MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

BYRON SHER AUDITORIUM

SACRAMENTO, CALIFORNIA

MONDAY, MARCH 18, 2013

10:02 A.M.

TIFFANY C. KRAFT, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 12277

APPEARANCES

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.

Catherine VandeVoort, Ph.D.

Tracey Woodruff, Ph.D., MPH

STAFF:

Dr. George Alexeeff, Director

Ms. Carol Monahan-Cummings, Chief Counsel

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

Dr. Poorni Iyer, Staff Toxicologist

Dr. Melanie Marty, Assistant Deputy Director for Scientific Affairs

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

ALSO PRESENT:

Mr. Stanley W. Landfair, Bayer CropScience, LP

Dr. Jay Murray, Murray and Associates

Ms. Gretchen Lee Salter, Breast Cancer Fund

Dr. Larry Sheets, Bayer CropScience, LP

Ms. Andria Ventura, Clean Water Action

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PROCEEDINGS

DIRECTOR ALEXEEFF: I'm George Alexeeff. I'm going to go ahead and bring this meeting to order.

So here we are at the meeting of the Developmental and Reproductive Toxicant Identification Committee on Monday, March 18th.

Couple of just sort of general sort of announcements. Housekeeping things. First of all, evacuation information. So you can see the exit doors behind here, and we do have a new evacuation location, not directly across the street. But if we did have to evacuate, you should exit any door going downstairs. And we're actually going to meet on 11th Street between E and F. So that's on that side of the building I believe, between E and F as opposed to the park across the street. There is a lot of construction going on there.

Also, there is a drinking water -- drinking fountains and rest rooms out the door and to your left when you exit.

And then there is food service downstairs on the first floor. We're planning on breaking for lunch. We'll see how the meeting goes.

So the first order of business, we have three members here for their first time. And so we're going to begin by swearing them in. So I'm going to ask them to

rise.

And actually, first of all, why don't we start -- before we do the oath, let's just have the members introduce themselves. And for the three new members, if you can say a little bit about yourself. We had all the other members explain a little bit about their background in the first meeting. Why don't we go ahead and do that first so we know who is being sworn in. Why don't we start at the far right?

COMMITTEE MEMBER VANDEVOORT: I'm Catherine VandeVoort. I'm a professor in obstetrics and gynecology in the School of Medicine at the University of California Davis.

COMMITTEE MEMBER WOODRUFF: My name is Tracey Woodruff. I'm a professor in the very same department, but not at the same school. Department of Obstetrics, Gynecology and Reproductive Sciences in the School of Medicine at the University of California San Francisco. And my research area is epidemiology, evaluating environmental chemical exposures during pregnancy, and how that might be linked to various types of birth outcomes.

DIRECTOR ALEXEEFF: And Dr. Pessah. Since we seem to be doing the three new members first.

COMMITTEE MEMBER PESSAH: I'm Isaac Pessah. I'm Professor and Chair of the Department of Molecular

Biosciences at the U.C. Davis. I was trained as a toxicologist with a specialty in developmental neurotoxicology.

DIRECTOR ALEXEEFF: Why don't we start at the far right and move back. This will wake everybody up.

COMMITTEE MEMBER BASKIN: Larry Baskin, UCSF.

COMMITTEE MEMBER ROCCA: Meredith Rocca, Director of Nonclinical Toxicology at Janssen Alzheimer Immunotherapy.

CHAIRPERSON GOLD: I'm Ellen Gold. I'm Professor and Chair of Public Health Sciences at U.C. Davis School of Medicine.

COMMITTEE MEMBER NAZMI: I'm Aydin Nazmi. I'm an epidemiologist and faculty member at Cal Poly State University.

DIRECTOR ALEXEEFF: Okay. Great. So now I'll ask the three new members to stand, and we'll do the oath. So you can just sort of repeat after me. And when we say -- say your name when we say, "I," and then space.

(Whereupon the oath was administered.)

DIRECTOR ALEXEEFF: Thank you. So I have a couple of introductory comments.

First of all, first, I want to thank all the members for being here today. And this is the second meeting we've had this year.

I also want to thank those in the audience who are attending, and I also want to introduce the staff that are here in attendance.

Before I introduce the staff, I just want to mention when we do speak, please use your microphone. And also members of the audience, if you would like to speak, please use the microphone as well. This is being webcast.

Okay. So I'll just start over here. On the far right here is Dr. Jim Donald. He is the head of our Developmental Reproductive Toxicology Section. And it's that section that produces most of the work for this Committee. So they develop all the materials, and they are our departmental experts in this particular area.

Next to Dr. Donald is Dr. Lauren Zeise. She is now our Deputy Director for Scientific Affairs.

And next to her is Carol Monahan-Cummings, our legal counsel and this Committee's legal counsel. If you have any questions with regards to -- that are more of a legal question, then Carol is the one you should contact. And she'll work as your counsel as well.

And next to Carol is Dr. Melanie Marty, and she's the Assistant Deputy Director for Scientific Affairs. And next to her is Allan Hirsch, our Chief Deputy Director. And always in the red -- it's always important to have someone dressed in red -- is Cynthia Oshita, who you

probably all have met. She's provided you many of the materials and she will be making a presentation later, I believe.

So that's the introduction. Oh -- hiding, someone I cannot see, is Dr. Poorni Iyer, who actually will be making ultimately the presentation for today's chemical for consideration.

Sorry, Poorni. I didn't see you there.

So there are a couple things I just wanted to mention. That is, you know, we prepare materials for the Panel to assist them in their deliberations. So as part for this meeting, we prepared materials for the chemical Deltamethrin, in particular. And so when you're considering that chemical, we consider the hazard materials -- the hazard identification materials. The information that we prepare -- in this case, it was a summary document, plus the public comments that are submitted, as well as the comments that are made during the meeting here today.

And then again as a reminder -- let me just mention one more thing. In this case, it was a bit unusual, but it came to our attention that there was some additional information we should supply to you. And so we did make a revised document a little bit later in early this March to you. And then also became aware that access

to some of the submitted studies from the registrant to the Department of Pesticide Regulation, that will be helpful for you. So we had sent you information about accessing those materials as well.

So since there was a lot of information there, you know, you have to -- if you feel you'd like ultimately more time after today, we can always defer a decision. You don't have to make a decision today. You can always defer, if that's what you needed to do.

So now I will -- I think that's all that I have for now. I think right now I will turn over to Dr. Gold, the Chair.

CHAIRPERSON GOLD: Thank you. And good morning. So I just have a couple of brief comments.

As I mentioned at our last meeting, we are devoted to having an open and transparent process. And so I have a couple of disclosures to make.

First of all, I received a letter from Stan Landfair on behalf of Bayer asking for one hour for three of their representatives to present their information. And we have decided to give each of them 20 minutes, because we did not receive any other request for additional time, as was posted on the website. If people wanted more time, they were supposed to contact us.

We will, however, in the afternoon see how many

people want to make public comments and how much time we have available and see how that goes. And as Dr. Alexeeff said, if need be and we feel like we need more time, we can always defer the decision. Because the goal is to be fair and equitable in terms of public comment, but also to make sure the Committee has enough information to make a decision.

Secondly, I think also a little bit redundant here, but all Committee members were offered an opportunity to review the full guideline studies. These were provided by Bayer on the condition that each member agreed to sign an affirmation regarding the use of this information. So members of the public can have access to the same information by requesting it from the California Department of Pesticide Regulation, which is here in the Cal/EPA building. Also, copies of both letters that I received are at the back of the room and on the OEHHA website for people to view.

I think that's all I have in terms of comments at this time. And I believe our Chief Counsel has a few words to say.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. Can you hear me okay?

I'm not going to make the lengthy presentation I made at the last meeting. I apologize to the new members.

Hopefully you were able to look at that material online. But I did want to remind you briefly that one of your main duties today and in terms of being a Committee member is to consider the chemicals that we bring before you to determine whether they have been clearly shown by -- let me read it off for you -- clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. So you may hear that phrase kicked around a lot today. But that is the standard that you need to apply.

And I wanted to just clarify for you that is not a legal standard. Your decision today if you decide to list or not list the chemical can have legal effect. But your appointments by the Governor were for your scientific expertise, and that's the expertise that you're asked to apply here. Even though clearly shown sounds a little bit like a legal standard that you might hear if you're on jury duty or something, it really isn't in this context.

So we're asking you to apply your scientific knowledge and then there is also materials that you received about guidance that earlier Committee members had developed for the Committee. And that may help you kind of look at the materials that you have received already. And also listening to the presentations and the public comments, you can use that material to kind of guide your

decision-making.

But the other two things that you don't need to consider today specifically are whether or not humans are currently being exposed to the chemical at a level that is problematic to humans, because that decision is made later. And later on this afternoon, we'll talk to you about one of the things that we ask you to do in that regard. But it doesn't have anything to do with the listing of a chemical. And also just to remind you that you can list a chemical based entirely on animal evidence. You're not required to find that the chemical causes cancer in humans. I'm sorry. I just said cancer. Reproductive toxicity in humans.

Does anybody have questions before we proceed? Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So the first statement that you read about the scientific standards and cause, is that directly from the statute?

CHIEF COUNSEL MONAHAN-CUMMINGS: That is directly from the Proposition 65 statute. And so that is the criteria that this Committee applies to any decision that you make.

And Dr. Gold will also restate that for you when you do get to a point where you want to make a decision. She'll ask you specifically whether or not the chemical

meets that standard.

Any other questions? Thank you.

DIRECTOR ALEXEEFF: I just want to add one more comment. That is since this is a newly-formed Committee and you may have questions about process or anything like that, so I think since all of our discussions have to be in public, that if you have questions that come to mind that either Carol can answer or you feel staff can answer, feel free to ask them either amongst yourselves or in general so if there is something that's kind of on your mind you'd like to get cleared, feel free to bring that up. That's all.

CHAIRPERSON GOLD: I believe we can proceed with the staff presentation.

(Wherupon the following slide presentation was made.)

MS. IYER: Good morning. Today, I'm going to be summarizing the evidence on the developmental and reproductive toxicity of Deltamethrin.

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MS. IYER: Good morning. My name is Poorni Iyer, and I'm a staff member at the Office of Environmental Health Hazard Assessment Reproductive Toxicology Branch.

And moving on to Deltamethrin itself, the chemical of the day. Deltamethrin is a synthetic

pyrethroid insecticide. Like most pyrethroids, it is neurotoxicant that interferes with normal production and conduction of nerve signals. It is a Type 2 pyrethroid. Has an alpha-cyano group and acts on nerve membranes by inducing long-lasting inhibition of the sodium channel activation gate. This is how it exerts its neurotoxicity.

The mechanism of action of pyrethroids, including Deltamethrin, is the same for target and non-target organisms. Formulations of Deltamethrin include emulsifiable concentrates, wettable powders, and flowable formulations, and granules.

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MS. IYER: Exposure to this pyrethroid insecticide is largely from its use in structural pest control. It is also used to control numerous insect pests of field crops, potted plants, and ornamentals. It has been registered for use on golf courses, outdoor perimeters treatments, indoor crack and crevices and pet collars.

Additional exposure to Deltamethrin comes from the use of tralomethrin, another pyrethroid that undergoes rapid debromination to form Deltamethrin.

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MS. IYER: Deltamethrin is considered to be readily absorbed when administered orally, and the carrier

or solvents can effect the rate of absorption. Absorption in the gastrointestinal tract and respiratory tract is higher compared to absorption through the skin. Oral absorption in humans is thought to be at least 50 percent. In the Sprague-Dawley rat, about 58.4 percent of absorption of an oral dose was noted. Rats absorbed 3.6 percent of the Deltamethrin when applied to their skin. And since human skin is less permeable than rat skin, the absorption of Deltamethrin through human skin is expected to be relatively weak.

Deltamethrin is distributed to nerve tissues and all regions of the brain tested. Studies with rats observed that orally administered Deltamethrin was recovered in fat at slightly higher concentrations compared to other tissues.

In rats, Deltamethrin had a half life in blood of 5.5 hours and a half life in the brain of one to two days, but it is more persistent in body fat with a half life of five days. Metabolism of Deltamethrin in rats involved rapid ester cleavage and hydroxylation. Only the parent compound is toxicologically significant.

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MS. IYER: Paresthesia was the most commonly reported symptom of acute dermal exposure in occupational studies involving pyrethroids such as Deltamethrin. Skin

sensations were characterized as tingling, itching, burning, and numbness of the skin after dermal exposure.

The paresthesia was reported to be transient and reversible, sometimes lasting up to 48 hours, occurring only at the site of dermal exposure and not associated with systemic toxicity.

The California Pesticide Illness Query Database revealed 41 incidents of illness reports that had probable to possible association with the use of Deltamethrin over a ten-year period.

In animals, the signs of toxicity associated with Deltamethrin are typical of Type 2 pyrethroids and include characteristic effects of choreoathetosis, which is sinuous writhing, and salivation presenting as pawing and burrowing behavior followed by salivation and tremors, progressing to clonic seizures.

Regarding the chronic effects of the chemical, no studies investigating mutagenicity or cancer in humans were identified. The U.S. EPA classified Deltamethrin as not likely to be a human carcinogen by all routes of exposure. There was no increase in tumor incidents in mice fed technical grade Deltamethrin in the diet.

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MS. IYER: Moving on to the reproductive toxicity of Deltamethrin and the studies that we examined, there

were no studies examining male reproductive effects in humans.

In vivo studies examining the effect of Deltamethrin exposure on the male reproductive system are available in mouse, rat, and rabbit. One in vitro study is also available. These studies are summarized in Table 6 in the documents submitted to the panel.

In a three-generation reproductive study, the test compound dissolved in corn oil was administered in the diet to adult rats before mating and continuing through weaning of the offspring for each generation, after which animals were sacrificed.

No adverse effects on the reproductive system, fertility, or survival were observed at any dose level tested. The only effects in males included a decrease in mean parental body weight of the F zero males between weak 11 and week 39 of study.

Also compared to controls, slight reductions in mean food consumption was noted in the F1 males and F2 females at the 50 parts per million level. Histopathology of parental animals was not presented. Overall, the study had several limitations, such as lack of test article purity and dose level justification, and hence, it is difficult to determine if testing had been done at adequate dose levels to elicit a response.

In a two-generation study, conducted to meet federal regulatory guidelines under FIFRA, exposure of rats extended from the pre-mating period during gestation and through day 21 of lactation when the pups were weaned. In this study, the absolute mean weights of the epididymis and testes of the offspring was significantly less than those of the controls in the high dose group of 320 parts per million Deltamethrin in the diet, which is about 21 to 35 milligrams per KG body weight, as estimated by the authors. The ratio of testes weight to brain weight was also reduced at this dose level.

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MS. IYER: Studies from the open literature are examined and are described in the next few slides. These include various routes of exposure and they were all non-dietary. The slides describe studies as they became available, with some information on the chemical used in the study and the dose level at which the effects were observed are in bold.

In a study with rats exposed to two pesticides, Dimethoate and Deltamethrin, a decrease in libido and ejaculate volume and sperm concentration was noted, along with an increase in the percentage of dead spermatozoa at 100th LD50 of Deltamethrin alone. But the actual doses were not stated.

