I mean, like we would have done them now. So we just have to take the available

data. But I'm going to then re-ask the question, because I am suspicious from the data present. And I'm concerned to vote positive for a neurotoxicity issue with this -- I don't see any reproductive toxicities, but can I equate that with a developmental problem? Because that's what we're really supposed to vote on, not specifically neurotoxicity.

COMMITTEE MEMBER PESSAH: Well, what you have to go on is this one study and some human assessments that were in the fact sheet that was provided here.

COMMITTEE MEMBER BASKIN: Yeah.

COMMITTEE MEMBER PESSAH: And they did see essentially that in the young offspring after developmental exposure that there was hyperexcitability, again scored in a very rough manner. That there was no numbers on it as we would do it today. And that there were other types of behavioral anomalies, again without really systematic analysis of behavior.

COMMITTEE MEMBER BASKIN: And along those lines, there's very impressive histology of neuronal degeneration on the axons. But again, like the testicular histology, if I'm reading this right, there's no statistics. In other words, they're not -- they didn't show the numbers that had -- compared to controls.

COMMITTEE MEMBER PESSAH: They didn't.

CHAIRPERSON GOLD: So I would just remind the Committee that what we're going to vote on is if they've used scientifically valid methods, and through those clearly shown developmental toxicity or reproductive toxicity. So could I invite you to comment sort of on the scientific soundness on whether you're clearly convinced?

Yes.

DR. ZEISE: I don't know if this would be helpful, but one of the options -- Hi. I'm Lauren Zeise. I am with OEHHA, Deputy Director for Scientific Affairs.

This is an NIEHS study. There is the possibility that we could provide you with more information on it. One of the options you have is to defer, if you'd like to see more information on a study. So I just put that out there as an option for you.

COMMITTEE MEMBER WOODRUFF: Can I ask a question?

CHAIRPERSON GOLD: Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: You mean the Peters study is an NIEHS study?

DR. ZEISE: (Nods head.)

COMMITTEE MEMBER WOODRUFF: So there's an underlying -- whatever that document that they put together for that might have more information, because there is some information here that's not -- like in the table on the food maze behavior, they don't have the

results for the -- all the doses, so...

COMMITTEE MEMBER ROCCA: They didn't do the test at all times?

COMMITTEE MEMBER WOODRUFF: Yeah, but would we be able to see more of that in the underlying documentation, you think? Have you guys looked at it?

DR. ZEISE: Well, we didn't have it in front of us, and that's why it's not discussed in the report. But if it would be helpful, we could go back to NIEHS, see if they have the individual data, see if we could run the statistics, and give you more information to make a decision on what is available, if we dig a little bit more.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: Again, I really would like to see that data based on what we know about how this chemical acts as a neurodegenerative agent.

CHAIRPERSON GOLD: Okay. So are we maybe suggesting then we'd like to defer and request from NIEHS more information on sort of a complete set of outcomes, the timing of those, the dosages for those, and the statistics that go along with them?

Anything else?

COMMITTEE MEMBER WOODRUFF: That's good.

COMMITTEE MEMBER BASKIN: This is from 1981.

CHAIRPERSON GOLD: Yeah, so there's a risk they won't have it.

DR. ZEISE: Yes, there is a risk.

CHAIRPERSON GOLD: In which case, it will come back to us with the same information we have right now.

(Laughter.)

CHAIRPERSON GOLD: But there's a chance, you know, that they keep really good records for long periods of time and they can get back to us and respond. So is that what we would prefer to do is to defer for that information?

I'm getting a general sense of yes?

Yes. Yes. Couldn't hurt.

COMMITTEE MEMBER WOODRUFF: Yes.

CHAIRPERSON GOLD: Okay. So that's what we'll do. We will not vote on this one right now.

COMMITTEE MEMBER BASKIN: For clarification, are we asking for more information related to everything or to reproductive or to neurotoxicity?

CHAIRPERSON GOLD: Well, it's the Committee's pleasure, but I think we should ask for things that are directly related to what we have to vote on. And so that would be developmental toxicity that could be in the form of neurotoxicity, but also anything additional on male or female reproductive toxicity if they have it. Is that

okay?

DIRECTOR ALEXEEFF: So I was going to ask if staff wanted to provide a clarification regarding the question that Dr. Baskin has trying to sort out the issue of neurotoxicity and how that plays out into the evaluation of reproductive toxicity overall? Maybe you could just clarify that for him.

COMMITTEE MEMBER BASKIN: Or developmental, I mean.

DR. DONALD: In someways that's two different questions. This, of course, was specifically a neurobehavioral developmental study. The exposure was during the prenatal development period. One of the criteria for conducting such a study is that there's some evidence that the chemical causes neurotoxicity in adults, but the intent of the study is, of course, to look specifically at the sensitivity of the developing organism to the neurotoxic agent. As was pointed out, in most instances, we would -- well, the reason for doing the study is that there's a high likelihood that there will be sensitivity during the developmental period.

With regard to neurotoxicity itself, it may well be a contributing factor in reproductive function. We know, of course, that the pituitary hypothalamic gonadal access is very important in reproduction. There may well

be aspects of neurotoxicity that have direct or indirect effects on reproductive toxicity.

But we would generally only consider evidence that those effects are occurring as relevant to reproductive toxicity as opposed to general evidence of neurotoxicity that was not directly or indirectly related to a reproductive outcome.

COMMITTEE MEMBER ROCCA: So that I have this correct, my understanding from what you said, is that if we have an effect if they were exposed during development, that then when they're tested later on as adolescent and adults, there is still an effect, then that would be considered a developmental effect?

DR. DONALD: That's absolutely correct.

COMMITTEE MEMBER ROCCA: So this doesn't have to do with whether if you give juveniles a neurotoxin you see effects, correct?

DR. DONALD: Well, for purposes of Proposition 65, that's correct. Normally, in neurobehavioral developmental studies, the exposure can continue postnatally into the postnatal period, but it happens in this case that the exposure was limited just to the prenatal period, which actually makes a simpler issue for the Committee.

CHAIRPERSON GOLD: Dr. Zeise.

DR. ZEISE: If it would help the Committee, we could layout this issue of the relationship between developmental toxicity and maternal toxicity in a little bit more detail at the next meeting.

CHAIRPERSON GOLD: I think that would be helpful, but I also have a question of whether you're clear on what our request is for NIEHS or do you need any further clarification?

DR. DONALD: It -- I guess I would paraphrase it and say that you would like us to find any additional relevant data that can be gleaned from the study that NIEHS did, is that about correct?

CHAIRPERSON GOLD: Well, that's certainly true, but if they need specifics, like if they can only dig up certain things, I think we're interested in dosage effect levels, and timing of those, and whether then they're developmentally related or not, and any statistical tests that they could run that maybe they have somewhere or they could run, if they don't have them already.

Dr. Baskin, did you want to say something?

COMMITTEE MEMBER BASKIN: Yeah, I have two points. So when you walk around a hospital or a children's hospital, there's typically a neurodevelopment department or clinic, and that's where the confusion lies with me. I kind of equate them as similar. If you have a

neuro issue that's going to affect your development? And I see that in patients all the time. So that's where, if indeed we found that from a neurotoxicity point of view there was concerns here based on the science, can I vote yes in the development column? Because that's where I'm asked to vote. And I kind of think yes is the answer, but I need guidance there.

The second point I want to make is I don't want to create a slippery slope on every paper that we're not happy with we ask for more data. I think that's the wrong thing to do. I thought we were supposed to evaluate this on the data that's available presently. So I don't want to create massive amounts of work, and we could essentially table every chemical. So I think we have to be a little careful here.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah, I wouldn't say we're tabling every chemical, because we just voted on -- well, how many did we vote on? Four, three. Thank you.

So, I mean, I think this one is -- I mean, I think what would be useful actually in these is when you have an NIEHS study, just generally going forward, is that -- I don't know. Do you normally go to NIEHS and say can you give us the underlying data? I don't know what your standard practice is?

DR. ZEISE: We typically don't do that. In this particular case -- for -- well, let me step back. On the cancer side, NIEHS maintains individual animal data. And if there is a question, we'll get that individual animal data and look. That's been our practice on the cancer side.

On the developmental and reproductive toxicity side, we're not -- there aren't as many studies, so we really haven't developed a practice around going to NIEHS, but -- so I think in this case, why don't we try, see what we find. If there are data -- individual animal data, we actually can do the statistics ourselves as well. So I don't see this as a large amount of work.

COMMITTEE MEMBER WOODRUFF: Well, I would just say generally that -- because I think there's often issues with limitations in terms of what you can publish in a paper online that there won't be all the underlying data in order to do all the statistics we might want to evaluate, that I would say going forward if there are papers that are published that NIEHS studies, that the -- just like you're doing for cancer, that the underlying data are collected from NIEHS and then evaluated, because I -- I know with the one we're going to be discussing next, having the individual animal data for me was very helpful, because I could like go back and basically grab

things and look at them. And you can't really get that necessarily from these published papers, because they aren't allowed to include all that information all the time in the papers.

DR. ZEISE: And you'll see at the next meeting, you have a pesticide in front of you, and the registrant has given us -- or given you the studies. So you have all the individual animals for those submitted studies.

CHAIRPERSON GOLD: I would say in the context of, you know, being concerned about overburdening the staff and these -- in these requests, I mean we can be judicious about them, but I think as the Committee is reading things, if they see things that maybe actually might exist that would be helpful, maybe we can transfer those requests to even ahead of time, if that would be helpful.

DR. ZEISE: Yes, you can certainly do that.

CHAIRPERSON GOLD: I mean, this is really at least the first one in recent memory that I can think of where we're asking for additional information. So it's not like we've been sort of going overboard on that, but -- okay. So the plan is to defer this for additional information from NIEHS, if they can provide it. And if not, you'll come back to us and we'll try and do our best to vote intelligently at that point.

Dr. McDonald(sic) you look like you had something

you wanted to say -- is that, no?

DR. DONALD: For what it's worth, I was just going to tell the Committee that it's not unprecedented. We have had other chemicals in the past which have been deferred for similar reasons. And we have gone back to authors of reports to ask for additional information.

CHAIRPERSON GOLD: Right. I do recall that, but I think this Committee has not done a lot of that. And so in terms of a burden, I think at least so far we haven't caused a major burden.

Okay. So we will defer that one and we will move on to methyl isopropyl ketone. And Dr. Moran is going to start us off with that.

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DR. MORAN: I hope you will like my accent by the end of the day.

(Laughter.)

DR. MORAN: Okay. We're ready. Number 42.

So a comprehensive literature search resulted in one reference with data on the potential reproductive toxicity of methyl isopropyl ketone in rats. In addition to this, we are presenting a summary of data from a guideline study submitted during the comment period. This report was made available in full to the Committee members and posted on the OEHHA webpage.

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DR. MORAN: This is a reproductive and developmental toxicity screening study by Bernard in 2001, where 12 males and 12 female rats were exposed by inhalation at 0, 1, 2.5, and 5 milligrams per liter -- there's a small mistake in the handout. It says per ml. It's milligrams per liter, the concentration -- for six hours a day, seven days a week, from two weeks premating to gestational day 19. Necropsy on day 51 for females and gestational day 23 for not delivering pregnant females or days four to six post-partum gestational day.

The endpoints analyzed were systemic toxicity, including body weight, food consumption; fertility; sperm parameters, epididymal number, morphology and motility; pregnancy outcome, postnatal growth and mortality on postnatal day zero to four.

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DR. MORAN: The systemic toxicity is summarized here. There was a decreased paternal food intake and body weight at 1 milligram per liter; decreased maternal food intake premating and first week of gestation at all doses; decreased maternal body weight second premating week and last week of pregnancy; maternal clinical signs during exposure.

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DR. MORAN: There was no reported reproductive toxicity. Body weights, reproductive organs -- yeah. For the offsprings result we have the body weights, reproductive organ weights, sperm motility, epididymal spermatozoan counts, and testicular sperm counts were comparable among the groups.

For offsprings we have that it was also reported we have decreased number of live pups on postnatal day zero and four at 5 milligrams per liter; increased number of dead pups on postnatal day zero at 2.5 milligrams per liter; increased pups dying on postnatal day zero to four at 5 milligrams per liter.

It was also reported that there was a significant decrease in litter weight at 5 milligrams per liter. This difference disappear when a single litter with four pups in the high dose group was not considered for the statistic analysis -- statistical analysis.

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DR. MORAN: This is a report that was made available to OEHHA during the comment period. It is developmental toxicity study in rats by Edwards in 2012. In this study, 25 pregnant rats were exposed by inhalation at 0, 300, 750, and 1,500 ppm for six hours a day, seven days a week from gestational day zero to gestational day 19, necropsy on gestational day 20. It's good to note

that this concentration range is comparable to the one used in the screening study by Bernard in 2001.

The endpoints were record clinical observations, body weight, and food consumption; laparohysterectomy on gestational day 20; uteri, placentae, and ovaries were examined, number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded.

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DR. MORAN: There was a decrease in food intake and body weight gain at 750 and 1,500 ppm. And for reproductive toxicity, it was reported as significant reduction in fetal body weight at 750 ppm with a similar but not significant decrease at 1,500 ppm. There was also non-significant effect on fetal survival.

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DR. MORAN: That concludes this presentation.

CHAIRPERSON GOLD: Thank you very much.

We now have time for public comments.

Thank you. Dennis Naas. I believe the podium is over here and you have five minutes.

MR. NAAS: Thank you. My name is Dennis Naas. I'm an independent toxicology consultant with 35 years of experience. I am here representing Eastman Chemical Company in their petition to delist methyl isopropyl ketone as a developmental toxicant from Prop 65.

A recent ECGIH assessment in 2011, and the subsequent Prop 65 listing in February of 2012 didn't consider this new study, the data that was just presented. It's important to point out, I think, that this study is very recent. It was completed in 2012 just about two years ago. It was a very powerful study. It was done in compliance with OECD and EPA test guidances, as well as the good laboratory practices for both here and Europe. And it was also, I'll note, done at a highly reputable laboratory with a great deal of expertise in both developmental toxicity and inhalation toxicity.

This study had -- oh, and it did not -- this particular study did not address reproductive toxicity. It's a developmental toxicity study. The definitive developmental toxicity study that we're talking about now, the new one, was very powerful because of its size. There's an N of 25 in each group. This allows very robust assessments of the littering data, and it also included detailed assessments of the offspring. This would be external examinations, fetal -- excuse me, internal exams, viscerals and also skeletal examinations. So this is all -- it's a very robust guideline compliance study.

And in our opinion, the study did not cause any developmental toxicity. There was that small difference in fetal body weight, which was only seen a the mid

exposure level and not at the high level, but there were no -- there was no evidence of developmental toxicity in this study. And on the basis of this study, we feel that MIPK should be delisted.

Thanks for your time.

CHAIRPERSON GOLD: Thank you.

Any questions?

COMMITTEE MEMBER WOODRUFF: Yeah, I have a question.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Why wasn't the study available when you guys were doing your review?

MR. NAAS: It's not published.

COMMITTEE MEMBER WOODRUFF: Oh.

CHAIRPERSON GOLD: Other questions?

COMMITTEE MEMBER WOODRUFF: Is it publicly available otherwise before this?

MR. NAAS: I don't believe so, no. It was a privately contracted study by Eastman Chemical.

COMMITTEE MEMBER WOODRUFF: I see. So just generally, could there be other studies that companies have on these chemicals that we don't know about?

DR. DONALD: Basically, we know about what we know about. There certainly may be studies of which we're unaware. That's one of the reasons why we invite public

comment on the process, so that parties who are aware of additional data can make them available to the Committee. But this study did not show up in our searches, which we made as comprehensive as we were able.

CHAIRPERSON GOLD: I mean, I guess I'd point out the plus of such efforts is that we see papers that haven't been published. That's also the downside. They haven't been subjected to peer review, in terms of the publication process. So we get more information, but it hasn't undergone review.

MR. NAAS: It is however a GLP compliant study.

CHAIRPERSON GOLD: Yeah. Okay. Thank you.

All right. So, Dr. Pessah, is going to lead the Committee off with some discussion of this.

COMMITTEE MEMBER PESSAH: Sure. Thank you for the presenters for a very nice job presenting the information. So based on what we do know, it seems that the female exposure developmental study between GD zero and 19 was adequately powered. And as far as the information that I had access to, there seems to be really very little to no evidence that there's developmental effects with relatively high exposure levels of methyl isopropyl ketone.

With respect to the male exposure study, which is a little less powered, it seems that the major effects, if

I'm reading -- if I went into the report correctly, were associated with lack of weight gain, and so systemic stressors that probably were not related to developmental outcomes.

So based on these two studies, I would say there isn't compelling evidence.

CHAIRPERSON GOLD: Okay. Dr. Woodruff next.

COMMITTEE MEMBER WOODRUFF: Yeah. I agree that the way the summaries are presented may -- I think they don't give a complete picture of all the information that's in the actual document. So I went through -- mostly because when we first got the studies -- well, actually let me just back up and say, when we first got the information about the summary, we had one study to evaluate.

And so I started with this study. And I'll just remind everyone, the things that I like about these studies is they both have the same dose groups, so that's very useful. The GLP generally, they're a little bit -- they're done later in time, so we have a little more confidence in the methodological, and there's good information presented about the methods.

The 2001 study actually reports individual information on each of the dams, and there -- from what they have for their litters. I only had summary

information from the one that was given out -- that was given to us during the public comment period.

I will note that the first study, the 2001 study, actually follows the animals pre-conception, during conception, during pregnancy, and follows the animals after they're born. The study that was done -- the second study that we were given only followed the animals after gestation, from gestation days zero to 19, and then did not follow the animals -- actually, they did not actually -- the animals weren't born. They killed the animals and then looked at the fetuses.

So those are important distinctions I think between the two studies. The reason I decided to look further into these studies is that if you'll note in the 2001 study, and as was presented, there is a decrease in the number of live births and an increase in the number in dead pups, which I know -- and those were actually postnatal days. So that's actually an independent finding from the second study, because they didn't follow the animals postnatal. We only have what the fetuses were when they were sacrificed.

So then my -- I went back and looked at some of the underlying data, because what we don't have in here is reported is some of the information about post-implantation loss, which is actually they're reported

both in the 2001 and the 2012 study. Also, the number of implants, which is indicative reproductive compromise or fetal viability, also reported in the -- both -- reported in both the 2001 and the 2012 study.

So the nice thing about that is that it gives us some information about -- both -- two different studies with different numbers of animals over the same dose range. And just to -- so then if you look at the actual data in the back that's in the charts and you compare them, so in the 2001 study, there is actually a decline -- or an increase in post-implantation loss starting with the control as it starts at a mean across the groups of two and goes up to 2.8, 2.5, and 8.2. So even though the highest group is significantly -- is higher, you see a trend. And if you run a regression line, it's significant.

And the thing that was pretty interesting was also in the Eastman study, you see increases in post-implantation loss. The control group is 4.5 and it goes up to 6.5. So you actually see a pretty similar increase across both the studies for post-implantation loss, which gives -- raises concern for me that this chemical is -- you're getting a dose response for exposure for post-implantation loss.

Also, you see a decline in -- I mean, the live

births and the percent of viable fetuses is slightly different, but in the Bernard -- in the 2001 study, as was said, the percent of live births actually in the control group is 98 percent and declines to 92, and then 92 percent in the highest dose group, so it's 98, 96, 93, and 92.

And in the Eastman, starts off the control group is 95, so a similar -- that's viable fetuses, very similar to what we're seeing in the Bernard study, and also it goes down 95.3, 94.3, and 93.5. So again, we're seeing a decline in percent either viable fetuses or percent live birth across the dose groups in both the studies.

Now, I know there is -- we did see in the 2001 study some decline in maternal body weight at the highest dose group. I think that that leads to some concern about potential effects on the female -- as the pregnant female, which I think is -- actually should be a concern, in terms of viability of the pregnancy, if there's effects on the pregnant dam.

So for these reasons, there's actually even -- if you start to read this even a little bit more, there's actually some -- also data in the Eastman on resorption as well as number of implants. And the number of implants also declines across the dose groups for both of the studies. So for these reasons, I think there is a concern

about this chemical.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: I have a question, because I didn't actually analyze. So the question is are the trends significant as you look over time and is there a dose effect?

COMMITTEE MEMBER WOODRUFF: Oh, there's definitely a dose effect. You definitely see a change over the dose range. If you combine them -- when I ran a regression line -- you know, it's a percent. So I ran a regression, yes, you did see a significant in the coefficient, if you adjust by the variance, because it's not completely fair to do that without adjusting by the variance, you still get a somewhat significant effect. I think the P value was -- it was less than -- I'd have to go back, but it was definitely -- depending it was somewhere -- sometimes the P value was not -- well, that was just for one of the studies. That was 0.07 or 0.0 -- less than 0.05.

So, I mean, I think the thing that was -- I didn't do, which I think would be very advantageous is because we have the same endpoint across both studies, is to actually combine the data and do an analysis of them statistically, which I'm sure because they were less than 0.1, the regression lines, that you would -- together they

would be significant.

COMMITTEE MEMBER PESSAH: Can you do that if one was a male exposure and the other was a female exposure?

COMMITTEE MEMBER WOODRUFF: Well, just looked at the -- I looked at the -- oh, I see what you're saying. This was all -- these were all pregnancy exposures though.

MR. NAAS: Does the public have an opportunity to respond?

COMMITTEE MEMBER WOODRUFF: The public is closed.

COMMITTEE MEMBER ROCCA: Question about how you handled your statistics. Was this done on the means or by the litter with the standard deviations?

COMMITTEE MEMBER WOODRUFF: Right. So the challenge is, is that for the Eastman study, the data is reported only on the means, and so -- but, we don't -- so that's one of the -- so I would actually -- in some ways, that makes the study less useful than the 2001 study, which we have all complete data, so -- and I would also caveat that there were significant findings, as you report here, for the live pups from the analysis.