In a rat study, oral administration of Deltamethrin for 65 consecutive days decreased the conception rate in non-treated females that were mated with the treated males, with decreases in sperm concentration noted at both one milligram per KG and two milligrams per KG. The decrease in live sperm and plasma testosterone levels continue and was noted 21 days after administration of the chemical was stopped, along with degenerative changes in testicular and accessory gland structures.

In another study, intraperitoneal injection of Deltamethrin to male rats at one milligram per KG were shown to induce testicular apoptosis.

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MS. IYER: In utero and lactational exposure to Deltamethrin induced subtle changes in reproductive behavior and physiology of male offspring such as reduction in the number of animals with ejaculate, along with a decrease in testicular and epididymil absolute weights and the diameter of seminiferous tubules in the highest dose group of Deltamethrin of four milligram per kilogram.

From studies examining dominant lethal effects, overall, Deltamethrin was found to exert a weak effect in the midweek -- that is the third week of the spermatogenic

cycle, in medium and high dose treated animals.

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MS. IYER: Sub-cutaneous exposure to Deltamethrin at doses as low as 0.003 milligram per kilogram per day for a period of 30, 45, or 60 days produced histopathological changes in testes and an arrest in spermatogenesis. A significant decrease in plasma FSH concentrations compared to controls was noted by the authors after 45 and 60 days, but not after 30 days.

A decline in LH and testosterone was noted after 60 days of treatment, and hence, the author suggested that the hormonal system is targeted by Deltamethrin. Additionally, in mice, oral administration at levels as low as five milligram per kilogram per day of Deltamethrin alone or Deltamethrin and Dimethoate administered together resulted in significantly decreased sperm count, motility, and viability, and a significantly increased percentage of morphologically abnormal spermatozoa compared with the controls.

Also, in vitro exposure to Deltamethrin at different concentrations caused a significant decline of sperm motility and viability and an increase in abnormal sperm morphology.

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MS. IYER: The first study on this slide, severe

degenerative histopathological changes in the testes, prostate, epididymis, and seminal vesicles were observed that were attenuated by Vitamin E and selenium mixture.

In the next study, gestational treatment in mice with Deltamethrin alone or in combination with Dimethoate produced significant reduction in the testes weights, epididymil sperm count, motility, and viability in male offspring.

Overall, there is evidence from a number of studies for a decrease in sperm count and increase in dead spermatozoa in mice, rats, and rabbits at relatively low doses of Deltamethrin via several routes of exposure.

Also, one study examined changes in hormonal levels. And the author suggests these pertubations may be the mode of action for this chemical. Effects on puberty -- that is, development of the male reproductive system -- are included later on in this presentation, along with developmental effects.

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MS. IYER: Considering female reproduction, there were no studies examining female reproductive effects in humans. Also, there are no studies evaluating effects of Deltamethrin on the estrous cycle.

The animal studies included those described earlier for the male reproductive system, in which a three

generation reproduction study submitted to regulatory agencies, such as U.S. EPA and the California Department of Pesticide Regulation, were in Deltamethrin in the diet was given to rats before mating, during gestation, and continued through weaning for three generations. No adverse effects on the reproductive system, fertility, or survival were noted.

Slight reductions in mean food consumption were noted in the F1 males and F2 females at the 50 parts per million dose level. As mentioned earlier, histopathology of parental animal tissues was not presented.

In the standard two-generation reproduction study conducted according to FIFRA guidelines, the absolute mean weight for the non-gravid uterus was less than that of the control for the P1 and F1 females of the high dose group.

Also, for the P1 females in the same dose group, the absolute mean pituitary weights were less than those of the controls. No other adverse effects were noted.

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MS. IYER: From the open literature, in a study examining the effect of the chemical on the response of the blastocyst-endometrium interactions in rats, the implantation process was effected. Histopathological alterations in the implantation sites, as well as a reduction in the number of sites were noted.

In another report, a smaller number of pups and reduced fertility was also noted subsequent to exposure to the formulation with no clinical signs of toxicity. Effects on puberty -- that is, the development of the female reproductive system -- will be presented later on, along with the developmental effects.

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MS. IYER: The next set of slides presents studies examining development. First will be those examining neurodevelopment, and this will be followed by those that examined other effects on development.

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MS. IYER: To better understand the neurotoxic effect of diverse hazards on the developing human nervous system, researchers and clinicians rely on data collected from a number of model species that develop and mature at varying rates. The findings from evolutionary and developmental biology show that the timing and sequence of early events in the brain development are remarkably conserved across animals and form the basis for generalization across species.

Several researchers that examined this issue and it is estimated from the work of Clancy, et al, that around postnatal day one through ten in the rat pup corresponds to the in utero period in humans for several

general limbic and cortical events in the brain.

And postnatal day 10 to 13 in the rat pup corresponds to the third trimester in humans for some cortical events of the brain.

These findings and other studies highlight a relevant issue that, given the relatively altricial state at which rat pups are born, exposure during postnatal day one through ten in the rat pup will be equivalent to a continuous in utero exposure in humans.

The second most relevant exposure scenario would be lactational exposure following dietary exposure of the dams, as this scenario would provide an opportunity for continuous exposure, as would occur in utero for humans.

Lactational exposure may also be relevant for premature infants. Accordingly, exposure during the postnatal period in rodents appears to be relevant to human neuro development.

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MS. IYER: Some of the ways the research community has attempted to equate brain development across members of the mammalian species include morphological comparisons, rules of thumb based on susceptibility patterns, event-based comparisons, and overall neuroinformatics technique approach by Clancy, et al, and Finlay and Darlington.

This is based on the acquisition and integration of large data bases of multiple data types, analysis using standard multi variate techniques made simpler by increased computing power. And these are publicly available through web-based interfaces. These tools have allowed for predictions of cross species developmental sequences based on multiple events in multiple species.

In this table, which is not in the hazard ID document, it summarizes a model developed to predict neuro development across three species to further illustrate the issue. It is calibrated to the rat in the first column, right here, and the gestational time for each species are in red.

The numbers in blue in each cell represent post-conception days in utero until birth, which is also marked in red.

The rest of the numbers in black represent postnatal days indicated by the PND before the number. This table allows translation by following a line across the columns. As you can see here, the yellow highlight.

For instance, by the birth time of rat and mouse, humans are past the first trimester of gestation. And this corresponds to gestation day 110 for cortex development.

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MS. IYER: In this context, we are presenting studies that include prenatal and postnatal exposure. These include studies to meet with the developmental neuro toxicity guidelines, as well as other studies.

On this slide, in the first study, the authors reported that in utero and lactational exposure to Deltamethrin induce subtle changes in reproductive behavior physiology of male offspring, such as a trend toward a reduction in the number of animals with ejaculate in the highest dose group of Deltamethrin at four milligram per kilogram.

Also included are studies that have prenatal exposure to a low dose of Deltamethrin with evaluations of alterations in offspring motor and dopaminergic activity systems as well as pertubations in biochemical parameters, which are effects that are not examined in guideline studies.

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MS. IYER: In the study by Lazarini, et al, the effects of prenatal exposure of rat pups to 0.08 milligram per kilogram of Deltamethrin on physical reflex and behavioral developmental parameters on forced swimming and open field behaviors and on striatal monamine levels at 60 days of age were observed.

According to the authors, forced swimming is an

inescapably stressful situation, causing a relatively short escape reaction, followed by floating without performing any activity.

The authors reported that prenatal exposure to Deltamethrin alter the latency to float and the activity of striatal dopaminergic systems and might reflect a persistent effect on animal motor activity. This occurred mainly in males, and the decrease in general activity observed in experimental male rats in relation to control animals suggested higher levels of emotionality induced by previous exposure to the swimming behavior.

In the work by Johri, et al, the authors contend that low dose prenatal exposure to pyrethroids has the potential to produce long-lasting effects on the expression of zenobiotic metabolizing cytochrome p450 in the brain and liver of the offspring. And this exposure may lead to the accumulation of Deltamethrin or its metabolites to an extent that is sufficient to induce behavioral alterations in the offspring evaluated postnatally at three weeks.

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MS. IYER: On this slide, the study was conducted to meet with developmental neurotoxicity guidelines and included prenatal and postnatal exposure. Effects included a decrease in postnatal body weight, a decrease

in fixed female brain weight, and an increase in resistance at removal with vocalization at the 200 parts per million dose level. The authors were not clear about the significance of this finding.

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MS. IYER: Several studies examined the effects of Deltamethrin exposure in utero on other non-neuro developmental end points in laboratory animal species. Some of these were FIFRA studies and other studies published in the open literature.

those submitted for regulatory purposes of pesticide registration included developmental teratology studies, developmental neurotoxicity studies that examined other developmental landmarks, and the two-gen and three-generation reproduction studies that had in utero exposure.

Some of these reported no adverse developmental effects, while some reported effects that may or may not have been examined in the other studies.

The next few slides describes studies as they became available and the dose level at which the effects that were observed are in bold. In the first study on this slide, no adverse effects were observed in rats and mice. In the next study in rats, also there were no adverse effects.

In the third study on this slide, a retardation of bone ossification was noted in the offspring with other variations.

Continuing with studies that were published in the open literature and examined the effect of Deltamethrin exposure in utero on other non-neuro developmental end points, again, the dose level at which the effects were observed are in bold, and the slide details the study design and the effects are noted as well.

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MS. IYER: In the next set of slides that examined Deltamethrin exposure in utero, in this slide, the study by Richard, et al, was submitted for regulatory purpose of pesticide registration and was the second standard developmental toxicity study in the rabbit and reported no adverse developmental effects.

The study in the rat published in the open literature also had a standard developmental toxicity study design and reported a decrease in maternal body weight gain during gestation with signs of lethargy and a decrease in uterine weight and an increase in percentage of resorbed fetuses, as well as malformed fetuses in a dose-dependant manner, along with a decrease in average body weight of the fetuses and incomplete ossification.

As stated previously, some of these studies reported no adverse developmental effects, while some effects that may or may not have been examined in the other studies were observed.

A number of these studies also had limitations that would preclude them from being acceptable for the purposes of pesticide registration, but they serve as non-guideline studies and contribute to the weight of evidence.

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MS. IYER: At maternal exposure to 200 parts per million, Deltamethrin in the diet in the developmental neurotoxicity study in rats where the parameter was evaluated, the mean age of attainment of preputial separation was delayed 1.6 days in high dose male offspring apparently associated with the delay in growth equivalent to about one day's body weight.

However, this parameter is also influenced by hormonal changes. And so it is unclear what may have contributed to the effects observed in the study. In other studies in rats, maternal exposure during organogenesis period resulted in a delay in the day of eyes opening for male and early vaginal channel opening in female offspring.

Additionally, according to Lazarini, et al, in

2007, findings from other researchers have demonstrated that administration of epidermal growth factor to new-born mice accelerates eye opening as well as delays of vaginal opening. Hence, it is possible that the delay in eye opening and the hastening of vaginal opening noted after exposure to Deltamethrin in this study could be a result of inhibition of the expression of epidermal growth factor. Because there was no other evidence of general developmental delay, the author suggested this to be a specific effect of Deltamethrin on this physical landmark.

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MS. IYER: In summary, the developmental neurotoxicity study in rats included exposure during the prenatal and postnatal period. And adverse effects, such as significantly reduced fixed female brain weight in F1 rats at termination and increased resistance at removal with vocalization in males at the high dose group of 200 parts per million were noted by the authors. However, no adverse effects were observed for auditory startle habituation. Learning and memory as measured by passive avoidance after weaning and the water maze task.

In other studies in rats, maternal exposure during the organogenesis period resulted in decreased locomotion frequency and increased immobility observed in male rates prenatally exposed to Deltamethrin and have

been interpreted by the authors as consequences of high levels of emotionality induced by the prenatal exposure to the pyrethroid.

These findings, along with those from other studies presented earlier, suggest that prenatal exposure to Deltamethrin may cause alterations in offspring motor and dopaminergic activity systems as well as pertubations in biochemical parameters, which are effects that are not examined in guideline studies.

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MS. IYER: Summarizing the other developmental effects observed, several studies examined the effect of Deltamethrin exposure in utero on neurodevelopment and other developmental end points in laboratory animal species. And some of these were FIFRA studies and other studies published in the open literature, which included prenatal and a combination of prenatal and postnatal exposure.

Some of the studies reported no adverse developmental effects. Some reported pup mortality after prenatal and a combination of prenatal and postnatal exposure, while some reported effects on developmental landmarks that may or may not have been examined in the other studies.

And this concludes my presentation for today, and

I'll be glad to answer any questions.

CHAIRPERSON GOLD: Does the panel have any questions for the presenter?

COMMITTEE MEMBER WOODRUFF: Thank you for the presentation.

I had a question. When you are looking for developmental toxicity studies, do you focus your search on studies -- any study that looks at a prenatal or post-gestational day exposure? Or do you also look for ones that are evaluating certain effects?

My question really comes down to do you look at the potential for a prenatal exposure to have more than just an immediate effect but perhaps some other types of what may not be longer term effects in the life of the animal postnatally?

MS. IYER: We look at all studies that come up in our research that have covered prenatal exposure. But also postnatal exposure, like I mentioned, if it corresponds to prenatal exposure in humans.

COMMITTEE MEMBER WOODRUFF: Do you go up to -- the postnatal exposures in the rats, do you go up to the -- all the way up to the equivalent of 270 days in a human? Is that right, from this chart?

MS. IYER: We basically looked at all the studies that are available.

COMMITTEE MEMBER WOODRUFF: I see.

CHAIRPERSON GOLD: Any other questions for Dr. Iyer from the panel?

Dr. Donald, you have a question mark next to your name.

Okay. So since we don't have any human studies, I've called upon a toxicologist to lead the discussion by the panel. We'll start with Dr. Rocca and go to Dr. Pessah. You decide to switch. Okay. So Dr. Pessah will go first. My error.

COMMITTEE MEMBER PESSAH: Thank you.

So some of the important questions that a toxicologist would ask about the data is essentially is there exposure. Deltamethrin is the Type II pyrethroid and is clearly one of the more acutely toxic pyrethroids. It clearly is widely used in several applications. So human exposure has, in fact, been documented in some studies, but their consequences have not been elucidated as we've heard, at least, in the published literature.

The half life of the chemical in the environment, although only one to two weeks apparently, could be sufficient if the chemical reached target organs at a critical time in development, both in terms of any consequences on the gametes of the parents, but also if the chemical were to reach the developing brain, both in

rodent models would be late prenatal and early postnatal. So essentially, the perinatal period is a critical sensitive target for Deltamethrin.

The animal studies suggest that distribution of Deltamethrin to the target organ, the brain, is, in fact, possible and somewhat efficient in these animal studies.

The half life in the brain is sufficient to alter certain developmental parameters that could impact behavioral outcomes.

Of course, metabolism via hydrolysis and hydroxylation limits exposure because, as far as we know, the metabolites are not active. They're not active neurotoxicants.

The question is, is Deltamethrin an acute neurotoxicant at levels of exposure that produce central effects? And the answer is clearly yes. The LD 50 is 30 migs per kig.

And the real question then becomes is it at levels that are either sub-over toxicity that produce overt toxicity and those that produce mild to moderate toxicity, is there potential of having trans-generational effect. That is, effect in the F1 and possibly in subsequent generations.

Several studies have looked at this, and these were summarized pretty thoroughly by OEHHA. Many of these

effects are thought to stem from the primary mechanism of Deltamethrin, which is essentially initially it delays the activation of the sodium channels that are in the neurons and subsequently inactivates them over prolonged periods of time, which essentially silences neurons, especially in the developing situation.

So the question is, what are the in vivo consequences in animal studies with respect to the central target, which is nerve development.

I think there are some themes that many of these studies essentially conclude, not all of the studies as we've come to learn, that essentially a motor activity, growth, and motor activity are in inextricably intertwined, but we don't know which begets what. Okay. So these studies really didn't look at cause and effect. They looked at the phenomenal logical outcomes that are standard measures.

These are relatively blunt instruments when we think about their translation to the human condition in that more subtle aspects of behavior were not addressed, such as the development of fine nuances in social behavior, the possibility that a second insult to another chemical may, in fact, produce more toxicity than just the one chemical that's been examined, in this case, Deltamethrin.

I'm not going to go back over the developmental and reproductive effects, but from a mechanistic perspective, if, in fact, these are robust effects, one should ask why would there be reproductive effects in the mother or in the males when this is a sodium channel active substance, which suggests that there may be other downstream or secondary effects that are produced by exposures that may be a consequence of altering general nervous system excitability.

Is there evidence of this? Well, in vitro studies, which haven't really been highlighted, there are several indications that very low levels of exposure to Deltamethrin typically in the nanomolar -- high nanomolar to very low micromolar can, in fact, change aspects of excitability and cell signaling that have not been really addressed sufficiently in my opinion.

One of these effects is that essentially there is very clear evidence that pyrethroids, including Deltamethrin, can change a fundamental signaling pathway in both neuro and germ cells, which involve calcium regulated genes and calcium regulated processes, which really have not been addressed.

And if evidence were to come out that, in fact, these effects can be obtained at sub nanomolar concentrations, then we might want to look at different

outcomes in behavioral studies which have not been examined to date.

So with that, I'm going to discussion.

CHAIRPERSON GOLD: Thank you.

Dr. Rocca, do you have something to add to that?

COMMITTEE MEMBER ROCCA: Good morning.

I reviewed the studies and have more individual comments on the studies to provide. And I think everything that you've just heard is very relevant as to what a toxicologist would be looking at. But of course, the first commandment, I guess you'd say, of toxicology is that the dose makes the poison.

And in this case, we're not always clear what these animals were dosed with and what the treatments were. In some of them, it does clearly say that the commercial mixture of the pesticide was used. In that case, either Butox or Dexcis -- I'm not sure if I'm pronouncing that properly -- was used. And those have between two and five percent of Deltamethrin, and the remainder are other solvents and excipients.

Because of that and not having any pharmacokinetic information from the animals in those studies, I think that those studies should be largely discounted.

So for male reproduction, those studies would

include the Abd el-Aziz for 1994 which used Butox, Oda in 2011 which used Butox, Shukla 2000 which used Decis, and the Salem study from 1988 which used Decis.

The studies that remain -- I'm doing this in species order -- is we have an in vitro study in which semen from one rat was taken and was directly exposed to Deltamethrin. We don't know the purity of this. It appears from my reading that the N of this experiment is one rat, which would not be up to a level of scientific muster. And it was a direct exposure to the semen. And I don't think that this will ever be a relevant route for humans.

The next studies we have in the rat is the El-Gohary in 1999, and this was an IP exposure once again with no purity data. Just injected things intraperitoneal I don't think is a relevant exposure either. And once again, we have no purity data. So we really don't know what the dose was.

The next one on the list would be a subcutaneous exposure. And that was done by Issam in 2009. Once again, we have no exposure data or purity data. But we do know they used a 70 percent ETOH vehicle control. This was a subcutaneous study. That seems like a very inappropriate vehicle for a subcutaneous study. The doses that they used appear to be very low compared to doses

that were used in other studies. And so I don't see the small effects they found there to be compelling either.

We have a mouse study that was done by gavage that was oral. That was the Ben Abdallah in 2009, which used a corn oil vehicle. But once again, we have no purity data on that. So really don't know how valuable that is. It was a 21-day exposure trying to look at different periods of spermatogenesis. But without seeing effects in other studies at higher doses, I don't find that one completely convincing either.

There are, however, some studies that do tell us some about male toxicity. And these were done in the multi-generational studies, in which animals were exposed during the pre-mating time, during the mating period, during gestation, and during lactation and sometimes for several generations after that.

The two that are relevant here are Hoberman and Wrenn. Wrenn was done in 1980. As was stated, this was not according to the regulations because there weren't any regulations that stated this at the time. But that does not preclude us from looking at the quality of the study. This was done with technical grade Deltamethrin. Test article analysis was performed several times, so they do know how much Deltamethrin was, indeed, in the feed. And in this case, they found in a three generational studies

no real effects on any reproduction.

Now, the caveat for this one is they really did only do full histology on the F3B generation. So this is -- the parents have been treated. The offspring have been treated. The grandchildren have been treated. And now we're down to the great grandchildren having been treated. So we have a lot of litters there, but it would probably have been much more useful to look at animals who had had that first exposure in the first generation.

So then we come to the Hoberman study. In the Hoberman study, this is a two-generational study that was done more recently in 1992. This had a very pure test article of 99.7 percent purity. A test article analysis was done at several times. So we can say that the animals were exposed and how much they were exposed to. The high dose was toxic to the animals of both generations. And so we had body weight effects, clinical observation effects. We even had some deaths in the F1s. And so at doses that are that toxic, you really have a hard time trying to understand whether a reduced organ weight is the result of toxicity to that organ or whether it is more due to the lack of body weight.

However, at any of the non-toxic doses, there were no biologically significant effects either on the organ weights or on any of the reproductive parameters.

This was the study that went up to approximately between 20 and 37 milligrams per kilogram per day, and so that was the dose that was toxic. The next one down was 80 parts per million, which comes out to be about five to ten milligrams per kilogram per day. And there was absolutely no toxicity seen at that dose. So that is one of the higher doses that we see here.

So next we go on to whether or not there are any female effects. And once again, I can go through the studies. For the same reasons of using the commercial mixtures, the Abdel-Khalik, 1993; Kandil, 2006; Lemos, 2011; and Lemos 2012 all use the commercial mixture that was at least 95 percent other ingredients. So I have discounted the results of these as most likely due to the solvents and other excipients.

The next study that we see then is a study by Kavlock. And it included both mice and rats published in the same study. Those animals were dosed during the period of organogenesis for the prospective animals. Gestation day 7 to 16 in the mouse. Gestation day 7 to 21 in the rat. They had very substantial Ns between -- for mice between nine and 17 pregnant animals per group and 20 to 28 pregnant animals per group for the rats.

They do see maternal toxicity at the high dose in both of those studies. So we know that we have dosed to a

high enough amount. And yet, in both of those, there were no effects on any of the female reproductive end points, nor were there any physical malformations in the offspring.

Next one is Lazarini 2007. This one we also have an unknown purity in a very low dose. There were no effects on the females, nor any physical malformations in that study.

Next one is Schardein 1990, listed as A. In the case people haven't caught on yet, I'm doing this alphabetically, if you wanted to follow.

This is a study where animals were dosed once again during the period of organogenesis. And it's 25 animals per group, 99.2 percent purity. We have a corn oil vehicle, which is the vehicle control. Doses went as high as 11 milligrams per kilogram per day. That high dose and the dose down from that, the seven milligram per kilogram per day were both maternally toxic. However, there were no effects on female reproduction or fetal malformations at those doses.

Next one is Richard, which is a rabbit gavage. We've moved on to our rabbits. And in that study, rabbits were dosed during the period of organogenesis, gestation day 6 to 28, at an N of 21 to 24 per group. There were four doses used. The material was 99.1 percent pure in a

corn oil vehicle. The maternally -- there was maternal toxicity at the highest dose seen. But there were no reproductive effects and no fetal malformations in that study either.

We have another study by Schardein 1990 B, in which rabbits were dosed from gestation day six to 15 and of 10 to 13. 99.4 percent purity of the test article, a carboxymethylcellulose vehicle, and went as high as 100 milligrams per kilogram per day, which was maternally toxic.

But even with that, there were no reproductive effects on the lower doses or fetal effects. It was noted that there was some delay in ossification at the high dose, but this is not unexpected when there is toxicity in the female in which both the female has lost weight and the fetuses also weigh less. Those are I think female end points.

I can go through the studies that also had postnatal evaluations, once again starting with the rat. And the ones that I have discounted for using the commercial formulation are Aziz 2001; Johri 2006; both A and B, and that's that for that one.

The first study that is there is Andrade 2002 where the animals were dosed from gestation day one all the way through postnatal day 21 by gavage. So

presumably, the pups were exposed lactationally, although we do not have an analysis of that. There were doses, the material was 98.8 percent pure. Doses went up to four milligrams per kilogram per day. There was no maternal toxicity, and there were no biologically significant effects on the offspring in terms of fertility end points.

Next one is a study by Kavlock that I discussed before where animals were dosed from gestation day seven through lactation day 15 using the technical grade Deltamethrin. There was a decrease in body weights at the highest dose, which is five milligrams per kilograms per day. And there were no effects on the growth or neural behavior of the offspring noted in that study.

Lazarini 2001, in this study, we do not know what the purity is, nor do we know what the vehicle is. The dose was 0.08 milligrams per kilogram, which is really quite low compared to the other studies.

There were a couple interesting things that came up, one of which was latency to floating in a rather unusual test. I believe in that one if you look at the data closely, you may see there was an outlier in the controls. But one would need to see more data, particularly as nothing was seen at much higher doses in other studies.

The next one I have is the Lazarini from 2007

uses the same dose. We do not know anything about purity or the test article. That's the one in which there was a slight delay in eye opening and earlier vaginal opening. However, there were no pup data weights or actual numbers for any of these events. Many of those things developmental, landmarks, are, indeed, tied to body weight. Without that information and particularly this being the only study that saw this result at this very low dose, I don't find that to be compelling.

The next studies were rat feed studies. And these studies rats were fed the diets from gestation day six through lactation. And it should be noted in the case of a feed study, that by the second week of life, the pups themselves are beginning to consume some of the diet. And actually by the time that they're weaned at three weeks, part of the reason they can be weaned at three weeks is they're eating a full and adequate diet at that time.

So it becomes a little more difficult to know whether these exposures were in the early part of the postnatal days, which might be more equivalent to the human late gestation or whether these were actually significantly later in that.

But nonetheless, in Gilmore 2006, test article was 99.6 percent pure at the high dose of approximately 16 milligrams per kilogram per day. We had decreases in

gestation and lactation body weights at the high dose. Not surprisingly, we also had decrease in pup body weights during lactation at the high dose and some delay in preputial separation, which is not unusual based upon the lower body weights. But no neurological end points were effected in this study.

The next feed study is the Hoberman study. This was the same two-generational study in which the test article was 99.7 percent pure. Test article analyses were done. There was toxicity in both the parental and the F1 generation and even some deaths in the F1s. But there was no significant reproductive organ weight effects. And in this study, there were necropsies done and organ weights taken in several generations.

Next one would be Wrenn, which is the three generation study we've talked about before that has the caveat of only doing histology in the F3B generation. But in this generation, there were no effects on the organs seen. And in the other generations, although there was decreased body weight in some generations, there was no effects on reproduction that were seen.

And the last study, our favorite study is always the last, is mouse gavage study, which was done by Ben Slima in 2011. This study has no purity data. There is an N of five animals per group in the F0 generation.

These five animals per group -- and there was only a control group and one dose group -- were treated from gestation three to 21. However, there were only four males evaluated for the end points in the next generation. So we have two dose groups, one of whom the dosed group with the Deltamethrin only evaluated four males.

And in this study, maternal body weight was decreased, and we don't know anything about what data necropsy was done, which was the only time maternal body weights were taken. There was no gestational data. It does say there were decreases in testis weight and affects on sperm parameters. However, we don't have any information on body weights or sexual maturity. And therefore, I find that one hard to interpret.

So that's my review of all the studies that we've been presented information for. And based upon this, I personally do not think that they meet the level of scientific rigor in order to list this chemical.

CHAIRPERSON GOLD: Thank you, Dr. Rocca.

Dr. Pessah, would you like to make additional comments?

COMMITTEE MEMBER PESSAH: I guess I'm a little concerned that most of the studies, whether they were faulted or maybe not so badly faulted, really missed the critical period in development because they do not extend

exposures into the postnatal period, which reflects the prenatal period in humans. And given the short half life, even in the brain, I think that in general we just don't have enough information.

Now, there are some of the studies that were mentioned that actually did see effects. For example, these supernumerary ribs in all the treated groups with the Kavlock, et al, 1979. This is in the mouse study.

And then what caught my attention in the Gilmore study, when actually did go beyond birth with the exposures, is that they actually saw a behavioral change that actually is being used quite a bit now to scan much more subtle neurodevelopmental outcomes, such as vocalization and anxiety. So I know that the extra rib can be, in fact, a consequence of maternal stress or anxiety. But that hasn't been fully worked out as to what the causation is there, whether it's direct or indirect.

But there is some indication that maternal stress can produce these abnormal growths in the offspring. But again, there are many behavioral tests that have never been put to bear after a relevant exposure extends into the lactation period. And what is there is suggestive, but obviously not definitive.

CHAIRPERSON GOLD: Thank you.

Are there other members of the panel that wish to

comment at this time?

COMMITTEE MEMBER WOODRUFF: Yeah. Those comments were very helpful, and I think one of the challenges have been reading through this is -- and I see that you've added -- modified the presentation materials a little bit. For example, some of the issues related to what the dosing is is helpful to clarify between the different studies.

I did note that for the male reproductive developmental studies is that there was -- there was variation in the type of outcomes that were evaluated. And some of these -- you talked a little bit about the Hoberman study, for example -- did mostly focused on weight changes, which, to me, is not going to be -- certainly, if there are weight changes in the reproductive organs, that would be a valuable indicator for that experiment. But it might not be as subtle an indicator as some of the other studies which looked at sperm, effects on sperm, whether it's increase in abnormal sperm or decreases in motility and viability.

And one of the things that I have been thinking about when you were giving your comments is sorting through the -- because there are a number of these studies that focused not on organ weights, but on evaluating the testosterone and sperm-related effects. Though they have some of the issues you were talking about in terms of

which ones used technical grade exposure versus something different. And so I think the difference between the document we got and the presentation here today in terms of -- because there's more clarity in this presentation about whether they were exposed to the actual pesticide technical grade is -- I think would have been helpful to have in this earlier --

MS. IYER: It's there in the appendix.

COMMITTEE MEMBER WOODRUFF: Yes, in the appendix. I like having it in the table. That's just my comment.