And not all the endpoints were analyzed in this way. Sometimes they're analyzed just by looking at individual comparisons to the control group. And I really think that we should be looking at comparisons of trends, because that's not as powerful a statistical test if we're

just looking at each of the dose groups compared to the control, rather than looking at the dose response across all the doses.

COMMITTEE MEMBER ROCCA: All the individual data is in Appendix F, I believe it is. So I was able to look at some of that.

COMMITTEE MEMBER WOODRUFF: And for -- yeah, for the 2001 study.

COMMITTEE MEMBER ROCCA: No, for the Eastman.

COMMITTEE MEMBER WOODRUFF: Oh, for the Eastman study.

COMMITTEE MEMBER ROCCA: Yeah, it's there. Yeah, the complete GLP study report is there. It's just not easy to find it sometimes in these very large studies.

COMMITTEE MEMBER WOODRUFF: Oh.

COMMITTEE MEMBER ROCCA: So I'm on page 222 to get to some of that data. And that may be what it is, is that it's reported differently.

Can I make one other comment?

CHAIRPERSON GOLD: Yeah, Dr. Rocca.

COMMITTEE MEMBER ROCCA: One of the things that's nice about seeing these two is that they are indeed at the same doses, and they did treat all during pregnancy. One of the big differences is that they were allowed to deliver in the first study and not in the second. But

there is a reason that you do developmental toxicology studies the way you do, in that you intentionally do not allow them to deliver, because what you're finding out is the totality of the uterine contents.

When you allow the females to deliver, and they are only counting pups when they first find the litter, what you'll frequently find is that if there have been any deaths, that they will have cannibalized the pups. And so it's possible that you saw something that was postnatal that --

COMMITTEE MEMBER WOODRUFF: I agree. And I actually checked on the viable fetus data from Eastman, which shows the percent of viable fetuses, like you're saying, which -- well, first of all, actually, they didn't say there was any cannibalization in the 2001 study, so --

COMMITTEE MEMBER ROCCA: Well, they wouldn't know, is the issue with that design.

COMMITTEE MEMBER WOODRUFF: Well -- anyway, the viable fetus percent starts at 95.5, goes 95.3, 94.3, 93.5. So we're seeing a decline across the dose groups in viable fetuses. And I would just point out that it's interesting because the viable -- I did look like at -- that's like, hmm, that's pretty interesting. And to look at the viable fetuses and you compare it to the percent of live births, which is in the 2001 study, and actually the

viable fetuses you have a lower percentage. So, for example, in the control group in the Eastman study it's 95 percent are viable fetuses. You have 98 percent live births in the control group. In the 2001 study, they're uniformly a little bit -- they're about the same as in the Eastman study, so it gives me more confidence that the cannibalization is not actually occurring, because otherwise you'd expect a lot lower in this 2001 study under that theory, I would think.

CHAIRPERSON GOLD: Any further Committee comments?

Did you want to respond?

MR. NAAS: I did, if I could, please.

CHAIRPERSON GOLD: Take two minutes. Can you come up here.

MR. NAAS: Thank you very much.

I'm thank you for finding the individual data. I knew it was there. These reports are required all to have individual data.

Maternal toxicity, I just want to address that very quickly. I think most of the Committee is aware that that is required to occur on a valid developmental toxicity study. And the presence -- there's numerous -- enumerable papers out there that we can't use the presence of maternal toxicity to dismiss a developmental effect.

We're not really allowed to do that, but we're required to show the maternal toxicity. Otherwise, the studies aren't considered valid, unless you go to some very high limit test type exposures.

It is important that these studies are different. The first study is a 421 -- OECD 421 screening study. The group size is only an N of 8. It does incorporate the two-week premating period, the entire gestational period, at which point it ends. That is very different from the other study, which was just the exposures only occurred during gestation. So I think any attempt to combine those data would be invalid because of the differences in the design.

And the other thing that's a very, very important point, and perhaps someone -- I was trying to check this. These laboratories keep exquisite historical control of databases. They're very specific for the strain of the animal, the age, and the laboratory. And they periodically -- I mean, they get changed.

So trying kind of to compare a 2000 study to a 2012 study, you might be talking apples and pears, but I would suggest -- I believe that in the recent study you will find the historical data have been appended to that report. And these minor differences in implantation rates are -- they're not statistically significant in a study

that's powered to detect those statistical differences.

And without seeing the data, I'm willing to state that those are within the historical ranges of the control animals. So I just kind of wanted to throw those out there. Thank you.

CHAIRPERSON GOLD: Thank you. So, Dr. Pessah, did you want to respond to anything to Dr. Woodruff said before we vote?

COMMITTEE MEMBER PESSAH: No.

CHAIRPERSON GOLD: Okay. Are we ready to vote?

COMMITTEE MEMBER WOODRUFF: I would say --

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: -- I do agree that they have different design features. So, you know, that -- and in some ways, we have more exposure -- we have more exposure data in the 2001 study. I just was struck though by how we see a very similar change in the parameters related to reproduction in both the studies -- across, what's really great is you have, the same dose range.

So I think that gives us -- well, it gives me more confidence in what we're seeing in terms of these -- some of these effects that were not really highlighted in the summary. So I think that's the other thing about the study that I just wanted to point out is I think it would

be very useful in the future to -- I mean, obviously, what the authors are saying about their summary is important, but I think it would be also good to dig into some of these other endpoints, that I would not have actually really dug into, unless I had seen the fetal deaths. That made me go back and look at the implantation and resorption data. And I think that would have been -- having more of a summary on that for this Committee would have been very useful for me.

CHAIRPERSON GOLD: Any further comments from the Committee?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: So you kind of brought up -- thank you.

So if this decline, this trend is within the -- within the limits of the strain age that --

COMMITTEE MEMBER WOODRUFF: Yeah, I --

COMMITTEE MEMBER PESSAH: -- and you're seeing this go across studies, would it suggest that we're missing information on the older study that says those declines are within what's expected for the strain?

COMMITTEE MEMBER WOODRUFF: Right. I agree that if they -- we didn't -- I think that's an issue for if that was -- we did not see a dose response. What makes me -- right, because you have in your historical -- if

these rats have a certain amount of post-implantation loss or fetal viability issues, those are always going to be -- that's going to be your baseline within your control.

But if you're seeing a change in that across the dose range from the control, then even though they're still historical -- or that's something that is a percentage of you see in the animals, even a change from that would be considered an effect. Does that make sense?

COMMITTEE MEMBER PESSAH: Right, but what's the range of the trend from high to low?

COMMITTEE MEMBER WOODRUFF: Well, the range is it depends on -- it goes from --

COMMITTEE MEMBER PESSAH: I think you --

COMMITTEE MEMBER WOODRUFF: What?

COMMITTEE MEMBER PESSAH: I think you stated it, but I forget.

COMMITTEE MEMBER WOODRUFF: It depends on -- the percent loss is anywhere from five to ten percent -- I think it's nine -- it's around eight is the high. The live births start at like anywhere from 90 -- it was 96 to 98 and go down to somewhere around 90 to 92. So you're seeing like a 10 percent change.

I would say I agree that there's -- you know, there's going to be noise in this, and that there's some

issues related to potential for changes among the historical controls. I think what we also have to think about is are we seeing a consistent finding among different endpoints? So whether there's viability in the fetuses, mortality among the infant -- of the pups when they're born, then was there an issue with post-implantation loss? So that's kind of in the spectrum. And then was there an issue with implantation?

So I agree if it was just one endpoint, that would be -- I'd be like, "Oh, okay. Well, that's just one thing". But we're seeing kind of along the spectrum of issues related to viability of the fetus a number of different outcomes that are trending in the same direction.

So I think that, you're right, it's -- we can't just let one study or one dose. Okay, but when I look at these different endpoints and look across them and they're related, it adds strength to the evidence.

CHAIRPERSON GOLD: Any other comments from the Committee?

Are we ready to vote?

Okay. So the question is has methyl isopropyl ketone been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? All those of who believe

yes, please raise your hand?

(No hands raised.)

COMMITTEE MEMBER ROCCA: Developmental, right?

CHAIRPERSON GOLD: I said development, yes.

CHAIRPERSON GOLD: I see no yeses.

Those who believe no?

(Hands raised.)

CHAIRPERSON GOLD: Five.

Abstain?

(Hand raised.)

CHAIRPERSON GOLD: One.

Okay. Has methyl isopropyl ketone been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? All those who believe yes, please raise your hand.

(Hand raised.)

CHAIRPERSON GOLD: One.

Those who believe no?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three.

Those who abstain?

(Hands raised.)

CHAIRPERSON GOLD: Two of us.

Okay. Has methyl isopropyl ketone 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: Zero.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Six.

No abstentions.

Okay. So for developmental toxicity, we have five out of the six voting no. And for female reproductive toxicity we have one yes, three noes, and two abstentions. And for male toxicity, we are in agreement unanimously of all voting no.

Okay. Given the relative lateness of the hour, the need for taking a break, et cetera. I'm going to recommend that we take a lunch break at this time. Perhaps reconvene about 1:15/1:20, if that seems reasonable for people, and take up the remainder of the agenda then.

Thank you.

(off record: 12:35 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: 1:21 PM)

DIRECTOR ALEXEEFF: Okay. We're going to bring the meeting back to order here. Here's Dr. Gold.

CHAIRPERSON GOLD: Okay. I think we're all reconvened. And so we're going to ask Dr. Moran one last time to make the staff presentation for alpha-methyl styrene.

--o0o--

DR. MORAN: Thank you. Good afternoon.

A comprehensive literature search resulted in two references with data on the potential reproductive toxicity of alpha-methyl styrene in rats and mice.

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DR. MORAN: This is a developmental toxicity study by Hardin et al. in 1981, where 15 -- 10 to 15 inseminated female rats per group were exposed to AMS by intraperitoneal injection at 0 or 250 milligrams per kilo from gestational day one to gestational day 15. Animals were sacrificed on gestational day 21.

And the endpoints were: Gross examination of internal organs, brain, heart, lungs, liver, spleen, kidneys, adrenals, and ovaries weighed and preserved for histopathological examination.

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DR. MORAN: Okay. For the offsprings endpoint, they considered weight, measured for crown-rump length, sexed, and examined for externally visible malformations. One half to two-thirds of each litter used for internal examination. The rest of each litter preserved in ethanol for skeletal staining.

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DR. MORAN: For the parents results, we have the no treatment-related weight changes, no histopathological changes. And for the offspring results, it was a significantly increased incidence of fetal resorptions, P was 0.05, altered fetal sex ratio with a deficit of female fetuses.

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DR. MORAN: In a three-months inhalation exposure study in mice and rats by NTP in 2007, ten animals per sex per group were exposed at 0, 75, 150, 300, 600, and 1,000 ppm for six hours a day, five days a week, for 14 weeks.

The endpoints were body weight, initially, weekly, and at the end of the studies. At the end of the three months and on the three higher doses epidiymal sperm concentrations and motility, cauda epididymis and testis weights, and vaginal cytology for the last 12 days were considered.