I would say that does -- I think we should sort through the studies based on the outcomes. Some are more subtle evaluations of reproductive effects than some of the others that were evaluated in these studies.

CHAIRPERSON GOLD: Thank you. Other comments from the panel?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: So to the panel, and Dr. Rocca specifically, the concern with the majority of studies is that Deltamethrin wasn't being tested specifically. I just want to verify that.

COMMITTEE MEMBER ROCCA: Yes.

COMMITTEE MEMBER BASKIN: So something in the gamish of chemicals could be causing decrease in spermatogenesis and apoptosis and some of the serious

effects we're seeing. But we can't directly relate that to Deltamethrin. That was your major concern.

COMMITTEE MEMBER ROCCA: Yes. It does appear that the mixture is a male reproductive toxicant, because that was a consistent finding where they used the mixtures. But in any of those that we know the purity and they did not use that, it wasn't seen.

COMMITTEE MEMBER BASKIN: Thank you.

COMMITTEE MEMBER WOODRUFF: Though -- but let me see. You said the ones that had the mixture were -- I wrote down were the Oda study, the Abd el-Aziz study, but not all the studies that saw an effect used a mixture; right?

COMMITTEE MEMBER ROCCA: Do you have a specific one?

COMMITTEE MEMBER WOODRUFF: I'm looking at the Issam study, Ben Abdallah two studies, and Ben Slima and Salem. Yes.

COMMITTEE MEMBER ROCCA: So for the male reproductive end points, do you want me to list those studies again? Would that be helpful?

COMMITTEE MEMBER WOODRUFF: I'm just -- I guess I'm saying not -- there were some studies in the male reproductive end points that used a mixture, but not every study that saw an effect used a mixture. I guess that was

my --

COMMITTEE MEMBER ROCCA: So the ones that used mixtures were the Abd el-Aziz, Oda, Shukla, Salem.

The studies for which we have no purity information were the in vitro, Ben Abdallah, the intraperitoneal study for El-Gohary, and the subcutaneous study for Issam 2009. So none of those have found any purity data whatsoever. So we really don't know what the doses were. And in some of them, the doses were not even stated. So for the male fertility end points, I was basing my assessment primarily on the Hoberman and Wrenn multi-generational studies.

COMMITTEE MEMBER WOODRUFF: Right. But those studies did not -- the Wrenn and the Hoberman studies did not evaluate sperm effect; is that right? Right? The histology and testis weight, and epididymal weight.

CHAIRPERSON GOLD: Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I think it might be important to point out that the commercial formulations -- you mentioned, for example, the Butox. I think it's important to mention that the majority of the ingredients are considered expedients and the common link between the commercial preparations is the base Deltamethrin. So I think completely disregarding those studies is a mistake.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: I guess the concern is that the formulation itself is causing the effects and none of the studies that you've dismissed are looking at an appropriate vehicle control, is that --

COMMITTEE MEMBER ROCCA: Yes. They did not have a vehicle control. They had a corn oil control or water control. If they had an appropriate excipient and vehicle control, that would have been very helpful.

COMMITTEE MEMBER PESSAH: Is there any evidence that we know that Decis and Butox, in fact, have these kinds of reproductive effects at the levels that were used in these studies? I mean, from other studies, regardless of whether they were looking at Deltamethrin.

COMMITTEE MEMBER ROCCA: The excipients, you're asking?

COMMITTEE MEMBER PESSAH: Yes.

COMMITTEE MEMBER ROCCA: I do not know.

COMMITTEE MEMBER PESSAH: So we cannot discount that the excipients are or aren't. Yeah.

And by the way, the technical mixture would essentially based on a mig per kig, that wasn't based on the active principle. That was based on the total weight, which means if Deltamethrin was causing these effects, it would be at a much lower level and would influence the NOEL.

COMMITTEE MEMBER ROCCA: Exactly. It would have been at less than, depending on which mix they use five percent of what the stated dose was. When you compare it to the studies, they use much, much higher doses. It just doesn't seem plausible that that's the chemical that's causing this.

CHAIRPERSON GOLD: Other comments from the Committee?

Okay. Hearing none, I think we can go to public comments at this time. I think what we'll do is start with them and then we will take a lunch break. Since we have three commentors and we've given them each 20 minutes, I think rather than go for an entire hour -- although if the Committee feels like it can go for an entire hour and also the recorder. Are you good for another hour?

We can give that to a shot, to try to fit in three public comments in the next hour. And so we have Stan Landfair first; correct? Thank you.

MR. LANDFAIR: For your benefit, Dr. Gold, I can be quite flexible. If you'd like me to go now, if you'd like me to split it up.

CHAIRPERSON GOLD: I'm going in the order in which they were received.

MR. LANDFAIR: Yes, I'm first.

CHAIRPERSON GOLD: That's fine.

MR. LANDFAIR: Well, to introduce myself, my name is Stanley Landfair. I'm an attorney with the firm of McKenna, Long, and Aldridge. And in one capacity here, I represent Bayer CropScience.

If I could have the next slide, please.

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MR. LANDFAIR: I'm also the author of the March 8th letter requesting the opportunity to make this presentation. And I want to acknowledge that that request was made by Bayer, but with the ascent of Valient Biosciences Corporation, Consumer Specialty Products Association, and Western Plant Health Association.

The reason I'm spending time on this, Chairman Gold and the Committee, is because we want to thank you for this opportunity to speak with you.

CSPA and the Western Plant Health Association made their request purely from a process point and we're concerned about the opportunity for the manufacturing community and the user community to interact with the Committee. This is the only opportunity we get. And I want you to know that our thanks are heartfelt for the opportunity to speak with you.

And what we hope to present to you is the opportunity of an interactive dialogue with other people

who are quite knowledgeable about these data and can help to inform your decision.

In that regard, I'd like to introduce the two speakers. The first is Larry Sheets from Bayer. Dr. Sheets holds his Ph.D. in toxicology from the University of Kansas Medical Center. He also earned a post-doctoral fellowship studying with U.S. EPA. He has studied Deltamethrin in various capacities. He has been a study director for much of his career. He has conducted dozens of studies, including pioneer work in developmental toxicity and developmental neurotoxicity. In his present position, he is a research fellow with Bayer. And he holds the position of the Human Safety Manager for Deltamethrin. He is, indeed, an authority, familiar with all the studies, and is prepared to address questions from all of you.

Our other substantive speaker is Dr. Jay Murray, consulting toxicologist from Murray and Associates. Dr. Murray's published works include many developmental and reproductive toxicity studies on chemicals such as Benzene, sulfur dioxide, TCDD, DBCP, chloroform, acrylonitrile. Dr. Murray was formerly a member of this Committee and he was, indeed, the Chair of this Committee for a period of time.

Before they begin, I'd like to speak just a few

words about the standard for living. I'd like to talk about the standard of living, but first we're going to talk about the standard for listing. And it causes me to say a word first just about the role of lawyers in this process. One of the former directors of this institution once said to me, "Stan, Prop. 65 is half law and half science. We all have to live with that."

Now, I know the lawyers tend to give short shrift sometimes to the science and the scientists tend to give short shrift sometimes to the law. But in order to implement this statute properly, we really need to marry the two together and observe both in order to reach the proper outcomes.

So the next slide, please.

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MR. LANDFAIR: I'd like to spend just a moment on this standard for listing and the oft-raised question of what it means to be clearly shown through scientifically valid testing according to generally accepted scientific principles.

The key word that we come to discuss from time to time is what it means to be clearly shown. And as Carol appropriately pointed out to you, that's not a legal term of art. It has no specialized meaning. It's just two English words, which we need to ask you to take in their

ordinary plain spoken English context. It means clearly shown. And if we seek any further guidance on that, I found some the other day in Roget's Thesaurus. Clearly shown is a synonym for proven. Shown there is no longer a doubt. It's proven.

So that does bare some elaboration in light of a recent court case. If I could have the next slide, please.

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MR. LANDFAIR: The California Court of Appeal had an occasion to address this issue recently of what it meant when chemicals are listed and had the chance to review this. And the key word that I'd like to bring to your attention here, the key sentence is the last one highlighted. It says, "Chemicals that are only suspect are not included those are not supposed to be listed." And the next slide, please.

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MR. LANDFAIR: In this regard, the panels of the committee's criteria document instructs that we are supposed to approach this from a weight of evidence approach. That's what we'll ask you to do as the manufacturers and distributors of Deltamethrin products is to weigh the evidence and determine whether or not the product is clearly shown in that context to cause

reproductive toxicity.

I have one last comment, if you give me the last slide.

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MR. LANDFAIR: I'd like to bring up just a note about another mechanism for listing, which is not at issue here, which is the authoritative bodies listing. As you probably know, but may not, there are other mechanisms for listing chemicals. One is the so-called authoritative bodies listing mechanism, which provides that if one or more of certain chemicals that are -- agencies that are designated as authoritative bodies would formally identify a chemical as causing reproductive toxicity, it would be listed automatically.

In this context, with this chemical, it is significant in our view that Deltamethrin is regulated around the world by pesticide regulatory agencies and in the United States is regulated and has been regulated since 1994 by the U.S. Environmental Protection Agency, which is an authoritative body. The U.S. EPA has reviewed the database constantly and repeatedly for this chemical for nearly 20 years. If they had ever deemed it or formerly identified it to be a reproductive toxicant, we wouldn't be here today.

In our view, the chemical does not qualify for

listing, but I don't want to over extend my expertise. I'd like to turn over the floor to Dr. Sheets and Dr. Murray, if you'd like to proceed now. Or if not, after lunch.

CHAIRPERSON GOLD: So you're not going to speak for a total of 20 minutes, is that it?

MR. LANDFAIR: I just want to be responsive to you. That's all I need.

CHAIRPERSON GOLD: That's all you need. Okay. Thank you.

Are there any questions for Mr. Landfair?

COMMITTEE MEMBER WOODRUFF: Yeah, I have a question. Are we going to get a copy of the slides, your slides?

MR. LANDFAIR: I'm sorry?

COMMITTEE MEMBER WOODRUFF: Will we be getting a copy of the slides?

MR. LANDFAIR: I've given a copy to Cindy, and I've got some extra copies right here if you'd like them. I'll pass them out.

COMMITTEE MEMBER WOODRUFF: My other question is has U.S. EPA made a hazard identification call on Deltamethrin?

MR. LANDFAIR: I'm going to let Dr. Sheets address all the questions about the data, if that's okay

with you?

COMMITTEE MEMBER WOODRUFF: Because it says on your slide that they are an authoritative body; right?

MR. LANDFAIR: That's correct.

COMMITTEE MEMBER WOODRUFF: And the other question I had was related to the guidelines. We got a copy of the criteria for recommending chemicals for listing, as known to the State to cause reproductive toxicity. And I've been looking through these because I'm trying to look at all the data and figure out how -- what the current guidelines are for evaluating. And it does have that there's different variations on the weight of evidence considerations. So, for example, they have a listing for what might be sufficient evidence in humans and what might be sufficient -- considered sufficient evidence in experimental animals.

Will you be talking about that in reference to these guidelines? So, for example, number of -- you can have this weight of evidence consideration for animals for sufficient includes consideration of data on a single species from a well-conducted developmental and reproduction study may be sufficient to classify an agent as a reproductive toxicant, provided they're not equally well conducted studies that show an effect and have sufficient power to call into question the repeatability

of the observation in the positive study.

So some of those things I've been thinking about, that is one criteria or data on more than one species or for more than a single study increase the confidence or classification of an agent on a reproductive toxicant.

So I think those are also things that are -- that I'm thinking about as we're looking through these studies and considering your -- some of the language that is legally binding for how we decide whether these are reproductive or developmental toxicants.

MR. LANDFAIR: As I'm sure Ms. Monahan-Cummings will tell you, the DARTs criteria document are guidance. They are published by this Committee, although sometime ago. And they serve as a tool for your use. They're flexible. They don't box you in. They encourage you to look at the totality of the data and consider the weight.

And to answer one of your questions, the complete criteria were attached to a copy of our submission on December 12th, I believe. Is that Attachment A?

COMMITTEE MEMBER WOODRUFF: Okay.

MR. LANDFAIR: And I know Dr. Murray would like to speak to you in terms of actually how he would go about weighing the evidence against those criteria in this case.

CHAIRPERSON GOLD: Ms. Monahan-Cummings, do you have a comment?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. A couple comments, just briefly.

In terms of your questions, Dr. Woodruff, where to begin here? You were asking about the guidance that you have from the Committee that was developed several years ago by this Committee, and it is considered general guidance. You actually as a Committee can modify that, change it in whatever way you think is appropriate. It was developed some years ago before some of the newer scientific methodology was developed. And we discussed that a little bit at the last meeting about what some of the duties of this Committee are and your abilities to change the various materials. And that also includes the criteria that is used for authoritative body listing. Mr. Landfair mentioned the authoritative bodies and also mentioned a decision -- a court decision in the Styrene Information and Research Council case against OEHHA. On both of those, the case actually dealt with a different listing mechanism. It's called a labor code listing mechanism. It has nothing to do with this Committee and neither does that decision. It was decided on a different standard, on different facts, and in a different context than what this Committee does.

In terms of the authoritative body listings, again, the criteria is different for that listing

mechanism. I mentioned this at our last meeting, but there are four listing mechanisms under Prop. 65. Each one of them is separate. Each one of them has a slightly different set of criteria. Criteria for this Committee that we mentioned already and so has Mr. Landfair is clearly shown through scientifically valid evidence.

So really, the criteria that you would be applying here has to do with the scientifically valid evidence clearly shown standard. And whether or not U.S. EPA has determined whether the chemical is a reproductive toxicant is really not relevant here. I understand our commenters may disagree. But from my perspective as counsel for this Committee, it doesn't have anything to do with it.

MR. LANDFAIR: Well, I think you may learn now why we don't like to have lawyers speaking before the Committee. I think Ms. Monahan-Cummings is trying to extend my remarks far beyond what I intended.

What I intended to point out to you here is EPA has considered this many times and has never declared the chemical a reproductive toxicant. Leave that as it may, as I said, if it had, it would have been listed by that mechanism.

With respect to clearly shown, the statute says clearly shown. And I've tried to explain to you how you

can use that term in your own use.

With respect to the DART criteria, of course, you may change them. We trust if you were to change them, you would do it in the future. You would not do it retroactively or on the fly at this proceeding.

And the point I tried to make with respect to the DART criteria is that they encourage you to use the weight of the evidence approach. I think we can all agree on that.

CHAIRPERSON GOLD: Okay. Thank you. Are you finished?

MR. LANDFAIR: Unless you have further questions for me.

CHAIRPERSON GOLD: Any further questions from the Committee?

MR. LANDFAIR: Thank you again. We appreciate the opportunity to be heard.

CHAIRPERSON GOLD: Thank you. So the next speaker is Larry Sheets, who will get 20 minutes. We did -- and Jay Murray will get 20 minutes. And then we have two other speakers -- we'll see how the time goes as to whether we do those before or after lunch.

(Thereupon an overhead presentation was presented as follows.)