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DR. MORAN: And the results for mice were that five to 15 percent decrease in body weight significant in both genders at 300, 600, and 1,000 ppm. For the reproductive toxicity they found a decreased cauda epidiymal weight at 600 and 1,000 ppm with a P of less than 0.05. No effect on other reproductive endpoints. Longer estrous cycles at 600 and 1,000 ppm from 3.9 days in the control group versus 4.8 and 5.2 respectively, both of them significant.

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DR. MORAN: There were no effects on body weight. Kidney toxicity were observed in 300 ppm or greater for males and from 600 ppm for females. For reproductive toxicity results there were no observable adverse reproductive effects reported in treated rats of either sex.

--o0o--

DR. MORAN: That concludes the presentation. Thank you.

CHAIRPERSON GOLD: Thank you. Dr. Rocca, will you take the lead on this please.

COMMITTEE MEMBER ROCCA: Yes, thank you.

CHAIRPERSON GOLD: Oh, sorry. No.

Public comments? Are there public comments?

Okay. Now Dr. Rocca.

COMMITTEE MEMBER ROCCA: Thank you for that review as well. The first study that was noted was the one in 2007 where the route of administration was intraperitoneal. So this one really is not relevant to human exposure. However, they still found that there was almost no toxicity. The only reproductive toxicity that they showed is one plus mark in one table for increased fetal resorptions, but there are no data to go along with this, and this is an I.P. study.

For the second where we have the chronic inhalation study for three months, they looked at the effects on organ weight, sperm parameters, and histology of reproductive organs. There they did have systemic tox of body weight loss at the top three doses. However, there were no effects on any of them on sperm parameters or histology of testis or ovaries.

The only result that they did have for that one was that they found a decrease in the weight of the left testis. However, if you look in the organ weight data, and look up the right testis, there was no difference. So I think it's one of those very small changes that probably does not make biological sense here.

So I think based on the data that we have here, I would not call this a reproductive toxicant.

CHAIRPERSON GOLD: Thank you. The only thing I

would add to that was the increased estrous cycling length that they showed which was a significant difference. It's a relatively small study. It's one study in one animal, and so I think I would not feel that I could conclusively state that there was a reproductive effect, but as they say, it's suggestive.

COMMITTEE MEMBER ROCCA: Yes. Thank you for bringing that up. I did miss that.

COMMITTEE MEMBER ROCCA: They did this for 12 consecutive days, and in the footnotes, it says several of the animals had unclear cycles. So I think that they didn't even do three complete cycles in these animals. And if they were unclear and they included those, then in the analyses it makes it really difficult to interpret. So I agree.

CHAIRPERSON GOLD: Thank you for that point.

Is there any further discussion among the Committee on alpha-methyl styrene?

Questions, comments?

Are we ready to vote?

Okay. So has alpha-methyl styrene been shown clearly 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 none.

If you believe no, raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see six.

No abstentions.

Has alpha-methyl styrene 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: Zero.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Six.

And no abstentions.

And finally, has alpha-methyl styrene 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: I see zero.

If you believe no?

(Hands raised.)

CHAIRPERSON GOLD: Six.

And no abstentions.

So the committee is unanimous on voting no for developmental, female reproductive and male reproductive toxicity for alpha-methyl styrene.

So thank you all. That concludes our discussions and votes about specific chemicals that we needed to reconsider under the Labor Code listing. And so we'll now move to the next agenda item.

And I actually have a couple of introductory comments to make before we engage in this discussion. It seemed like it would be helpful in the purposes of background and to provide some focus to this discussion to give just a very brief sort of summary of where we were and what initiated this process.

So let me say -- so I have several points. The first is that the public comments that we received and that OEHHA received concerning the tables for the animal and epidemiology studies were collated and were distributed to the DART Committee for them to review and consider in today's discussion. And specifically by way of providing some focus to this discussion, I want to briefly review the origin of these tables and this discussion.

Originally, over a year ago, some Committee members had suggested -- had made some suggestions for

improving the summary table for animal toxicology studies, which is one of the tables under discussion today. We have two. Then about a year ago, OEHHA asked for similar input regarding the table summarizing epidemiologic studies and a draft was provided, which is the other table that we'll discuss today.

These tables were meant to be summary tables, always accompanying the original papers on each chemical that the Committee reviews, and generally accompanying the text that OEHHA staff provides to the Committee.

So these summary tables were not meant to replace the text that OEHHA has generally provided to the Committee, nor to replace the Committee members' reviews of each of the original data papers for each of the chemicals as you've heard we do today. They were just intended to be summary tables to highlight the methodologic approaches and results in each paper, so as to facilitate the Committee's review.

This point may have been lost a little bit in the last couple of meetings because we've just focused on the reexamination of the chemicals that were originally listed under the Labor Code in the hazard identification documents to determine if they should still be listed, and no text accompanied those tables for this purpose. Although, we did receive the original papers.

However, it is intended that for consideration of new chemical listings that will be coming before us, that the text will accompany -- the summary texts will accompany the summary tables and Committee members, of course, will be provided with the original data papers for them to review, each of them critically.

So we are aware that -- also that several national and other groups and agencies, including committees of the National Academy of Sciences and the National Toxicology Program and others are reviewing and considering systematic reviews for weight of the evidence, evaluations for chemicals, and for ways to present data in tables to assist in these reviews, but no final accepted formats have been agreed upon for these reviews for developmental and reproductive toxicity.

So in conclusion, the purpose of today's study is not to vote on the tables, but rather for the Committee to provide input to the OEHHA staff as to what would be most helpful to us as a Committee for them to summarize for us, so that we can make our decisions based on the materials that we received to review on the topic, and all of the -- and that the Committee members will use all of their experience in critically reviewing published papers to draw their conclusions and to provide this guidance.

So we are providing -- so we're here today in

this piece of the discussion to provide guidance to the OEHHA staff. Again, the summary tables are not intended to replace the text that OEHHA staff generally provide for each paper on each chemical nor to replace Committee member's own reviews of those papers. The tables are meant to be helpful to the Committee, so the Committee should be sure to give their input today, as to what would be helpful to them to have included in the tables by OEHHA.

And I think that concludes my sort of general introductory comments. I just wanted to put everything in context and try and focus the discussion a little bit.

Okay. At this point, I invite public comments on this topic of the animal and epidemiologic summary tables. Again, I'll reiterate we did receive public comments. The Committee has received them. They were collated by OEHHA and given to -- staff and given to us, and so we've reviewed those.

And I see no further comments?

Okay. So then I open it up to the Committee and I have not appointed any one person, because this is an open-Committee discussion for this purpose. So I invite comments of the Committee to advise OEHHA on these tables.

Dr. Baskin.

COMMITTEE MEMBER BASKIN: I like the tables you

provide presently. I think they're extremely helpful. And a few additions would be -- I'm not a statistician, you know, epidemiology expert, but we're all kind of required now to give kind of a -- when we see a paper, you know, is this a five star paper or a one star paper, you know, perspective, you know, double blinded, you know, control study versus a case report, so to speak. And in the scientific literature, it's done like that too.

So I don't know if I'm an advocate for like, you know, a rating of whether this is a good paper or not, because I think that's very subjective and maybe going down the wrong road, but I would like to see a little more detail about, you know, power analysis statistics, and maybe more right-hand column.

I think now Dr. Moran's presentation today, and in the tables, you know, it's listed no statistics or some statistics, but maybe just a little more embellishment in that area.

CHAIRPERSON GOLD: Thank you.

Anyone else?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I like having the tables. I think the tables are new, right, relatively?

CHAIRPERSON GOLD: No, I think we've always had tables.

COMMITTEE MEMBER WOODRUFF: I mean before this meeting.

CHAIRPERSON GOLD: They've just been slightly modified recently. Yeah, but there have always been summary tables.

COMMITTEE MEMBER WOODRUFF: So I like the tables. I think we provided comments on the tables and the kinds of information that would be -- I think would be helpful to have in the tables to give a little more information, and because I know we're going to -- we've only actually really seen information for animal studies. Have we actually even evaluated any human studies? I don't even remember anymore if that's happened at any of our Committee meetings.

So -- and I think having information -- well, I'm not going to go over all the details of what we presented, but I think more information about the study -- about issues related to interpreting the study are useful. I think in terms of thinking about evaluating study quality, which I snow is a very actively discussed topic right now going on in environmental health, I know NTP has an approach and we have been looking at methods that have been applied by Cochrane and GRADE. And also EPA has been starting to look at this, as well as there are things going on internationally that if -- I would not do study

quality issues right now on this table, but it would be worth having a discussion about those different aspects, because it's pretty -- that is a whole field in itself, in terms of evaluating study quality and strength of evidence across all the different endpoints.

And I think we have discussed this, and I think it is -- would be very useful to have NTP come to do a presentation about how they're evolving in terms of their strength of evidence evaluations, so -- and their tables. And they have also been putting together a lot of tools for extracting study data and information to make it easier to see both things that are going on with the different methods in the studies, but also to have all the data available for the different endpoints, so that they can easily be graphed and evaluated.

For example, I do not actually think -- it's not really -- I actually do not like just reporting statistical significance in the study or not, because that actually does not give you the underlying information about the study, and it's evaluating the study basically on a finding. And it's better to have graphical information about outcomes, so that we can look across different studies across the same outcome, so...

CHAIRPERSON GOLD: Thank you. Others?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: So I really appreciate the tables. If I may make one technical suggestion. Instead of providing the primary literature as separate files, if you could just link them onto the table where you cite -- so, for example, I'm looking at Potter 2003, if you'd just make a soft link to PubMed or to the PDF, it would be so much easier. That can easily be done, I think.

CHAIRPERSON GOLD: We might have to be careful about PDF, depending on where people are, but -- a PDF would probably work, but PubMed may or may not, so depending.

Other comments?

You want to make a comment?

DIRECTOR ALEXEEFF: Yes. George Alexeeff.

Yeah, so we have been providing tables always from -- for years. And so this has been kind of a process to improve -- improve the information that the Panel receives in the tables. So we're constantly listening to the types of issues that the Panel members are identifying in papers, and the kind of things that they like to see. So we'll be continuing to do that, but I think this process has been helpful to us to hear, you know, what sort of things you look for.

I mean, it was -- I forget who actually said this

of the Panel members, or maybe I'm just paraphrasing a few Panel members, that basically they themselves were kind of making tables and -- of the data. And so if we can actually address that and make the kind of tables that the Panel can use to -- you know, to organize the data or to quickly glance or refresh their memory or to, you know, look at the data as whole, that's something we would like to accomplish.

So we'll just continue, you know, improving them. And if as comments -- as we continue to provide you tables -- and one of the reasons that one of the chemicals is delayed that we had thought of working on, chloroform, because it is a more complicated -- it has epi data and other data, and it's a much more complicated analysis, a bigger challenge in terms of addressing the table.

So my guess is when that chemical comes before the Panel, you may have some more ideas about tables as well, because that's a little more complicated one than some of these here where you only have three or four studies. It's not as difficult to -- especially when the studies don't have a lot of information, it's not too difficult to add a lot -- whatever they have, so -- but when the studies are much more complicated, that might be something that, you know, you can provide us advice on at that time, because there will be different types of

endpoints and information in those studies.

So we'll do our best to sort of figure out what's best for the -- what the Panel is looking for, but we're always open to improvement.