DR. SHEETS: Thank you for letting me speak

today. I appreciate all the time and effort you've put into evaluating the data with Deltamethrin, and I appreciate the comments that were provided.

I promise not to overly repeat what you've already discussed. But I think the approach I'm going to take is to really systematically go through the information that we have, starting with the guideline studies, to determine whether Deltamethrin is a reproductive or developmental toxicant. And I want to go through each of the principle findings that were identified in the HID and evaluate those in the context of a weight to evidence to say are these findings credible relative to all the available information? Are there some indications in there that raise uncertainties with respect to findings of a given dose that contradict or contrast, for example, with findings we have at much higher dose levels in other studies.

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DR. SHEETS: So it's already been mentioned Deltamethrin is a Type II pyrethroid. Its principle effect is certainly on the nervous system, effecting the voltage-gated sodium ion channels and nerve membranes. And the principle effects we see in the Tox database, whether it's by an acute bolus dose or a chronic dietary

exposure are indications of acute neurotoxicity. The driver for chronic risk assessments are acute neurotoxic signs in a one-year dog study, for example. It's really not a cumulative toxicant, by and large.

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DR. SHEETS: I will be emphasizing the relative value and the weight that I think we ought to place onto the guideline studies. It's not to say I think my studies or our studies are better than someone else's. But I think a lot of the questions you've raised in terms of uncertainties with regard to what the animals received and how and what they were -- some of the test elements, et cetera, really point back to the importance of and the added value of GLP studies, conducted in accordance with standard guidelines where we have a lot of data and a lot of experience running the tests that we performed.

GLP, as most of you likely know, really gets down to very rigorous documentation and oversight of everything that's done in the laboratories. The staff follow standard operating procedures. And protocols are established in advance, to be sure the studies are conducted in accordance with the test guideline requirement to satisfy global registrations.

These study designs, the tests and design of the

study is not something that the individual labs come up with. These are stringently designed to -- in accordance with standards that really lend themselves to help toxicologists and the regulatory bodies evaluate the data, the significance of the findings. We work with a very high grade technical material. You look at the guideline studies, you know what the dose was. You know what the treatment was the animal received. Everything is very rigorously documented in terms of purity and doses and things like that.

Standard study design always requires we run at least three dose levels with an appropriate control. And that control is something -- is the animals receive everything, but the test materials, so we really have a very good standard reference to know what is the effect of the chemical Deltamethrin on those animals at different dose levels. And guidelines require that the low dose be one that we expect to show no adverse effects. The high dose is the highest dose the animals will tolerate without overly interfering with the interpretation of the data.

As I discuss the two-gen study in a second, we slightly exceeded that. It really compromises to some extent the ability to interpret the data at very high dose levels. The mid-dose is something in the middle typically halfway between the low and the high dose. You look for a

graded increase in the effect, obviously, to help with the interpretation.

I already mention reference to appropriate controls. We also have a lot of historical controls that are referenced, so if we have -- if we had values that are either trending or statistically significant, or we see some controls that seem a little abberant we have a rich database to refer back to to say how do those animals at various dose levels, including the controls, compare with the controls in the current study. And that's something that's sorely missing in a lot of the published data that we have to look at where we're comparing one group treated to one control group and any difference is considered to be a potential effect.

We have sufficient sample sizes. And I do have to be cognizant of my time here and move along. But in many of these studies, you'll see samples of three, five, eight animals. The guidelines specify what sample size. And for these developmental repro tox studies, typically it's a minimum of 20 animals per dose group using a route and duration of exposure that's relevant for the purpose. Route being relevant to potential human exposures with the appropriate selection of end points.

If I can have the next slide.

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DR. SHEETS: These are the complements of developmental and repro tox studies that we have with Deltamethrin. It's already been mentioned kindly we've got the two and three generation studies. We have developmental toxicity studies, and the two standard animal models, the rat and the rabbit with exposures to implantation through gestation. And we have the developmental neuro tox study. And as I go through my slides, I'll also try to attend to some of the questions that were raised that I think I can answer. For example, with the DNT study, those animals' exposure stopped at lactation day 21, but we extend the testing of those animals until they're adults at 60 to 70 days of age to look for latent effects or persistent effects.

I think we should also point out that we have a lot of data in adult animals that's relevant here with 90 day and one year exposure studies in three species where we look at reproductive tissues for evidence of histopathology. In all cases, these tissues have shown no specific ffects and no histological changes.

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DR. SHEETS: The two-gen study I think in the context of what we're looking at here is a key study, because it's a very rigorous and extended exposure study.

This study was performed at Argus labs, which is very well renowned for their experience and expertise with developmental and reproductive toxicity studies.

In this study, very briefly, the study design starts at twelve weeks. The exposure starts twelve weeks before the animals are co-housed for mating to make sure you cover the full spermatogenic cycle and extends through the delivery of those offspring. Those animals are raised, mated, and until the offspring of those pups go out to postnatal day 21.

In this study, there's 30 animals per sex per dietary level. Four dose levels, including a high dose where we actually produce a pretty considerable toxicity, with one dam in the P generation that died and another animal showed signs of neurotoxicity. Those were most clearly seen during the lactation phase when the dietary intake, the intake of the treated diet, increases in the mothers. So we see signs of neurotoxicity.

There were no histopathological effects. There were decreases in body weight in those animals and tissue weight decreases in the females which has already been mentioned.

The F1 animals showed also acute neurotoxicity, including mortality, at the time they started eating the treated diet. Those animals eat a lot of feed per

kilogram or gram of body weight. And they expressed clear acute neurotoxic signs, including a significant number of those pups that died.

The tissue weight decreases in those animals was clearly secondary to decrease in the body weight. There was some reference to the brain weight being conserved. We always see that in these studies. Brain weight is conserved relative to other tissues. That's very common. It doesn't take anything away from the fact that the effects on tissue weights in this study were associated with a decreased body weight during growth and development.

Going to the next slide, please.

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DR. SHEETS: There were two findings that were cited in the HID. As I go through the rest of the material, I'm going to go through these principle findings that were identified and evaluate them. In this case, these are two findings that were cited as evidence or potential evidence of reproductive toxicity in the two-gen study.

I've already mentioned the fact these decreases in tissue weights were associated with significant decreases in body weight. So it was only absolute tissue weight reduced and not an effect on relative weight when

you take into consideration the body weight of these animals.

These findings occurred only at the high dose level. They were associated with a dose that produced mortality, decreased body weight. And there was no evidence of histopathology in these tissues.

So the conclusion is the findings at the high dose that were cited in the HID are secondary to decrease in body weight and mortality and not evidence of reproductive toxicity. Next slide, please.

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DR. SHEETS: And what I just said is consistent with the evaluation performed by the California Department of Pesticide Regulations, U.S. EPA, the European Union, and the World Health Organization. They looked at the results from this two-gen study. They noted the signs of neurotoxicity and decreases in body weight in the parental and the F1 generation pups. And they conclude there is no evidence of reproductive toxicity, even at a dose level that produced lethality.

And really, the evidence that developmental toxicity were not effects that were expressed during fetal development, but rather were expressed postnatally, particularly when the animals started eating the treated feed and received very high dose levels.

Before I go on to the rest of the studies, I'd like to ask if there are any questions about the guideline study information we have before I go on to the rest of the material and digging into the details.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: I just want to make sure I understand this correctly. In the three-generation study, the second generation actually had reduced effects on body weight and mortality? But they continued to receive the --

DR. SHEETS: So there were two multi-generation studies. The Wrenn study from 1980 predated the guidelines. And one of the main deficiencies that were identified in that study is it didn't meet MTD criteria. There was essentially no toxicity shown in that study up to a dose equivalent to two and a half milligrams per kilogram per day.

I point that out because I think that information is also useful as we're looking at other studies that show findings at one and two milligrams per kilogram per day.

The study I'm dealing with here is the two-gen study by Hoberman. Those animals are treated through the diet throughout the P, the F1, and the F1's delivery of their offspring. Does that answer your question?

COMMITTEE MEMBER PESSAH: There's an increase in

resistance to the compound, given there's fewer effects in the second generation?

DR. SHEETS: No. There were more toxicity in the second generation in terms of there were more deaths. And the pups, when they started eating the treated feed, their dose level really goes up significantly.

So the findings that we see are really associated with the dietary intake and the acute effects from what those animals are receiving on a daily basis. Does that answer your question? Okay.

CHAIRPERSON GOLD: Other questions before we proceed from the panel? Okay. Go on.

DR. SHEETS: Thank you.

Next slide, please.

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DR. SHEETS: What I'm doing now -- and I don't want to belabor the point, but I think in some cases some of the questions you had in terms of really we need to look back and say, well, so why did this study show one thing and another study didn't, or do we have the evidence from -- do we just have a finding in one study that's either unexplained or we have some frame of reference.

So I've gone through the principle findings identified in the HID and tried to -- I've highlighted in this red some points that I think are critical issues for

us to evaluate.

And in the interest of time and your attention span, I'll try not to dwell too much on those, but rather to move through these very quickly.

So there was one other pair of studies from one lab that looked at female reproductive toxicity. In this case, I just point out what Dr. Rocca has already noted. This is one of the studies that tested a formulation that has 2.5 percent Deltamethrin. I think it's important for you to know that the other 97.5 percent formulating agents are not just detergents but also included aromatic hydrocarbons.

One of the things with Deltamethrin is it's very water insoluble. It's necessary to formulate these in a fashion that allows it to be mixed in a way that it can be dispensed and used in the real world. And as was already pointed out, it's critical deficiency to note the controls didn't receive the formulation minus the Deltamethrin. They received water. So it's really inappropriate for a reference.

So the conclusion from the female reproductive toxicity perspective is really there is no credible evidence to indicate that there is a current -- an issue. And in fact, the guideline studies indicate quite clearly that there's not, even at dose levels that produce

lethality.

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DR. SHEETS: I have a few slides that deal with the male reproductive toxicity and including the question about the sperm parameters that were mentioned earlier, because those aren't evaluated in this same way in the guideline studies as had been reported in a couple of publications.

To quickly point out the same deficiency with the first study dealing with sperm effects, this was a Decis five percent formulation. It was 95 percent formulating agent, including aromatic hydrocarbons. The controls again received water.

In this case, the effect on conception rate indicates that was actually lethal to the fetuses at dose levels of one or two milligrams per kilogram. I've already said in the two-gen study, we tested 26 milligram per kilogram. And in the developmental neurotox study, the high dose was 16 milligrams per kilogram per day. So there is a real inconsistency that says this formulation is really much more toxic than Deltamethrin.

The second one refers to a study where the subcutaneous dose administration at a very low dose level, as Dr. Rocca pointed out, we don't know the test material purity. And it's really not appropriate to have a study

with just one dose level for reference.

So succinctly I would just say -- I'll be more succinct on some other slide, there's critical flaws in these studies. And the findings are inconsistent with the absence of histopathology and the two-gen and the adult studies looking for histopathology in the testis and epididymis.

Although, in those studies, they don't specifically look at live sperm and sperm motility, as some of these studies do. And I'll talk to that in the next slide.

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DR. SHEETS: Continuing with effects on the testis, this is a study by El-Gohary, and an IP dose, which is not relevant, they report really arrested spermatogenesis at a dose of one milligram per kilogram per day. Obviously, that's not something that would have been overlooked in the guideline studies that have been performed. So there's something going on there that raises a flag. We don't really understand what they tested, what they did. They referred to testing Deltamethrin, but that's really an inconsistency. So we don't really know what they did test.

One dose level -- generally just a flawed study and with findings that are inconsistent with, frankly,

more credible data from other studies.

The study by Andrade, those findings are interesting. As you've gone through the papers, you see the more you dig into some of these, a little more clear. There are things that are unclear. And so in this study, it was -- in some ways, it looked like a pretty good study with high purity test material and three dose levels. When you look at the findings -- and I'll give the author's credit. They say they were subtle changes. But the number would decrease to ejaculate that was not statistically significant. The findings weren't dose related. Without a historical control reference group to look back to, you don't know whether the controls were a little bit odd or what's going on. It's really not a very strong finding.

The decreased tissue weights that was identified in the HID again are associated with decreased body weight. And it's interesting that the effect on -- they reported a decrease in the seminiferous tubule diameter. If you do the calculations, it was a 5.7 percent difference from that control group with no reference to historical controls. So it's really a very minimal difference from one control group. So it's really insufficient evidence to say there are concerns here of an effect.

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DR. SHEETS: I think this will wrap up the male repro tox.

These are the findings with sperm parameters, decreased sperm count, motility and viability.

As Dr. Woodruff pointed out, we look at histopathology in the testis and epididymus in multiple studies. There is no evidence of histopathology even at much higher dose levels.

In the guideline studies, we didn't specifically look at these parameters. We need to look at these studies at face values to see how credible we think the findings are.

The first study by Abdallah 2010. They tested one dose level. The purity was unknown. It's one of those where you're comparing one control group to one treated group.

And the question is: Is that really biologically significant or robust finding? Or is it an incidental finding?

The second study by Salem in 1988 with a decrease in ejaculate volume and sperm concentration with increased dead sperm in the rabbit, sample size of three animals is grossly inadequate for this kind of study. We don't know

what doses the animals received. They only reference it to a percentage of an LD 50 dose. And we don't know anything about the test material purity. Very limited report of a finding that would obviously require verification from other studies.

So to conclude from these, we have a number of flaws -- critical flaws in these studies that I've gone through. There is no reference to the range of biological variability in their control groups, just comparing to one control group. And we don't have any histopathology in the two-gen study. So really very limited findings here that would require verification to warrant support that these are real effects.

Next slide, please.

CHAIRPERSON GOLD: Can I just point out, you're at 20 minutes now? We did interrupt you for a couple minutes. So I'll give you a couple more. But it would be helpful if you can wrap up.

DR. SHEETS: I'll do my best.

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DR. SHEETS: So the DNT study, there were findings. This was a study I was involved in reporting a decrease in fixed brain weight in the females. By fixed brain weight, these animals were profused. It's critically important to understand that the non-profused

animal's brain weight wasn't affected in a study in the females and neither fixed nor fresh brain weight was effected in the males.

The effect on -- the other thing I would point out from the DNT, we did look at motor activity at multiple time points. The other studies that refer to effects on motor activity, it should be understood that there was no effect on motor activity in the DNT studies during the period of exposure 60 days of age and at 120 days of age.

In the interest of time, I just need to move to refer back to the Lazarini study. I think the deficiencies for that study were already pointed out and really the limited findings could be due to biological variability.

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DR. SHEETS: I think we've already discussed the fact that there is multiple studies that report no evidence of teratogenic or developmental toxicity in the classical sense. I won't elaborate on those.

I think the findings in terms of effects on the ontogeny of eye opening and vaginal opening. You look across the studies, there's really no consistency. One study reports no effect on eye opening. Another one says

a delay. And the same with vaginal opening. And Dr. Rocca appropriately pointed out when you have effects on body weight, you can get modest delays in sexual development or development of these markers.

Next slide please.

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DR. SHEETS: I think the second study here, the Kandil 2006 with the formulation again. I don't need to reiterate the limitations of studies with formulations.