CHAIRPERSON GOLD: So it might be that when we review the chloroform, since you used that as an example, that we take a few minutes at the end to say how hopeful was this table? How could we tweak it to make it better?

DIRECTOR ALEXEEFF: Yeah, I think so. I haven't seen the tables myself, but that's the inclination -- the sensing I get from the staff, that it's a much more challenging chemical than the other ones we've seen thus far.

CHAIRPERSON GOLD: Okay. Dr. Woodruff, did you have another comment?

COMMITTEE MEMBER WOODRUFF: Yeah. Well, I think that we should have information about all the endpoints that are relevant and related. And there should be data -- one, it would be easier to group by endpoint. So endpoint and then have the studies, and then endpoint and then have the studies, rather than study and then endpoint, because then you're looking across studies for one endpoint.

And then I would have all the endpoints that are relevant to our discussions, so not just the ones that are

necessarily highlighted by the study authors.

CHAIRPERSON GOLD: So I would make a little caveat on that. And I think maybe this is a Rorschach test of who likes what. But the one caveat I would make is that I think it's important to list endpoints, whether they show a positive relationship or not, so that everything that was examined should be listed whether or not they found an association or a difference, because that's informative as well.

Yes.

COMMITTEE MEMBER WOODRUFF: Yeah, I agree. And also this DRAGON tool that NTP -- I think it's -- I don't know if EPA is involved with this too, but NTP has been putting together. It allows you to like get all the data from the studies, put it in, and then you can actually regraph them, so you get all -- a visual of all the information.

DIRECTOR ALEXEEFF: Yeah, we are looking at that tool --

COMMITTEE MEMBER WOODRUFF: Yeah, I know.

CHAIRPERSON GOLD: -- but we haven't actually used it in any report that we've prepared as far as I know.

DR. ZEISE: Well, that's another -- there are a variety of tools that are under development, and so we've

been looking at DRAGON at ICF/Clement, which is very interesting, but it isn't -- it's still in a state of flux, and actually they're -- we've been talking with them and they've been --

COMMITTEE MEMBER WOODRUFF: Oh, it is.

DR. ZEISE: Yeah, they're basically iterating the tool further. So that's under --

COMMITTEE MEMBER WOODRUFF: Oh. Okay. I got it.

DR. ZEISE: That's still under development. And there's another tool out of the University of North Carolina that also looks very good, but again, that's in a state of development. So we're following these tools and we're going to see how we should be adapting them as we go along to see how useful they are.

COMMITTEE MEMBER WOODRUFF: Um-hmm.

CHAIRPERSON GOLD: I mean, there's also the CONSORT tool. And then I think you wanted to use the -- so there are lots of tools around. And I don't think there's any one -- accepted one.

But you could even think about the analogy to meta-analysis data. And then, you know, the point estimates then, if you -- let's just say you had one for each endpoint. Are the size of those endpoints are determined by the size of the study? Which is an issue that we come up repetitively -- you know, in all these

animal studies, some of them are quite small. Some are sort of medium sized, and the point estimate ought to reflect that along with the confidence interval.

So that's jumping way ahead though. I'm not sure we're there yet.

Yeah, Isaac.

COMMITTEE MEMBER PESSAH: So there is something that came up today that really has me stumped about how to deal with. And that is when you presented proprietary information, I don't know, but up till now it's been generally negative information. In other words, not a lot of clear positive effects. That's okay, if that's all the information.

But we've heard that maybe there's other information that are not forthcoming. Can we at least get some indication of whether there's information that's being withheld as opposed to not being able to get all of the information?

CHAIRPERSON GOLD: Yeah, given that it's proprietary, I'm not so sure, but maybe Carol has something to say.

CHIEF COUNSEL MONAHAN-CUMMINGS: The short answer no.

We really rely on the folks that do the studies and the companies that pay for them to provide us with

what they feel is relevant information. But there's no way for us to know what studies are out there, unless somebody tells us, when they're not published.

DIRECTOR ALEXEEFF: But I would like to -- George Alexeeff -- comment that, you know, we've often received studies from organizations about chemicals. And they often have positive results as well as negative results. There's very -- really no distinction. These are -- at least the studies that we've seen are those that are required to be submitted for various things, such as, you know, pesticides, or maybe FDA or something like that.

So those studies are -- although they're not published, they're some place, and there's usually very -- there's no reluctance, or oftentimes -- let's just put it -- I'll just put it bluntly. Oftentimes, we've received reports and we've identified more endpoints than we previously had thought, so -- and so that's definitely there -- they're just providing us the information.

But if there's an in-house study that's not required for any particular purpose, then it's up to the -- you know, the people who own the study to decide, you know, if they even hear our call or request, and to submit it if they desire. There may be -- you know, a lot of these times, at least in people that I've spoken to, you know, the study was useful information for them to

proceed along their lines, but it may not meet the kinds of standards that they would have wanted for publishing or it wasn't meant for that. It was meant for them just to make a decision. And it was good enough for that, but not necessary for this Committee, and maybe they wouldn't want to release a study like that.

CHAIRPERSON GOLD: And I would just add that that goes beyond proprietary data. I mean, authors make their own choices about what they're going to submit for publication. And we know that there's publication bias, and the negative studies often don't get published. And we'll never, I don't think, hear about those.

Okay. Yes, public comment, for a couple of minutes.

DR. LAWYER: I'm Dr. Arthur Lawyer, Technology Sciences Group, Davis, California.

Just a comment to -- on the proprietary studies. I was involved in deltamethrin, which you might remember from last year and involved in the one coming up in your next meeting, chlorsulfuron. For those heavily regulated chemicals, such as pesticides or pharmaceuticals, and even the TSCA industrial chemicals if they're new -- let's take the pesticides. When there is a study done, whether or not they thought it was -- or it wasn't required or not, if there's an adverse effect found, they're actually

required under those various laws to submit them.

So for a pesticide, for example, something that everybody cares about, there are laws about adverse effect reporting, and those databases, in fact, are available. They're not as easy as Medline and such, but they are available to us. And this staff is very, very good at finding those studies.

But to George's comment, often, you know, it's in everybody's interest to report them, but I just wanted to make sure you understood that the -- there's very -- it's very difficult in the heavily regulated chemicals to withhold anything that would be a positive finding. I thought that might help.

CHAIRPERSON GOLD: Thank you.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. That's very true for the pesticides. So for a lot of TSCA chemicals we just aren't going to know if they have them. And the chemical that was spilled in West Virginia, those studies came out six days after the spill. So I just think we -- unless you have a legal authority, we're not necessarily going to know whether we have those studies or not.

DR. LAWYER: I'm with you. Thank you.

CHAIRPERSON GOLD: Okay. One further public comment.

MR. SHESTEK: Thank you. Good afternoon. Tim Shestek with the American Chemistry Council. Just kind of a question and also a comment. We were one of the organizations that did submit comments. I was curious, what sort of the next steps, in terms of dialogue, that we might have with OEHHA staff or this Committee as this issue goes forward? I wanted to just let folks know that we're certainly available. And there are technical folks that did put together our comments. I'd be more than happy to try to answer questions or engage with OEHHA staff as this moves forward. So thank you.

CHAIRPERSON GOLD: Well, we appreciate the efforts. As I said, we've all seen them. OEHHA staff has seen them. I think they're reviewing them in their considerations of how the tables might be revised or made more helpful. I assume if they have questions, they'll contact you.

Good enough. Okay. Anything further on this?

All right.

So we have a couple of final issues. One is the update on Section 27000, list of chemicals which have not been adequately tested as required. Who's making this presentation?

Carol.

Oh, yeah, it says Carol.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. This has to do with some more chemicals that I can't pronounce. As you may recall, I think that you've done this once before as this particular group of members of the Committee. There's a second list that's required under Prop 65, a list of chemicals that I don't know who uses this list, but it's mandatory under the law for us to maintain the list and for you to opine on taking chemicals on and off of it.

The criteria is that these are chemicals that -- where the government has requested testing or required testing on the chemicals, and those have not been completed, whatever the tests are.

There's different kinds of testing that's required. And I think that in your materials you've got some examples of what those might be in terms of endpoints and different kind of testing requirements for both cancer and reproductive toxicity. So once a year generally we give you the two different things to vote on.

One is chemicals that should be added to this list, because the U.S. EPA or Department of Pesticide Regulation are requesting studies be done, and the second job is to confirm that we should remove certain chemicals

from the list, because U.S. EPA or DPR have verified that the testing has been done.

So it's kind of an odd thing for you, because you're just really deferring to U.S. EPA and DPR. We don't have other agencies that we are able to collect that information from, but under the law and the regulations, you're required to do this task, so -- and, you know, if in some -- in the perfect world we could, you know, amend Prop 65, which is virtually impossible, we would take this provision out, because, like I said, I don't know of anybody that uses the list. Maybe somebody does, but we never get inquiries on it.

So in any event we've got two slides here for you of chemicals that we're requesting that you add to the list. The first has been up for here a while -- as I mentioned, I'm not going to read off the chemicals. These were in your materials, so if you had a chance to look at them.

So there's two slides here.

--o0o--

CHIEF COUNSEL MONAHAN-CUMMINGS: The second slide of additional chemicals. And these are ones that we want to add to the list. So I don't know if, Dr. Gold, you want to ask for a vote on that before we get to the one about taking chemicals off the list.

Yes.

CHAIRPERSON GOLD: So these are actually to be listed or for us -- or for you to investigate for us to make a decision about what they --

CHAIRPERSON GOLD: No. These having nothing to do with the Prop 65 list that you work on normally. This is a separate list that's maintained under the law. That's in the Section 2700 of the -- of our regulation that, as I mentioned, I don't know what the purpose was at the time it was required.

CHAIRPERSON GOLD: So in other words, they're being listed because they haven't been adequately tested?

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

CHAIRPERSON GOLD: They're just going on a list of inadequately tested chemicals?

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct. And then periodically -- and we'll have a second group here, the two agencies let us know that they have received the tests and we can take them off.

CHAIRPERSON GOLD: I see. Okay. Yes, some questions.

Dr. Rocca.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Rocca.

COMMITTEE MEMBER ROCCA: Are any of the chemicals listed here currently listed under Proposition 65 as

causing reproductive toxicity?

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't know that. We don't compare the two lists.

COMMITTEE MEMBER ROCCA: Well, I think that would be important. If we say it's not adequately tested here, and we have another list that says it's a toxicant.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it kind of depends on what the testing that is required by the agency is. It's not necessarily -- they don't necessarily fit together. So, you know, in the event that we know that the chemicals have had some testing done, we can always follow up on those and find out if -- you know, that it's something that we should consider -- you should consider for listing or we should under the authoritative bodies, we can do that, but this is a -- it's not normally compared, the two lists.

CHAIRPERSON GOLD: This is unrelated to listing under Prop 65, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

CHAIRPERSON GOLD: This is just whether you're putting on our list that it says there hasn't been adequate testing.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. And, you know, just a -- you know, my somewhat educated guess of why it's in there in the first place is that when the

proposition was passed, the people said that they weren't getting enough information about exposures to chemicals that cause cancer or reproductive toxicity. And so one of the ways that they wanted to kind of put some pressure on the government would be to put out this list that says, you know, folks haven't done the testing that they're required to do. That's my guess, but I don't know that that has that effect. I doubt that U.S. EPA checks our list.