Next slide.

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DR. SHEETS: So down to my last two slides, so I think maybe I'm going to make it, if you don't cut me off.

I think it's important in a weight of evidence context then and the way that we've tried to evaluate the data to say the DART studies that have been performed in accordance with GLP and global standards have determined Deltamethrin is not a reproductive toxicant. Findings from other sources are generally unreliable for the reasons I've pointed out and are insufficient to challenge this determination.

With respect to the developmental toxicity, the same point is that, from our studies, the guideline studies that have been performed over decades have shown it is not a developmental toxicant. And the findings from

other sources identified in the HID are generally unreliable for the reasons I've mentioned or associated with general toxicity to the mother and the offspring. Next slide, please.

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DR. SHEETS: To conclude, I would point out these are not just the judgments from me or anybody else in this room, but these are evaluations consistent with reviews by regulatory agencies around the world that are responsible for protecting the public health in their regions of the world. And they've determined that Deltamethrin is not a developmental reproductive toxicant. And that includes reviews that are quite current.

So with that, I'd like to close and ask if there are any questions.

CHAIRPERSON GOLD: Thank you.

Any comments or questions from the panel for Mr. Sheets? Dr. Pessah.

COMMITTEE MEMBER PESSAH: You were involved in the Gilmore 2006. And so one of the findings was that there was early behavioral abnormality that was detected in terms of -- would you speak to that, because it seems to be missing from your presentation?

DR. SHEETS: I'm sorry. The vocalizations? So we looked at the data and based on the pattern and

occurring at the high dose we figured that that was an effect.

And that's not unusual with the Type II pyrethroid. They tend to be hyperreactive. They tend to react to being perturbed and picked up and things.

We don't know whether that was actually an acute neurotoxic effect or whether this was the very young animal, these pink erasers as we call them. With the Deltamethrin in the diet, they also get a certain amount of feed on their skin. And that could have been due to the paresthesia. When you handle them, it's irritating and somewhat painful to them, because you get the feed dust in the bedding material.

We didn't know which it was. But it's common to get a hyperreactivity to Deltamethrin and other Type II pyrethroids. So I would attribute it to a manifestation of acute neurotoxicity. But we don't know that specifically.

But I would just say it was just in one sex, just in the male pups, and only at the one time point. So what you make of that is -- I speculate what I think it was due to, but we didn't put that in the report because we don't like to speculate in our reports. We like to stay with exactly what the data say.

CHAIRPERSON GOLD: Other comments or questions

from the panel for Mr. Sheets?

Yes, Dr. Rocca.

COMMITTEE MEMBER ROCCA: Are the evaluations by the other regulatory authorities available publicly?

DR. SHEETS: Yes.

COMMITTEE MEMBER ROCCA: Thank you.

CHAIRPERSON GOLD: Dr. Alexeeff.

DIRECTOR ALEXEEFF: Thank you very much for your presentation. I had a question about these two formulations, Decis and Butox. Are these like standard formulations? Are these produced by Bayer? I was just wondering if you have any information.

DR. SHEETS: Well, I mean, to some extent, the actual formulating agents that are used in there is confidential information, because it could be used by your competitors. So it's -- but you can go online and look to the same extent I can.

And the reason I'm kind of hedging a little bit because I don't know exactly how they're -- they're using these in terms of I guess the source that they received it from. It was identified as Decis. I don't know -- that doesn't specifically mean a specific formulation. I can say that.

The Butox, I don't know about it, what it is, other than the information I can pull off online that says

that it generally includes the aromatic hydrocarbons.

Of course, what we are looking at today is what are the effects of Deltamethrin. When you have other agents in there that constitute 95-plus percent of what's there, clearly we're not just testing Deltamethrin. That's why I think you look to see, well, are the findings, for example, consistent with what we see with a known high purity test material or not. If they're not, you say, well, can that be explained by other agents that are in there? And then you're really a considerable step away from evaluating Deltamethrin.

DIRECTOR ALEXEEFF: The question I had was --

DR. SHEETS: I'm sorry.

DIRECTOR ALEXEEFF: Are these third party formulations?

DR. SHEETS: Yes, they can be. They can be. And that may be -- I don't know about the Butox specifically, because Deltamethrin is generic.

COMMITTEE MEMBER WOODRUFF: Does Bayer make Butox?

DR. SHEETS: Honestly, this is getting beyond toxicology in terms of what I know. That's why I'm looking over my shoulder.

The point they were sharing with me is these formulations are prepared in many countries around the

world. Some are manufactured by Bayer. Some, it's third party. And I'm sorry I can't answer you get better.

COMMITTEE MEMBER BASKIN: It sounds like you don't know what's in your product is what everybody's confused about.

DR. SHEETS: It's not my product. I'm not a manufacturer. I'm a toxicologist who works for Bayer.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER ROCCA: As you said, one can go online and find out some of this information. So I do actually have a copy -- if the group would like to see it -- of the MSDS for Decis, and it contains 2.9 percent Deltamethrin, between one and five percent tetrapropylene, benzenesulfonic, calcium salt, between one and five percent of isobutanol, and greater than 50 percent solvent naphtha petroleum-like aromatic.

DIRECTOR ALEXEEFF: Does it indicate who produced the MSDS?

COMMITTEE MEMBER ROCCA: It has Bayer CropScience on it on the top of the version I got. I don't know if that means they produced it or produced MSDS for use in some of these studies.

CHAIRPERSON GOLD: Thank you.

Maybe Dr. Baskin first and then Dr. Pessah.

COMMITTEE MEMBER BASKIN: Couple questions.

Can you tell me what happens after you put it on crops? There is some data in the literature we have. From your perspective, this washes away and disappears or is there metabolites or any problems?

DR. SHEETS: Well, that's again specifically not toxicology. What we do is we have to evaluate the degradation in terms of identifying how much of the Deltamethrin or biologically significant metabolites are present on the crop at the time that it's harvested and that's strictly regulated, that the amount that's on there, the residues that remain on there, don't exceed tolerances that have been established by the EPA.

COMMITTEE MEMBER BASKIN: What happens to the Deltamethrin?

DR SHEETS: Well, there is a certain amount of environmental degradation. So it does degrade over time, both from light and environmental conditions.

COMMITTEE MEMBER BASKIN: Let me get back to this formulation question.

I understand from a scientific perspective, if you want to do a perfect study, like all of us would like to do, you want to take the chemical Deltamethrin and have a perfect control. But the problem I'm having is there is an association that we can't ignore. Whether it's Deltamethrin or not, when you use the chemical that comes

from Bayer or other companies that make it, we have to evaluate all that data. How would you respond to that?

DR. SHEETS: Well, the excipients and the solvents that are in there don't persist to the final product. So it's not -- so what someone that would be consuming, for example, a piece of fruit or come into contact with the material in other uses wouldn't come into contact or consume the formulation.

The residual that would be the Deltamethrin that is not volatile, doesn't volatilize and remove. So the Deltamethrin, as opposed to the formulation, is the common element that someone could be exposed to through multiple different formulations.

COMMITTEE MEMBER BASKIN: So getting back to the first question, everything else disappears, but the Deltamethrin?

DR. SHEETS: Yes. I would expect so. They would either volatilize or wash off.

COMMITTEE MEMBER BASKIN: Thank you.

COMMITTEE MEMBER PESSAH: But if we talk about exposures to either people that are applicators or people that bring it home, the technical mixture really should be transferred into an animal in a very well-controlled study. So we can fault these other studies for not doing vehicle controls that are appropriate, but using a

formulation that typically is not used by crop protection or home use is equally faulted because you could change the pharmacokinetics.

So related to that question is have you measured brain levels and reproductive tissue levels of Deltamethrin with your exposure?

DR. SHEETS: So to get at the first inference before your question, if I could, in terms of potential exposures to women of child-bearing age and children, in cases of the person doing the application, that's going to be taken into consideration in the risk assessment. It's also taken into consideration in the label and the recommendations in terms of personal protective equipment that has to be worn by the person who's applying it.

So that person with these commercial formulations are professional applicators who are trained in how to apply it, where to apply it, for example, in and around the home or in the field, as the case may be. And the label identifies what PP is required, whether for respiration, long sleeves, gloves, things like that.

The other thing is if the use allows for exposure of women of child-bearing age or children, there is an additional safety factor that's applied to extend the margin of safety between potential exposures and the studies that we have from our toxicology studies. So

they're protected in that fashion as well.

And then I forgot your question.

COMMITTEE MEMBER PESSAH: But the distribution to target organs that are of concern to this Committee, have you measured levels of Deltamethrin? And what might they be if you've measured them?

DR. SHEETS: As a preliminary study towards developmental neurotox study, one of the things we have to do is to establish that there is exposure of the pups. So in that study, at least we did measure brain levels to verify that the pups are exposed through the milk during lactation. So during that critical stage of development, not only during gestation, but also early postnatally through the milk, as well as through the milk and the treated diet when they start to eat the treated feed.

In that study, we verified there was exposure, starting exposure on postnatal day ten before the pups start getting into the diet. And obviously, the presence of Deltamethrin in the brain is consistent with the fact that we do see CNS types of neurotoxic effects we didn't measure it in reproductive tissues.

CHAIRPERSON GOLD: Other questions.

Dr. VandeVoort.

COMMITTEE MEMBER VANDEVOORT: I do have some concerns about the fact that the data that we're looking

at in terms of dermal absorption seems to be on the compound itself and not in conjunction with the detergents or hydrocarbons or solvents that are being used to get this into solution.

So, I don't know. Part of me you're saying that there's -- the people who are preparing and applying these materials are sufficiently protected with personal protective equipment. But on the other hand, if they're using it on lawns and gardens and golf courses, how long is the wait time between application and potential exposure for people just walking through areas?

And I guess I'm having a tough time deciding maybe the dermal absorption might be very different once this compound is in contact with detergents and solvents as well as the intestinal uptake might be very different if it's still in solution with those.

So I'm kind of back to what Dr. Pessah said about how are these formulations in total effecting the studies.

DR. SHEETS: Well, so for each formulation, we do have to do a set of acute toxicity studies to evaluate potential hazards. We have to do acute oral toxicity to determine and LD 50 value. In particular, if the LD 50 above 2,000, between 200, 2,000, et cetera, of certain categories.

We do also an acute dermal LD 50 assessment so

then you get the comparison of how toxic is a material by dermal route versus oral. We do an acute inhalation exposure study with four hours exposure typically by nose only to look at potential toxicity from inhaling an atmosphere of each of the formulations. We do eye and dermal irritation studies. And we do dermal sensitization study to look at sensitization potential.

Based on that profile, the label identifies not only what PP are required, but the potential hazards. And it also informs emergency personnel what are the appropriate steps to take in case of an inadvertent exposure.

COMMITTEE MEMBER VANDEVOORT: I guess with those acute studies for the LD 50, you aren't looking at reproductive end points?

DR. SHEETS: That's correct. We are not.

CHAIRPERSON GOLD: Other comments or questions from the panel?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: Are you aware of any non-monotonic dose/response relationships for pyrethroids? Just in general. I'm sure there's probably none for Deltamethrin.

DR. SHEETS: Well, I mean, obviously, there is a lot of end points. I mean, yes, I can think of one. With

a Type I pyrethroid in the -- after an acute exposure, you get a nice dose-related increase, and the acoustic startle response up to the point where the animals are physically debilitated then you see a decrease. That's clearly explained by the acute effects it's having on the function of the nervous system.

I mean, that's an example. Did you have something more -- another example in mind or --

COMMITTEE MEMBER PESSAH: I was thinking more at lower doses rather than at repetitive high doses that --

DR. SHEETS: No. The answer would be no.

CHAIRPERSON GOLD: Do we have any further questions or comments for Mr. Sheets?

I'm going to ask the panel a question since the discussion has gone a little bit longer than anticipated. Should we take a lunch break or just a five-minute break? Do we have a preference?

COMMITTEE MEMBER WOODRUFF: I'd like to eat lunch.

CHAIRPERSON GOLD: Okay. If that's okay with Jay Murray, we'll postpone your comments until after lunch.

Ms. Monahan-Cummings.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just a quick note as you go to lunch, just a reminder that since this Committee is supposed to discuss and deliberate in public,

if you could avoid discussing this chemical or other questions you might have during lunch and just save that until we come back to the meeting.

In the event you do have a discussion with anyone, I certainly can't tell you you can't, then when you get back, you need to disclose that, that you had a discussion with someone and the general subject matter you discussed.

CHAIRPERSON GOLD: Thank you for the reminder. What I'm going to propose is that we come back by 1:20. And then we'll start with Jay Murray. And then we have two other people that have asked to give public comments. So we'll continue with those as well. Back at 1:20. Thank you.

AFTERNOON SESSION

1:20 PM

CHAIRPERSON GOLD: Good afternoon. I think we're all gathered back. And so we should reconvene and continue the public comments. So I'm going to ask Jay Murray to give his public comments.

DR. MURRAY: I'm Jay Murray. And thank you, Dr. Gold and members of the Committee, for the opportunity to speak, and also for reading the written materials that were submitted by SC Johnson as well as others. I know you had a lot of stuff to read prior to this meeting.

So I'm going to briefly describe how I evaluated Deltamethrin as a scientist. Basically, I'm going to walk you through how I would have evaluated this compound --

CHAIRPERSON GOLD: Would you get the microphone closer to your mouth, please? I'm having a little trouble hearing you.

DR. MURRAY: I'm going to tell you how I evaluated Deltamethrin and basically how I would have done it if I were on the Committee, just as something for your consideration.

So it's important to keep in mind that this is a hazard identification process that you're going to be asked to determine whether Deltamethrin meets the listing criteria of Prop. 65. And so you are not being asked to

give Deltamethrin a clean bill of health or to say that all the studies that have ever been done are great studies of Deltamethrin. But you'll be asked to determine whether it's been clearly shown to cause reproductive toxicity.

So the best conducted gold standard studies indicate that Deltamethrin is not a reproductive and developmental toxicant.

In contrast, there are the other studies reported in the literature that do report a variety of effects on a variety of end points. And there are two issues with these studies. The first is that many of them have serious flaws and limitations, and you've discussed that among yourself. You've heard others talk about those limitations. And the second is a lack of consistency in the findings in these studies. And Dr. Sheets pointed out a number of the inconsistencies across studies. But in addition to that, there are also inconsistencies within some of these studies.

And I'll give you an example. In the Lazarini study, you were talking earlier about latency to float in the swimming test. And latency to float is the average number of seconds it takes or the number of seconds it takes for the average in the group to start to float is what that is.

And in the control group, the value is about 13

seconds. In the Deltamethrin treated group, it was three seconds. And that was a statistically significant decrease. And as one of you pointed out, it really looked like that there was an outlier in the control group so that the anomaly was the control group rather than the treated group. And if you look at the data for females in that same study in the same table, the values for the controls in the treated females was two seconds and one second. So the control males, 13 seconds. The control females, two seconds.