CHAIRPERSON GOLD: All right. First, Dr. Woodruff, then Dr. Pessah.

COMMITTEE MEMBER WOODRUFF: So are things that go onto this list only things that EPA is considering for testing or could we say -- could you add other things to the list? Is it a requirement that it has to be being considered by U.S. EPA?

CHIEF COUNSEL MONAHAN-CUMMINGS: It has to be a chemical that's being required to have testing by a State or federal government. So what we used to do is send out requests to a number of different federal agencies and ask them, you know, do you have any chemicals you think would qualify for this list. And the only folks that ever get back to us are U.S. EPA and Department of Pesticide Regulation. So that's why -- I mean, I would imagine that many of these have to do with pesticides.

COMMITTEE MEMBER WOODRUFF: Right. I guess I'm wondering is like -- so like we were -- some of the chemicals we were considering this morning, and it was like, well, I wish we had more data on this. Can you stick those on the list?

CHIEF COUNSEL MONAHAN-CUMMINGS: Not this one. No.

COMMITTEE MEMBER WOODRUFF: I see.

CHIEF COUNSEL MONAHAN-CUMMINGS: Although, you know, to the extent that we could mention to U.S. EPA it would be nice if we had some more testing. I mean, they're probably aware that the -- some of these chemicals need to be looked at again, but there's so many for everybody to look at, it's -- like I said, this is a very odd ministerial kind of act for this Committee.

CHAIRPERSON GOLD: Dr. Pessah, did you have something.

COMMITTEE MEMBER PESSAH: She actually answered one of my questions. How long is the list, at this point? Do we know? Just roughly.

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't have it in front of me.

COMMITTEE MEMBER PESSAH: Hundreds or thousands?

CHIEF COUNSEL MONAHAN-CUMMINGS: No, no, no. No, I would say it's probably not much more than 100.

COMMITTEE MEMBER PESSAH: Okay. And the list is found at the OEHHA website?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, you can get it on the website. I kind of was thinking that you had received it with your materials.

CHAIRPERSON GOLD: It is kind of buried, this list, but it is in there. It's in the 2700 --

COMMITTEE MEMBER PESSAH: Got it.

CHAIRPERSON GOLD: -- section, but towards the middle of it.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, towards the end there's this -- there's a document that says draft. And if you look at that, there's -- it shows where we were going to be adding and deleting from that list. And so you can see that it's not very long, not nearly as long as the Prop 65 list. We've got, what, 750 chemicals on that list. Except now, we're taking five of them off today.

So other questions?

COMMITTEE MEMBER PESSAH: No, that was it. Thank you.

CHAIRPERSON GOLD: Any other questions?

So we need to take a formal -- Dr. Baskin.

COMMITTEE MEMBER BASKIN: Are we just like signing onto it? I'm kind of getting the impression I'm

just -- I don't seem to have a lot of information. Is this like these chemicals could be bad, not be bad, and I'm --

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's not the determination you're making. So essentially, this is, what we call, ministerial where you don't really have much of a -- any discretion. And so -- and you are deferring to the two agencies that they -- that they know that they've asked for certain information, and they've either received it or not.

COMMITTEE MEMBER BASKIN: Okay. So --

CHIEF COUNSEL MONAHAN-CUMMINGS: So you're not really determining whether or not these are bad chemicals.

COMMITTEE MEMBER BASKIN: So other people who have looked at this carefully have decided that we don't have a lot of information.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think that U.S. EPA, for example, has a certain set of tests that they require for say new pesticides or other chemicals that are coming on the market. And so they have this set, and so they periodically will make sure that all of these -- the box has been checked that all of the tests have been done that they required. And then they use those to make their own decisions, which may or may not impact our Prop 65 list at some point, but...

CHAIRPERSON GOLD: So like if we had information that one of these chemicals had been extensively tested, we would vote against this? Is that another way of thinking about it?

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Although we could get back to U.S. EPA and say I don't know if you know this, but there's, you know, a number of tests that have already been done on this chemical and -- or whatever. I mean, we could do that for you as -- you know, to -- because we're staff for the Committee, but it's just an odd thing. I'm sorry, I can't explain it to you any further than that. It's -- you don't -- the actual phrasing in the statute just says that the Committee identifies the chemicals.

So I suppose that you could say something about, you know, that you think the U.S. EPA has the data, but I mean I don't know that that would have a lot of effect.

CHAIRPERSON GOLD: Right. No, I was just posing the question to try and get a handle on what it is we're trying to do here. And so if we knew that there were -- was extensive data, then we wouldn't vote in favor of putting it on this list. But in the absence of that, we can vote to put it on the list?

CHIEF COUNSEL MONAHAN-CUMMINGS: Pretty much, yeah. And, you know, it's not -- the data requirement comes from the federal or State agencies, right? And so they say the things that they want to see. And that's why, you know, the list has -- it looks different than the Prop 65 list because it's got a list of different kinds of tests that need to be done.

So, for example, they want a rabbit test or a mouse test or that sort of thing, a cancer test. And so that's under their requirements for whatever program they're considering the chemical under.

CHAIRPERSON GOLD: Dr. Woodruff, you have a question.

COMMITTEE MEMBER WOODRUFF: Yes. Then it could be that, you know, if there's a bunch of chemicals that we consider and we decide there's not enough information really to make a decision about their developmental or reproductive toxicity, could OEHHA send a note to EPA to that effect, so that then they can look and consider it about whether it goes into this queue of things that need testing information?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sure we could pass that along. I don't know what would happen to it --

COMMITTEE MEMBER WOODRUFF: Well, I don't know.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- after it gets to U.S. EPA, but we'd be happy to do that. I mean, I'm -- if you're familiar with any of these chemicals and you have concerns about them, then we'd be happy to let U.S. EPA know that or DPR.

COMMITTEE MEMBER WOODRUFF: Right. I mean, I think one of the things that's come up in our discussions is, "Oh, this chemical is used a lot", and we have no data on it, and then we can't vote to list it, but that doesn't mean it's safe, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

COMMITTEE MEMBER WOODRUFF: So I think that an outcome could be for the Committee is to say well, maybe this is one that should be passed along to EPA that should be considered for that -- whatever process they have to decide about testing.

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. These are only chemicals that are already -- there has to be a jurisdiction by the particular agency that says, you know, you can require certain information on say pesticides or toxics under the TRI program or other kinds of authorities.

And so say it's a food chemical, you know, we'd have to let FDA know that they should probably do some testing, but FDA doesn't give us information for this

list. So in any event, we can pass along the information from the Committee and say, you know, we've got -- here's some chemicals we considered, you know, on behalf of the Committee, and these are the ones, and it was not possible for the Committee to make an informed decision with no data. I mean, we could do that certainly.

CHAIRPERSON GOLD: What you're asking us to do right now is just to vote on whether these should be listed as having inadequate data?

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct. Inadequate data for the first two sets, and then one more slide has the ones that we can remove because they received it.

But just based on the conversation here, we could also, if you want to, point out chemicals that you want us to bring to the attention of these groups, we can do that too.

CHAIRPERSON GOLD: Okay. Well, why don't we take them one at time then.

So are we --

DIRECTOR ALEXEEFF: I have a question. So I was wondering, Carol, since I'm now asking you now in front of everybody -- but I should have asked you someplace else. But based upon this discussion here, I'm wondering if we're able to modify the motion in a way that basically

says this list of chemicals has been reported to us from U.S. EPA as being inadequately tested and meet the requirements of Section 27000?

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. Yeah, and I think that's kind of the finding we're asking for.

DIRECTOR ALEXEEFF: Okay. So we're just -- so that way they're not making the determination that it is inadequate, but they're just saying, yes, these are the chemicals that EPA has informed OEHHA.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. And that information is in your packet also, where we got the letters back from U.S. EPA and DPR saying this stuff. So essentially, what you're -- what you'd be voting on is are you willing to defer to them that these are the -- basically the chemicals that they would like to have put on and removed from this list? It's not an independent finding.

It's kind of like, as an analogy, we do these listings under the Labor Code that we talked about earlier. And essentially, we have to look at did this agency say that this chemical causes cancer, for example. And if they did, we have to put it on the list. If they've identified it, then we have to do that. We don't do independent scientific determination. We just list it.

And that's the way this law is set up. And so I

think that's probably -- the carry-over to this list is that, you know, we just want to know in one place what chemicals that people should be testing, for example, or that they have -- did you have something else?

COMMITTEE MEMBER PESSAH: So I was just wondering so these are specific chemical structures that -- I mean, the ones that you're presenting here are specific. But I'm looking on the list and you've got nicotine and derivatives. That's a pretty extensive list if you just say derivatives, because there are neonicotinoids and -- so how -- are we saying chemical by chemical or we can do classes of chemicals?

CHIEF COUNSEL MONAHAN-CUMMINGS: You can do classes, you can do combinations, you can do whatever is, you know, reported to us that needs to be on there. And, you know, since we're -- this list isn't a -- it doesn't have any impact in terms of warnings or discharges or any of that stuff. It really has no regulatory purpose, so that's all I can tell you.

CHAIRPERSON GOLD: So are we ready to vote on the ones that EPA -- that should put on their list as having inadequate testing?

Is the group ready to vote on that? I'm hearing that we have at least three things maybe to vote on. Yeah. Ms. Rocca.

COMMITTEE MEMBER ROCCA: I just wanted to be sure of the exact wording of what it is we're voting on.

CHAIRPERSON GOLD: So I'm going to ask Dr. Alexeeff to repeat his wording.

DIRECTOR ALEXEEFF: We should ask the stenographer to read it back.

CHAIRPERSON GOLD: We could do that too.

DIRECTOR ALEXEEFF: No. Let me just see if I can restate it, that --

CHIEF COUNSEL MONAHAN-CUMMINGS: George, do you want me to read it off from the statute?

DIRECTOR ALEXEEFF: Well, let's see what it says.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. It says, "On or before January 1989, and at least once per year thereafter, the Governor shall cause to be published a separate list of those chemicals that at the time of publication are required by State or federal law to have been tested for potential to cause cancer or reproductive toxicity, but that the State's qualified experts have not found to have been adequately tested as required".

Okay. So if you want to -- if you want to frame it as a voting question, I guess what we'd be saying is you as the State's qualified experts, do you find, based on the information you have from U.S. EPA, that these chemicals have not been adequately tested according to the

requirements of U.S. EPA?

COMMITTEE MEMBER ROCCA: I can vote on that.

CHAIRPERSON GOLD: Now, are we ready to vote?

Oh, No. Dr. Pessah, you have a question.

COMMITTEE MEMBER PESSAH: So are there criteria that we can refer to that U.S. EPA uses to deem them --

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

COMMITTEE MEMBER PESSAH: No. We just take their word for it.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

COMMITTEE MEMBER PESSAH: Okay.