So unless you believe that there is really a six or seven-fold difference in sex in that parameter, it just doesn't make sense. It's more likely it's an anomalous male control group. That's one of the problems when you have studies with only one dose level and no historical control data is you don't have a read on variability. If there had been other dose levels, you'd at least have an opportunity to evaluate dose response and see if that is really an unusual control. So that's just one example. There are lots of others, and I'm not going to go into any of the others.

So the other -- as I said, the other problem is the quality of the studies. And you all recognize it's important to consider the quality of studies. And it's especially important under Prop. 65, because the listing

criteria in the statute says it's got to be clearly shown through scientifically valid testing according to generally-accepted principles. And you can't list a substance based in whole or in part on a study that is not scientifically-valid testing according to generally-accepted principles.

And you know, I'll weigh in on the Decis issue. I do think it's appropriate to discount those studies and set them aside. Now, that's not to say that it doesn't raise some concern as some of you have pointed out because there is an association. But think about what you're being asked to reach a decision on. It's got -- it's not a decision on a mixture, and it's not an association. It's Deltamethrin. The compound has to be clearly shown to cause.

And the reason I said on the Decis studies, it's a formulation. The formulation isn't the fatal flaw in my opinion. The real problem is there is no appropriate control group. The control group isn't the vehicle and all the other substances that were in the commercial mixture. So there is no way you get to a causal relationship with Deltamethrin under those circumstances.

Also, the male sperm effects, it's been pointed out that there have been a number of several studies -- a number of studies that reported effects on semen

parameters and that the guideline studies that were done before there was a requirement for semen evaluation. But if you look at those underlying studies, in my opinion, every single one of the studies that looked at a semen end point had serious and significant limitations. And in the interest of time, I won't go through them. But if you have any questions about that, ask me about the specific studies, and I'll tell you why I concluded that.

So if you determined that some of the positive studies are scientifically valid testing according to generally-accepted principles, then you have to do a weight of the evidence evaluation. You've got to figure out whether you have enough scientific weight. And those positive studies would have to be very convincing and compelling, given the results of the well-conducted guideline studies.

And in my view, even if we didn't have those guideline studies, I don't think the other studies that give you positive results are of sufficient quality to be able to reach a conclusion that Deltamethrin is clearly shown to cause reproductive toxicity.

So the issue is not really whether the positive studies had the power to call the results of the well-conducted negative studies into question. The positive studies have to be so strong that they show the

negative studies are clearly wrong and contribute virtually nothing to the weight of the scientific evidence. Otherwise, there is really no way to get to clearly shown to cause.

Even if the positive and the negative studies had equal scientific weight -- and I don't think they do -- but let's assume they did, you still can't get to clearly shown to cause under those circumstances. So in my opinion, it falls far short.

So Prop. 65 sets the bar at a high level. If you have concern and you think that you'd like to see more studies, better conducted studies, that's fine. But that doesn't get you to clearly shown to cause. If you think Deltamethrin is a suspect reproductive toxicant or a possible reproductive toxicant, that doesn't get you to clearly shown to cause. There has to be enough evidence for it to be clearly shown to cause reproductive toxicity through scientifically-valid testing according to generally-accepted principles.

So in my opinion, it doesn't even come close. But it's your call. It's not my call. And it's a decision you have to make. And I appreciate your consideration of my comments. Thank you.

CHAIRPERSON GOLD: Thank you.

Are there any comments or questions from the

panel for Mr. Murray?

COMMITTEE MEMBER WOODRUFF: I do have a question.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Thank you for your presentation.

I had a question when you were talking about the -- I may pronounce this wrong -- Lazarini 2001 study with the difference in the latency time to float, which is 13 for the controls and three seconds for the dosed animals.

Can you explain -- you said there's something about the controls that changes your interpretation? Can you show me -- I couldn't find it in the papers.

DR. MURRAY: Yeah, I'd be happy. Do you have the paper in front of you?

COMMITTEE MEMBER WOODRUFF: Yeah.

DR. MURRAY: Go to page 669 and take a look at Table 2. And it's a little confusing, because I didn't do a great job with the legends.

COMMITTEE MEMBER WOODRUFF: It's in the document that we got from OEHHA. Yes. Table two.

DR. MURRAY: So the first row in that table that is -- the parameter is LF, that's latency to float. That's the time it takes from when you drop the rat into the water to when they start to float.

So if somebody sits there with a timer and times the number of seconds it takes for a rat to decide to float rather than to try to swim when they're dropped in the water and you can see the control group value is 13.1 plus or minus 4.3. And the experimental group -- there was only one dose level, and it was .08 milligrams per kilogram, that value is 3.2 plus or minus 1.2. That's statistically significant.

And if you look at that in a vacuum, you would say, gee, looks like an effect. And in fact, that's what the author's said, this was an effect on latency to float. And they attributed that to an effect -- I think they called it on emotionality. But look at the female values right next to them, the next two columns --

COMMITTEE MEMBER WOODRUFF: Right. I see they're not that different. But --

DR. MURRAY: Not only are they not different from each other, but look at the female control value relative to the male control value. It doesn't make any sense. The female control value is 1.9, plus or minus 0.7. And that suggests there's something funny about the test. And that's why I said it's a shame they didn't have additional dose levels so you could evaluate whether there is a dose response. But it's not obvious to me that the real difference is attributable to Deltamethrin exposure in the

experimental group as opposed to --

COMMITTEE MEMBER WOODRUFF: I understand what you're saying. I guess I just wanted to clarify there is nothing in the paper that says there was something odd about -- we don't have any data on anything else about the controls, other than what's in this table.

DR. MURRAY: No. That's correct. The only clue is when you look at the standard deviation, the standard deviation is so high in that control group and that -- for whatever reason, there is more variability in the male controls than in the female controls or than any of the exposed groups.

And often when you see that, your first thought is that there is an outlier. But I haven't seen the individual animal data to know whether that, in fact, is the case. But I look at that and I say it's less than clear that Deltamethrin is really having a significant effect on this particular end point, which is latency to float, time to float.

COMMITTEE MEMBER WOODRUFF: But I would be -- another interpretation could be that there is more of an effect on male. There is a gender effect.

DR. MURRAY: Absolutely. There are alternative explanations. All I'm trying to point out is that that one is anything but clear-cut. And the authors obviously

attributed -- did attribute this as an effect to Deltamethrin.

And what I'm raising is that there is an alternative explanation. Without more data, without the individual animal data, it's hard to know for sure. And it's a shame they didn't provide historical control data or more than a single dose level, and then we'd have another way to look at this.

COMMITTEE MEMBER WOODRUFF: I mean, I agree that it's not that useful to read what the authors write about the interpretation of their studies in any of the studies, because we should just look at the data that we have. So I think if -- when we look at this data, if we have some other data that show us -- I mean, we could expect high variability and we could expect various interpretations of this.

But I think that we should look at whatever data that we have that may -- just explain our alternative judgments. And in this case, this is -- what we have only is in the paper. We don't have any data other than this.

DR. MURRAY: There are no other swimming tests. Nothing else like this that I found.

The only other thing that you have -- and it's not identical -- is the Gilmore study where they did look at a number of end points of locomotion and maze tests and

so on. But again, it's not exactly the same test.

DR. DONALD: If it would be helpful to the Committee, Dr. Mari Golub in my group is a well-recognized expert in neurobehavioral developmental toxicity and could give her opinion on how this type of data is usually evaluated.

CHAIRPERSON GOLD: Could we first see if there are any more comment for Dr. Murray and then we'll see -- comments or questions from the panel?

Seeing none, thank you very much.

Mari Golub, if you want to come up and tell us about neurotox tests.

DR. GOLUB: My name is Mari Golub. I'm a staff toxicologist with the Developmental and Reproductive Hazard Assessment Branch.

I wasn't involved in the Deltamethrin evaluation of the data, but I did, of course, read this paper because it's a very interesting paper and it's in my area. And it's a good table to look at, Table 2. One of the interpretation that Dr. Woodruff brought up was the possible sex differences in these behaviors. And if you look at the float time, the second variable in that table, it does clearly show a sex difference.

So part of the contrast of that treated male group to the females I'm not sure you would want to make

that comparison, given the sex differences.

Also, the male open field behavior also shows sex differences. And it also shows a reduced activity or possibly freezing in that there was lower locomotion in the males. So it's not entirely inconsistent with the pattern in the swimming behavior.

This particular swimming test is called a Porsolt swimming test. It's fairly widely used to look at depression and anxiety behavior as stated by the authors. And in the rat and in the mouse, it's used for both of them.

So this is just to add a little bit of thought about sex differences that came to my mind when I was looking at this data set.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER ROCCA: Thank you for that.

Are you privy to any historical control databases on this test that would help us interpret this?

DR. GOLUB: I cannot call that forward for you for the Porsolt test. I don't think we really had any presentation of historical data in connection with any of these experiments that we're discussing today.

CHAIRPERSON GOLD: Any other questions for Dr. Golub?

Thank you.

Okay. We'll move to the remainder of the public comments. So the next one is Gretchen Lee Salter.

MS. SALTER: Thank you very much. My name is Gretchen Lee Salter. I'm a Senior Program and Policy Manager with the Breast Cancer Fund.

And I'm also here today speaking on behalf of Dr. Sarah Janssen from the Natural Resources Defense Council who could not be here today.

So, first of all, I want to thank you very much for allowing us to speak today and for some of the work that you've done to try to ensure a fair process.

My comments today are really going to be focused on the process. I don't really have an opinion on Deltamethrin. My organization has not studied this issue, and I wouldn't be able to give you an informed opinion at this time.

But I do want to talk a little bit about the process that has gone forward today and talk about the process in the past and give you some context for some NGO concerns about that.

We are a bit dismayed that yet again vested interests have been given extra time to present their case. To give you a bit of context, in the past, both the DART Committee as well as the Carcinogen Identification Committee had given the chemical industry and their

lobbyists 30, sometimes up to 90, minutes to present their cases for why a chemical should not be listed. And when NGOs requested similar times, we were either denied or told we had to have a certain number of people here to cede our time to our given scientists, but that the industry didn't have to have that because they were technically a member of a group or they were representing a group.

So that's why we requested a meeting with OEHHA staff as well as the former DART Committee Chair to discuss the process and our concerns with process. And we want to make sure that people are given equal time and are given equal opportunity to represent their concerns.

The letters that we saw from SC Johnson as well as Bayer asked for more time, citing that they should be given as much time as OEHHA staff. And I would just like to point out that OEHHA is a disinterested party. They are here to assist the staff. Whereas, SC Johnson, Bayer, the CSPA, and other chemical interests that may come before you in the future are not disinterested parties. They represent a vested interest. They have a vested financial interest in what happens in this Committee.

And so if experience is any indication, they will likely cherry pick the science to make it look as though the chemical in question is not as bad as it would seem.

Or as we saw today, discount every single study that comes before you as if there's some vast grand conspiracy among a host of independent scientists to cast a certain chemical in doubt.

So while it's true that no NGO may have asked for additional time today, I would say that Dr. Gold's announcement at the beginning of the hearing today was the first that we had heard that industry will be given more time. NGO's weren't told that this was an option for us to request more time. And so I would hope that in the future if one party is going to be given more than the allotted standard five to ten minutes, that that be announced prior to the start of the meeting so that other interested parties be allowed to have the same amount of time and prepare the similar kind of remarks.

Regardless, though, even if that does go forward, I think it's important to note that unless you have the means to be at a physical meeting, you're at a distinct disadvantage. Non-governmental organizations just do not have the means to be at every meeting.

Independent scientists who have conducted all these studies that you see today do not have the means or the funding or the time to be able to come to this meeting and to defend their science against attacks that you've heard earlier today.

Workers and consumers who are going to be affected by these chemicals and who are currently affected by these chemicals work full-time jobs, sometimes two jobs if you are a person that's applying pesticide, you sometimes work more than one job because usually it's a low-income job. You do not have the time to be at these meetings.

So we, therefore, in the public interest community are at a distinct disadvantage from other members from vested chemical interests who are here today presenting their case before you.

So I would request that, regardless of who was asking to present, and regardless of how much science they have on their side, that because people on the public interest side of this will always be at a distinct disadvantage from what the chemical industry will be from where they are that nobody be given anything more than ten minutes to present their case to this Committee. Otherwise, it is just patently unfair. And that's not at all what we're trying to achieve here.

Also, I would ask you to look at other committees that have public comment periods. My understanding is that the California Air Resources Board only allows three minutes for each speaker. And my understanding -- again, I could be wrong, and I apologize if I am. But the

information I've been given is that that is not extended, regardless of who asks for more time.

So I just put that forward. I think that the Committee today has asked some very thoughtful questions, and I really appreciate the time the Committee has put into looking at this chemical. I've been very impressed with the level of discussion here today.

So I'm very impressed with the Committee. I just hope that -- this is a new Committee and as we move forward that we make every endeavor to make sure that those of us in the public interest community are not given short shrift for the lack of resources. Thank you.

CHAIRPERSON GOLD: Thank you.

CHAIRPERSON ALEXEEFF: Thank you for those comments.

And what we've announced on the last agenda, what we were planning on putting in our agenda that basically -- you know, that we basically plan the meeting on the assumption that comments will be five minutes long per speaker, roughly speaking.

However, we also indicate in there that if there is a need for more extended time period, to let us know, and we will attempt to accommodate that, with the intent -- and I think as Dr. Gold mentioned earlier today -- we want to make sure the panel has access to all

the information that they need in order to make whatever the best decision.

So I do understand also your point about the issue of the means and the public interest groups and things like that. I don't have a resolution to that concept. So maybe we can think about that issue.

But that was what the intent was. One is to try to set a rule, but at the same time be flexible enough that if it requires more understanding for the Committee to listen to this. And basically a decision will be made in large part by Dr. Gold in consultation with me. Because that's sort of the plan.

Sorry you were unaware of that. But that's -- we're flexible to adjust it if we need to. But that's what our current thought is in terms of trying to get all the information out, and at the same time, be fair so as not to overly prolong the meeting.

MS. SALTER: I understand that. And I appreciate that is exactly what you're trying to do. I think, however, you will always find that those who have financial means to be here will be presenting a certain side of the science.

What we see here today discounting the science that's been presented by OEHHA staff and saying almost every single study should not be given any weight, it's

not new. This is something that has happened for over a decade at DART and CIC meetings. So we shouldn't be surprised that what we heard today from the chemical industry says that, of course, Deltamethrin shouldn't be listed because none of these studies should be relevant.

And I guess the issue that I have is that those people who are conducting the studies, they don't have the means, they are not given funding to be at this meeting to defend themselves. So you are hearing a one-sided account of it. You're hearing an account from OEHHA staff, who has gone through the data, and now you're hearing from another side. But you aren't hearing from the actual people who conducted the study. So you're always going to have a one-sided opinion. If you said you want all the information to be presented, because the independent scientists can't be here, you'll always only have the detractors.

So I don't have a solution for that either. But I hope that we can work together and come to a conclusion and that this just doesn't remain the status quo because we don't have a solution yet.

CHAIRPERSON GOLD: If I may, I would just sort of underscore what Dr. Alexeeff has said that the goal was to post this on the website so everyone can have the same information about the time limit and have the opportunity

to appeal for more time, if they wish for it. That's point number one.