CHAIRPERSON GOLD: And in essence, for this first thing, we're just voting on your first two slides, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct. So we're wanting to add these chemicals and the -- you know, the types of tests we don't have on, you know, the slide, but there are certain types of tests that U.S. EPA says that they need to have.

CHAIRPERSON GOLD: Okay. So is the group now ready to vote on whether these chemicals that have been listed on the first two slides that Carol has shown us have not been adequately tested as required by EPA?

Okay. All in favor of voting in that direction, please raise your hand?

(Hands raised.)

CHAIRPERSON GOLD: Okay. I have six and that would be zero noes and no abstentions.

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

CHAIRPERSON GOLD: So you want to take your second point?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. What -- let me just point out without trying to make this discussion too long is that also in your materials, there's a -- the copy of our actual regulation, the 2700, and it does go in a little bit more detail about what the various mandates are that DPR and the Environmental Protection Agency have, and what they're actually requiring them under, for example, the Birth Defect Prevention Act of 1984, the FIFRA, which is the Federal Insect Fungicide and Rodenticide Act, and that's for both U.S. EPA and CDPR, so -- and then, you know, there's some discussion of what a data gap -- what it might be, that sort of thing. So if that helps with the criteria question.

And then for this list that's up here now, there's one, two, three, four, five, six -- six chemicals here that either Department of Pesticide Regulation or U.S. EPA says that they now have the testing that they required for those chemicals. And so the question would be do you, based on the information that you have -- we've

received from U.S. EPA or CDPR, agree that we should remove these chemicals from the list of those that need to be tested?

CHAIRPERSON GOLD: Okay. So are there questions about this vote?

All right. Are we ready to vote?

Okay. So can we approve this list to be removed from the list of inadequately tested chemicals?

All those in favor aye?

(Hands raised.)

CHAIRPERSON GOLD: Six. So that would be zero noes and no abstentions.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

CHAIRPERSON GOLD: Do you have one more? Oh, well, the other one I guess relates to Dr. Woodruff. If there are questions about chemicals that we would like to add to EPA's list of things -- of chemicals that require additional testing or have been inadequately tested?

And the question is whether you want to take that up now, which we can spend a few minutes on, or we can think about it and come up with a list for next time. I'm -- whatever the Committee's pleasure.

COMMITTEE MEMBER WOODRUFF: I'm flexible about doing it, but I do think though that when we have these -- I mean, I think we should -- we could put on the agenda

for next time to look back over our -- all the previous chemicals we've looked at, because I would say almost in every situation if we didn't vote to list it, it was often because we didn't have information. And I think California should be telling EPA that those are chemicals that are inadequate and they should consider for testing.

CHIEF COUNSEL MONAHAN-CUMMINGS: That's fine.

CHAIRPERSON GOLD: So what I would suggest is for the agenda for the next time compile the list of chemicals that we've reviewed --

CHIEF COUNSEL MONAHAN-CUMMINGS: For what time frame?

CHAIRPERSON GOLD: -- re-reviewed under the Labor Code.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Good.

CHAIRPERSON GOLD: I would start there.

COMMITTEE MEMBER WOODRUFF: Not all. I think that's doable.

CHAIRPERSON GOLD: I think that's a manageable list. And the ones that we decided there wasn't enough information -- or at least it seemed there wasn't enough information, that would be a -- we could start with those.

COMMITTEE MEMBER WOODRUFF: That's fair.

CHAIRPERSON GOLD: Does that sound -- Dr. Rocca.

COMMITTEE MEMBER ROCCA: I have a practical

question about your list here. Your last chemical, maneb, it says it's been removed for reproductive toxicity, but remains on for teratogenicity. So will this be a chemical that should be coming before this Committee again, now that there's additional information?

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's the question we talked about earlier, of whether or not we compare -- whether we track these chemicals, I guess, Jim -- or do we normally compare this list to any of our others? I'm not sure you know that.

DR. DONALD: No, we don't generally directly compare this list to the list of chemicals either that -- the existing list of chemicals or our tracking database for chemicals that may become candidates for this Committee to look at, but we certainly could do that.

COMMITTEE MEMBER ROCCA: Yeah, I'm suggesting that this should be a candidate, since EPA says it's a teratogen.

DR. DONALD: Well, no, what EPA is saying is that it has not yet been adequately tested for teratogenicity, but they're now saying it has been adequately tested.

COMMITTEE MEMBER ROCCA: But there is reproductive toxicity data.

DR. DONALD: Yes.

COMMITTEE MEMBER ROCCA: Okay. Thank you.

CHAIRPERSON GOLD: I'm actually thinking since it's kind of fresh in our thinking, if we went over the list of chemicals that we did today, perhaps we could come up with a list that we think could be added to the list of that have inadequate -- inadequately tested, and then ask the staff to go back to November's meeting, since I -- I'll speak for myself -- can't remember those, and bring them before us, and then we can make a similar determination about those. Is that --

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

CHAIRPERSON GOLD: Okay. So just going back over the list -- are people up for this? Is this okay to take five minutes to do this?

Okay. So n-butyl glycidyl ether, we've all voted no for all three outcomes. Is that one we want to send to EPA to recommend that they put on their list as having been inadequately tested?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: According to the papers that we reviewed, there is no developmental toxicity information here.

CHAIRPERSON GOLD: And you would like some?

COMMITTEE MEMBER ROCCA: Not I, but --

(Laughter.)

CHAIRPERSON GOLD: You would like EPA to add it

to its list of chemicals for which they might want developmental toxicity --

COMMITTEE MEMBER ROCCA: Right. And I don't know what this chemical is regulated under. I just know that based upon what has been presented to us here, that I would say we all voted that it wasn't a developmental toxicant just because there was no data.

CHAIRPERSON GOLD: Right. So this seems like a good candidate. Anyone disagree with that?

COMMITTEE MEMBER NAZMI: Can I come back to Dr. Baskin's slippery --

CHAIRPERSON GOLD: Dr. Nazmi, please.

COMMITTEE MEMBER NAZMI: -- slippery slope ideal, because is it not quite feasible that we may vote that we would like more research and more studies to be conducted among nearly all of these chemicals that we're voting on?

CHAIRPERSON GOLD: And so does that mean we shouldn't indicate?

COMMITTEE MEMBER NAZMI: I'm opening it for discussion. I mean, at what point do we say well -- you know, when would it be bad to have more information and more research on a chemical? I guess that's the question. Why would we not want more?

CHAIRPERSON GOLD: Dr. Baskin.

COMMITTEE MEMBER BASKIN: I mean, I don't know a

lot about a lot of these chemicals. And my wife's a chemist, and she goes, "Wooh, you're looking at a chemical formula". And I go, "I am".

(Laughter.)

COMMITTEE MEMBER BASKIN: So I Google the chemical as part of my review. And I find out that New Jersey has a list of every single chemical I think in the workplace if you get splashed with it. It's kind of actually very practical.

And some of these chemicals are incredibly dangerous and nobody would touch them with a 10-foot pole. However, the reproductive toxicology and developmental toxicology there's either no information or the information we have says it's not dangerous. That doesn't mean the chemical is not dangerous, and shouldn't be used.

And so, I mean, I think we're reviewing this the best we can, but I try to remember that I think we're looking at a little microcosm sometimes. And so I kind of worry the same thoughts. I mean, you could take every single one of these and say we don't have any information.

For example, the one today that had incredible histology of a bad testes, but it was N of 1, I'd like more information on that. But economically, do we want to put every chemical on the list?

I mean, if we have some obvious chemical that

should go on the list, obviously. And I think when I first got on the Committee, we talked about like low-lying fruit. A lot of that has been chipped away and some of the stuff we're reviewing today is just because there's been legislation changes.

So I'm for safe chemicals and a safe environment like everybody, but I'm also for being practical. So I don't know. That seems like some of this needs to come down from above as opposed to filtering from us outward.

CHAIRPERSON GOLD: Yeah. I would just add that maybe we could put the caveat that from our perspective, we would like more reproductive toxicity and developmental toxicity information. What we have before us pertains to that, but is inadequate.

COMMITTEE MEMBER BASKIN: I mean, if somebody were to ask me what chemicals would be on the list, I would go at it a different way. I would say what are the most ubiquitous chemicals in the environment and we should throw our resources at them, as opposed to kind of the other way around.

CHAIRPERSON GOLD: I think those were the low-hanging fruit though.

(Laughter.)

CHAIRPERSON GOLD: But, Dr. Woodruff, you had a comment.

COMMITTEE MEMBER WOODRUFF: Yeah. I would just say that one of the challenges that we face in this Committee is that we don't have information about these chemicals. And I think, for me, to just say, oh, well, it's not a reproductive or developmental toxicant does not cover adequately the range of what we know -- what we might know about this chemical, because a lack of data does not mean it's not a problem. It just means we don't know.

And I do think if you're saying that these chemicals are being widely used in commerce, I think it is something that we should ask the Government or the companies to provide data on, because people are exposed to them.

So I -- if the list is very long, which it could very well be, I think that's fine, because this is -- we have to be concerned about what the public health issue is with this. And I feel very uncomfortable having to vote on all these chemicals where I have no data.

CHIEF COUNSEL MONAHAN-CUMMINGS: One thing I could -- sorry -- just clarify though, it's true that maybe the general public doesn't understand what it means to have a chemical on or off the list.

COMMITTEE MEMBER WOODRUFF: Right. I totally agree with you. I know that the criteria is different. I

just guess I'm saying is if we have the ability to ask, in some way, to say, yes, we agree that there's -- for whatever reason this is not developmental or reproductive toxicant, we agree that it shouldn't be listed, because, A, it's either been proven to be that, or B, because we have no data.

But I do think that it's something that if we have like some mechanism like this to be able to comment on no data, that we should provide that information, because I think it provides transparency to our process. And I'm not sure it's really -- that's, I think, makes the process more transparent, and I do not think it's our responsibility to -- you know, those kind of issues about how much the cost.

I would not want us -- if we're going to really talk about what the costs of these are, then I'd want us to have a fuller discussion about this, if that's going to be an issue in how we vote for this, because that concerns me that we're thinking about the cost to the -- doing the tests, but there's also a cost to the public, and that's -- well, A, that's seems beyond this Committee, but B, if that's a factor, then we should maybe take this up at another meeting.

CHAIRPERSON GOLD: Dr. Pessah, did you have a comment?

COMMITTEE MEMBER PESSAH: Well, just that we had a proof of principle here today with methyl n-butyl ketone. We, I think, decided that one should go out for more information before we could make a decision. But I think the whole point there is if you know the chemistry, and you know the metabolic route leads to a real baddy, and you want to err on the safe side if you don't have the information, you want the information.

So I view that as not a slippery slope, but a real scientifically based way to proceed. You know, mechanisms, metabolism, if the information isn't there for the parent compound that we're entertaining, but it is there for a metabolite, then we better know that we have all the information we need.

So that could be one criteria is, you know, what's known about how the chemistry of this compound goes and what the metabolism is and what the metabolites do?

CHAIRPERSON GOLD: Dr. Nazmi.

COMMITTEE MEMBER NAZMI: Completely agree with you. So you're referring to -- I guess, correct me if I'm wrong -- biological plausibility of the mechanism. Is that not going to be somewhat dependent on concentration? In, you know, industrial or in practical settings, it will be largely based on concentration or exposure or method of exposure, right?

COMMITTEE MEMBER PESSAH: Right. So again, I think for this particular compound, there is some very weak epidemiological data or workplace data that suggests people that are being exposed have ill effects. I saw that on one of the documents.

COMMITTEE MEMBER NAZMI: Right.

CHAIRPERSON GOLD: So I think going back to Dr. Woodruff's point, I'm not sure we should be afraid of telling them that there are chemicals out there that have sort of, you know, a hint of a concern, but inadequate data and getting those on the list, because I think that's how the science advances is that people see that we have data needs, in order to make policy decisions. And I personally don't see a problem with pushing that process along a little bit.

DIRECTOR ALEXEEFF: George Alexeeff. I have another suggestion to overlay on these, and that is that the criteria that we used to bring these lists to you has to do with, at this point, DPR, Department of Pesticide Regulation's and U.S. EPA's criteria for those chemicals for which they can request data for.

So possibly we should go back and come back to the Committee and let you know what were the categories of information. I think we can all guess for Department of Pesticide Regulation has to do with pesticides. So if a

pesticide came before this Committee, and we came across a situation and say, okay, we're telling you it's a pesticide and you're looking at the information. You're saying, "Boy, we wish we had more data".

Then the question is well, is it still a pesticide? Is it really still registered? And if so, then that would be definitely a reason to ask DPR to -- you need to look at this one again or -- and maybe the same thing with U.S. EPA. I don't exactly know what the actual statute is that they're required to report under, if it's TRI or others. But we could look at that and then we could report back to the Committee on that, and then we'd have some -- a narrower criteria if, as opposed to requesting U.S. EPA to -- that there's chemicals to be tested for which they have no authority to ask the test, except maybe under TSCA, which is actually kind of a high bar.

CHAIRPERSON GOLD: Dr. Rocca.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it is -- right now, it's TSCA for U.S. EPA and FIFRA. And that would be true for DPR, because they wouldn't be asking for information on anything but a pesticide.

COMMITTEE MEMBER ROCCA: Several comments. That clarification as well as some of the other comments have been persuasive to me that there is an authoritative body

here, in fact two of them, that that is their full-time job, and that probably we don't need to tell them that we want more data.

The other thing is before we would do that, I think it's important that we compare the list of chemicals to what is already considered to have adequate information or inadequate information. It could be that some of the chemicals we reviewed today have already been considered inadequate by the EPA or by Pesticide. So I think that we would want to do that before we would just come up with lists.

CHAIRPERSON GOLD: So we have two possibilities it seems to me. One is we could request the staff to tell us which among the chemicals that we've reviewed at this meeting and the prior meeting are already on the list as having inadequate data, and then we could review them at the next meeting and say we would like them listed, or we could just go ahead and say from the ones from today which ones we think have inadequate data are in need of more data, and suggest -- have the staff compare that to the existing list. And if they're not on there, to suggest to EPA that they should be listed.

So does the Committee have a preference for which way to go on this?

Dr. Rocca.

COMMITTEE MEMBER ROCCA: I would rather see the list first than have us debate something and then find out that it's moot.

CHAIRPERSON GOLD: It's already here.

COMMITTEE MEMBER ROCCA: Yeah.

CHAIRPERSON GOLD: Other people have thoughts?

COMMITTEE MEMBER WOODRUFF: Yeah. I think that that's fair. And then I think also, just thinking about some of the comments that people are raising about this, I think it actually -- it's something we might want to think a little bit more about, because I think for -- part of this is being able to comment on the adequacy of some of the data to make a decision.

And I'm not -- you know, if we decide, oh, there's not enough data, then we've kind of made a decision. So I think we need to think about that more carefully, so -- and I'm happy -- I think we should check the list and see if there's anything that's already underway, as a first step.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, one thing to point out is that you have the list -- the entire list of the chemicals that U.S. EPA and DPR have said they need more data on. And sometimes what we do is just take one of the tests off. We don't take the actual chemical off like, for example, this last one here the maneb with ETU,

would stay on for teratogenicity testing, but we're just taking off the little -- on the list, it's got the names of the types of tests that they want.

So if -- but if you just glance through here, there's only -- I mean, less -- maybe 75 chemicals on here at the most, and none of them, from what I can see, have been considered by this Committee, so -- but one of the -- one thing to also keep in mind is once U.S. EPA has enough of the test data, then one would presume that they would use that to make their decision under FIFRA or TSCA or whatever, and once they do that, then we would rely on U.S. EPA's decision and proposed listing of the chemical under an authoritative body listing mechanism.

So those are -- I just don't think you can compare these two lists and say, you know, there's -- you can take one and graft it onto the other as easily as it might appear.

But having said all that, what I would suggest is if you -- I can't remember if you voted on this second list about removing them, but in the event that you do that, and then what we could do for the next meeting is we can do a little bit more coherent presentation to you on what all of this does, and we can also contact U.S. EPA and DPR and see if they have a process whereby we could make some recommendations to them. So we could, you know,

maybe at the May meeting, if we had time.

CHAIRPERSON GOLD: Yeah, I think if you could get organized for the May meeting to give us a little more detail about these listing mechanisms, because personally I'm having trouble mapping these chemicals on these lists that are in our handouts. And so right away I have a discrepancy. And so that's number one is if we could get a little more clarity on the process than what's actually on the EPA list for being inadequately tested.

And then also, if the staff could take a look -- so we won't do it now -- at the chemicals that we looked at this time and last time and where we seem to suggest that, gee, it would have been nice to have more data, you know, put those in a list and we can consider them alongside the EPA list next time. Would that be possible?

CHIEF COUNSEL MONAHAN-CUMMINGS: We can do that, sure.

CHAIRPERSON GOLD: Okay. So do we still have something remaining to vote on? I'm --

CHIEF COUNSEL MONAHAN-CUMMINGS: Did you guys already vote on whether or not --

CHAIRPERSON GOLD: I think we did, yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- we should take these off?

COMMITTEE MEMBER WOODRUFF: Yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

CHAIRPERSON GOLD: I think we're done with this topic for today.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

CHAIRPERSON GOLD: All right. Let me get my agenda back out.

COMMITTEE MEMBER NAZMI: I'm sorry. Can I make one final comment?

CHAIRPERSON GOLD: Yes, please, Dr. Nazmi.

COMMITTEE MEMBER NAZMI: For the agenda item, perhaps for next meeting, if we can maybe more precisely define what we might mean by, it would be nice to have more data if we're going to develop some sort of a protocol or some sort of a process by which we determine, yes, this chemical for this reason requires us to have more data. That might just clarify how we want to approach that new list.

CHIEF COUNSEL MONAHAN-CUMMINGS: We could maybe give you some suggestions on that for you to discuss at the next meeting.

CHAIRPERSON GOLD: It occurs to me -- sorry.

CHIEF COUNSEL MONAHAN-CUMMINGS: And we'd be happy to hear from you all some suggestions for that, too. And we can just kind of put them together and put it as a discussion item.

COMMITTEE MEMBER NAZMI: Right. Sounds great.

CHAIRPERSON GOLD: I think things that we -- just as a first stab at that, things that we saw some suggestive evidence, but the evidence was really inadequate to make a definitive statement, that would be a good place to start for where having some additional data would be helpful. I'm sure there are other points that the Committee can think of, but that comes immediately to mind.

Okay. Now, are we done with this topic?

So we have staff updates next, is that correct?

DIRECTOR ALEXEEFF: I think we're done with staff updates. We have a general public comment.

CHAIRPERSON GOLD: Yes, I know okay. So no further staff comments beyond what we had this morning.

Okay. I understand there is a general public comment to be made?

CHIEF COUNSEL MONAHAN-CUMMINGS: The person left.

(Laughter.)

CHAIRPERSON GOLD: So we will have no general public comment today.

So Dr. Alexeeff is going to summarize our Committee actions, is that correct?

DIRECTOR ALEXEEFF: Okay. Well, I think before I summarize the Committee actions, I just wanted to announce

that, you know, this is -- unfortunately, this will be Dr. Rocca's last meeting on the Committee. And we're really sorry to see her go. She's actually contributed quite a bit to this process in the short time that she's been on the Committee. And I think that she's left a really good mark and a really high bar for anyone who wants to follow her.

And, you know, it's -- she's going to be reunited with her family on the east coast, and, you know, being transferred back there to the Philadelphia area, so that's wonderful for her. And, you know, if you know those east coast kind of little towns and things, it can be a wonderful place to live. And I'm sure she's going to be really happy there, even though, I mean, the south bay. I mean, you know, who could complain about that.

So we -- you know, we really appreciate all the work you've done, and I mean you've really done an incredible insightful job on almost every chemical, whether you are a leader or not. And I think everyone in the panel really appreciates the effort that you displayed in your tasks here. And we know that you have a lot of other things to do. And we, at OEHHA and with the State, really appreciate your service that you've offered to the State, because we realize that it's essentially, you know, a lot of work on your part that's not really being, you

know, compensated. So we really appreciate that.

I don't know if you had any parting comments?

COMMITTEE MEMBER ROCCA: Actually, I do, as long as you've brought it up. Yeah, I wanted to thank the staff for all the help that they have given us in preparing these materials, and in getting us all the extra materials that we asked them to find at the last minute. And I also want to say it's been an honor and a pleasure to serve on this Committee.

DIRECTOR ALEXEEFF: As we were thinking about Dr. Rocca, we're not really sure if we made an adequate statement that Dr. Hillary had to -- also had to leave the Committee due to being transferred out of state or having a new job out of state, Hillary Klonoff-Cohen. So consequently, we will be considering the need for additional members and such. But we also just wanted to make a mention that Dr. Klonoff-Cohen as well.

DIRECTOR ALEXEEFF: All right. Now, we're down to the summarization of actions here. So the Committee actually did a lot of things today, so I'm just going to summarize the actions.

The Committee considered -- well, let's say it this way. The Committee identified the following chemicals to be placed on the list of reproductive toxicity, based upon them -- well, actually, the Committee

considered a number of chemicals to be placed on the list and did not identify any to be placed on the list today, based upon clearly shown through scientifically valid testing, according to generally accepted principles. So the chemicals that the Committee considered were n-butyl glycidyl ether, phenyl glycidyl ether, diglycidyl ether, methyl isopropyl ketone, and alpha-methyl styrene. And the Committee also deferred an action on methyl n-butyl ketone.

The Committee also provided comments with regards to the tabulation of epidemiologic and animal data. And the Committee also added chemicals and deleted chemicals from the Section 27000 list of chemicals, which have not been adequately tested as required.

So I think that summarizes the actions of the Committee today.

CHAIRPERSON GOLD: Okay. Does the staff have anything else that they want to bring to our attention?

Public?

Committee?

So I want to thank the Committee for their hard work and diligence in reviewing all these materials and for the staff for preparing them and getting us all organized for this meeting. The work is greatly appreciated, and we will reconvene in May. So have a good

evening.

Thank you.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 2:42 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 1st day of April, 2014.

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