Point number two, I've been making notes about comments people have made about items that the Committee might discuss among themselves and publicly, of course. But one of them might be how we handle the issue of time limits, because I think both sides have issues around that. We really just want to be fair and equitable in making sure that all sides are heard and feel they've been heard and that we have enough information to make an informed decision. So I've got it on my list of things that the Committee ought to take up.

MS. SALTER: One suggestion I could make -- I don't know if this would actually make things absolutely equal. But right now, the Committee doesn't take comments via the web. And unless you're physically in the room, there is no way to give comment. Most of these meetings happen in Sacramento and sometimes in Oakland, but rarely do they happen around the state. So that may be something the Committee wants to consider.

CHAIRPERSON GOLD: Thank you. It's a good suggestion. I don't know about the feasibility.

I think the other piece -- I'll speak for myself -- I regard the OEHHA staff reports to be sort of objective. In other words, I would hope they give us

pluses and minuses of every study.

But I think perhaps one other item I have on my agenda is that we give them more guidance on what the Committee would benefit from hearing from them in terms of pluses and minuses.

But the web comment is an interesting one. I don't know about the feasibility, but we can look into it.

MS. SALTER: Thank you.

CHAIRPERSON GOLD: Anyone else on the panel have any comments?

Dr. Rocca has asked if all written comments that are given to the staff are given to the Committee. I'm assuming yes. And they're all nodding yes. And we did receive an extensive group of written comments. So I assume they just pass them all on.

Anything else, staff panel wants to say on this issue? So thank you very much. Sorry.

COMMITTEE MEMBER VANDEVOORT: Is it common knowledge that the written comments are passed onto the Committee?

CHAIRPERSON GOLD: I don't know if I would know the answer to that.

MS. SALTER: I did not know that.

COMMITTEE MEMBER VANDEVOORT: So maybe that needs to be --

CHAIRPERSON GOLD: Ms. Monahan-Cummings has a comment.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry. I believe that is part of our notices for each of the documents. When we publish them, the hazard communication -- hazard identification documents, when we publish them for public comments, we do say in there that all of the public comments will be collected and given to the appropriate Committee.

And that's our practice. We don't respond to those comments from by the office, because they're considered part of the same materials that you're receiving. You get the information from us. You get the public comments that are written. And then you get the public comments that are spoken here. There is no page limit for comments. And there are no restrictions on what the content of those comments would be.

CHAIRPERSON GOLD: I would just underscore that the letters I received from industry I announced at the beginning have been made public, but they know very well I didn't respond to them. If I had, those would have been made public as well. But I don't want the perception there's back-room conversations going on.

Okay. Andria Ventura. I apologize if I mispronounced.

MS. VENTURA: No, you didn't. Most people mispronounce it, but you pronounced it perfectly. So thank you.

My name is Andria Ventura. I'm a Toxics Program Manager for Clean Water Action. And I will be very brief actually.

First of all, I want to support everything that Ms. Salter said. I won't repeat it obviously. We've discussed it. But many of the comments that she made are in line with our own thinking.

Just a couple of things based on what I heard today that I just want to get out there and clarify. We heard the discussion about what clearly shown means. We've heard a little debate about that. It's been equated with the idea of proof.

You know, my thinking and my education, the idea of proving anything is a really an elusive goal most of the time. And one of the things that has to be remembered is that we have things on the Prop. 65 list that have not been definitively proven. We haven't proven, for instance, that cigarette smoke causes cancer. But there is a lot of great deal of evidence that shows it should be on the Prop. 65 list.

This is not -- as you heard from your own counsel, this is not a legal standard. It is something

that you are given the task of interpreting as far as what is clearly shown about this chemical or any other chemical that you are considering and whether it should be on the list. So I think that your legal counsel as opposed to Bayer's legal counsel is probably the appropriate one to follow on that.

The court case that was mentioned before, we need to reiterate that that was cited in one of the previous speaker's comments. That was specific to carcinogens. Meaning, it pertained to a different process than what you're going through here. It referred to the authoritative body's listing. You're not reliant on the authoritative bodies. You are the experts here. And it's your role here obviously to review the chemicals and the science around those chemicals that you are considering. In fact, often is the case that you will be considering a review of chemicals that authoritative bodies have not done an adequate job at examining. So I think we need to clarify that.

And just finally, I'll close by saying I was a little concerned earlier about the comments about dose. Okay. And I just would like to respectfully remind you that again the dose here is not applicable and the counsel has said that. What your decision is not based on what is the safe or the dangerous dose. Your decision is, is this

chemical, whatever it be on a given day, is this chemical toxic and should it be on a list that indicates that there is -- it's clearly shown that there is toxicity related to reproductive harm.

So I would leave it at that. Just wanted to make sure that we have a little balanced approach to how some of these things are being defined.

CHAIRPERSON ALEXEEFF: Thank you very much.

CHAIRPERSON GOLD: Thank you very much.

Are there any comments or questions for Ms. Ventura? Thank you.

Okay. We now turn to the Committee's discussion of the consideration of Deltamethrin listing. So I'm going to open it up to see comments the panel might have. Dr. Pessah.

COMMITTEE MEMBER PESSAH: As a toxicologist that has performed research and collaborated with researchers at all levels, looking at both molecular and cellular mechanisms as well as animal models that might portray risk to human beings, I have to admit when I read the quality of the studies that you so well presented, Dr. Rocca, that I was appalled at such studies would actually make it through the peer review. But then I also am cognizant that we did get one side of the story today. If we had Issam, et al, here who published in Toxicological

Science, which should be a rigorously reviewed journal, maybe they would have answers to your questions. But they weren't here. So we are getting one side.

The fact that animals can exhibit frank toxicity during pregnancy and literally have no consequences in their offspring just flies against the data in the human literature. Epilepsy excitotoxicity has ramifications in humans on their children.

CHAIRPERSON GOLD: Other comments from the panel? Dr. Baskin.

COMMITTEE MEMBER BASKIN: You know, as we make these decisions and look at the scientific evidence, I'm still very concerned and also performing scientific studies where we can't find out from industry what is in these chemicals, i.e., the formulations, to be able to do the proper studies, which I think is emphasized in the studies we reviewed in the literature where we know the agents we're looking at, but we don't know the other agents so we can't eliminate them to do proper controls and add different solvents and different compounds.

And understand propriety and patents and the concept of one company doesn't want to give the other company secrets. But we somehow have to come to some type of compromise when it comes to the health of ourselves, our children, and our future children. It's more an

editorial comment. But that I think needs to be taken into account.

CHAIRPERSON GOLD: Thank you. Others?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I have a question for Dr. Pessah. I was interested because everybody today has commented even in the document or whether they've given public comments about the neurotoxicity of pyrethroids and this pyrethroid in adult acute studies.

I was wondering if you could talk a little bit about the relationship between chemicals that cause acute neurotoxic effects in adult animals or adult humans and how that relates to developmental neurotox.

COMMITTEE MEMBER PESSAH: Well, I guess it depends what you're measuring in the developmental studies. Typically -- and I think some of the people that have dealt much more extensively with animal studies in the developmental period can probably correct me if I'm wrong, so please do.

But many of the outcomes that are actually measured may not be at all relevant to complex human disorders such as Schizophrenia, autism, asthma, the likelihood of diabetes or metabolic disorders. Those are very complicated human issues that have not been adequately modeled in animals, especially as a consequence

of chemical exposure.

And so I think most of the data presented was looking at blunt instruments. In other words, if you don't really have huge effects on the developing nervous system, you won't see them in those outcomes.

I was particularly intrigued by the effect on ultrasonic vocalization, but that was dismissed as, well, it's just because they're slightly immature. Well, many of us actually measure that. And very few DNT studies measure the quality and consistency of the types of vocalization these mice make, which is now very much at the forefront of trying to understand behavioral outcomes. So it really depends on the questions you ask and how sensitive they are to neurotoxic events.

COMMITTEE MEMBER WOODRUFF: That's a little funny, because I just want to comment on the proceedings before I ask you another question, because I know we're not supposed to talk about this off line. We have to have all our conversations transparently. So when I am asking you these questions, it's because some things I'm listening to the discussion and then I have questions myself about some of the scientific underpinnings. But of course, I can't -- I can't call you on the phone and ask you. I have to ask you in this public setting. So my questions aren't always as clearly articulated maybe as

I'd like.

So just to follow-up a little bit because I'm wondering about -- and this is just a scientific principle. Because we see a lot of chemicals that are -- have been neurotoxicologically active in adults, early exposure like occupational exposure. I'm thinking mercury and lead are very classic. And then we find out they're developmental neurotoxicants. I'm wondering what the likelihood is between the link if we found out it's neurotoxic in an adult, what is the data that we might expect, even if we don't have very good measures. So you're saying the measures we have of the toxicity in adults is somewhat crude because they're very acute testing. What we can infer from other data for development.

COMMITTEE MEMBER PESSAH: Well, clearly, there are quite a bit of data on persistent organic pollutants. Certainly, those compounds that have clear effect on developmental outcomes are much more persistent than Deltamethrin. But in fact, we don't know what the average exposure of an adult to a single compound is. It may not even be a relevant question because there are many, many pyrethroids that we have exposure to.

One piece of data that didn't come out here which I feel is somewhat relevant is nobody mentioned the

relationship of neonicotinoids and the pyrethroid, which wasn't Deltamethrin, in the recent Nature paper that was published last year which shows clear influences on social behavior in social insect. That may be completely irrelevant to Deltamethrin, but it does show proof of concept that if one uses a very sensitive measure that's in context of a particular organism that one can see neurodevelopmental effects.

CHAIRPERSON GOLD: Are there any other comments or questions about the panel? Are we ready to vote?

COMMITTEE MEMBER WOODRUFF: I have a question. I just have a clarification.

Can you just clarify from this state -- this was raised in an earlier comment -- maybe several comments. But in order to do the finding for a reproductive or developmental toxicant, that's independent -- you could have a study that found it at any dose; is that correct? It's not dose dependent, the hazard call?

CHIEF COUNSEL MONAHAN-CUMMINGS: Do you want to answer that? I don't want to presume to be a --

COMMITTEE MEMBER ROCCA: I think I can answer that, if we can discuss it among ourselves.

No, I don't think dose comes into this at all. We do not know the doses humans may or may not be exposed to. And that really is not I don't think relevant for us.

If we believe that it is a reproductive toxicant, regardless of how low the dose is or high the dose is, I think we need to say that.

However, what you would expect from good scientific principles is to see some sort of dose relationship. And when the only place that you see effects are at doses that are maternally toxic and that are toxic to the pups, it's very difficult to sort out whether that toxicity has to do with loss of body weight, nutrition, and other factors.

So I think some of the very high doses which we actually had animals die, you really can't say whether or not these things are reproductive toxicant. And that's pretty typical of these guideline studies that they are supposed to include a dose, which is expected to cause some toxicity and then you need to interpret it.

CHAIRPERSON ALEXEEFF: So just to clarify this a little bit more. If you're looking at a study, such as the studies that were discussed here today, you should look at the doses that were administered and to understand whatever you can about the mechanism and that sort of thing. Because there could be a situation that what's happening in the study is not applicable outside the study. So that's something -- that's one thing to understand.

The other question, which Dr. Rocca referred to -- that's why I'm speaking just to separate, is the dose to people in outside the environment. Not in the experimental study. So the dose that people are receiving is essentially not part of your deliberation right now. But what's happening in the study, you should take into account everything.

COMMITTEE MEMBER WOODRUFF: But also if we see a study where there's an effect at a high exposure and not a low exposure, that still could be an effect that's relevant to decide whether it's a male reproductive effect, a female reproductive effect, or a developmental effect, whether they're all separated here in this document -- or we're deciding on that separately; right?

DR. DONALD: If I may, this is going back a little bit to the presentation I made at the last meeting, which I realized some of the current members didn't hear.

It's always a little difficult to express exactly what the generally-accepted principles are in any area. But what I tried to clarify at that meeting is the position that's been taken by some of the more reliable bodies or some of the major regulatory bodies.

And U.S. EPA, as I expect Dr. Woodruff knows, has taken the position that developmental toxicity co-occurs with minimal maternal toxicity. It's still developmental

toxicity and should not be discounted. And that if there is excessive maternal toxicity associated with the development toxicity, then that makes it very difficult to interpret the effects in the study.

The European Union more recently has taken the position that developmental toxicity that co-occurs with maternal toxicity should be interpreted as developmental toxicity, unless it can be clearly determined that the developmental effects are entirely secondary to the maternal toxicity.

COMMITTEE MEMBER VANDEVOORT: I have a comment.

CHAIRPERSON GOLD: Dr. VandeVoort.

COMMITTEE MEMBER VANDEVOORT: I think one of the things I'm struggling with at this point is I understand Dr. Rocca's -- at least I think this is an accurate assertion, that unless you have known material as the actual technical material for the dose, unless you know what that dose is, that you really have to discount that study.

And I agree on scientific principle. But I think also that sets up this real catch 22 for investigators, because when you're dealing with compounds that are proprietary mixtures where a scientific investigator will not be able to know what control they should be using and you don't know what those other ingredients like

detergents and solvents may be having on the compounds that you're testing and yet it is in that mixture environment where the public would be exposed, you really have a difficult -- you put science in a difficult position of trying to determine anything. Because they don't have access to the proprietary mixture in order to perform proper controls.

So I think -- I just want to make sure that as a scientist myself, I would -- I don't want to just discount some of these studies that actually use the commercial compound, because I'm sure that many of them would have used controls if they only knew what the control was. So I do have concerns about that. And not with respect to this particular compound, but whenever you're using commercial products.

COMMITTEE MEMBER ROCCA: I have a question about that that I'm going to refer to Carol, which is, does Proposition 65 have any mechanism for dealing with mixtures? I know that's something the National Toxicology Program has been struggling with and taking up.

CHIEF COUNSEL MONAHAN-CUMMINGS: There are a number of listings already on the list for mixtures of various chemicals, combinations of chemicals.

One of the things that I was going to suggest to you -- and I'm not trying to influence the outcome of this

at all. It's just a suggestion is that there's different ways that you can list chemicals or identify chemicals. And there are other listings that, for example, are formulations or mixtures.

So, for example, if you wanted to say something like Deltamethrin formulations, Deltamethrin commercial mixtures, something like that, if that gets to what it is that you believe is the chemical or the substance that causes reproductive toxicity, then you're identifying it specifically -- as specifically as you can since you don't necessarily know what all the chemicals might be in the mixture, if that makes sense.

So certainly under Prop. 65, you can list -- for example, we have -- I don't know -- automobile emissions. We have secondhand smoke. We have, you know, marijuana smoke. We have a number of things that have a whole mixture of different kinds of chemicals in them and we may not know specifically which one is causing the effect or perhaps they're causing it together. It's not clear. So does that help answer the question you had?

CHAIRPERSON GOLD: You raised a question for me though. When those other ones -- mixtures were taken up, were they announced as passive smoke or automobile exhaust? They were announced as mixtures. Whereas, this one was not announced as a mixture. Does that effect our

deliberations today?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think that you're correct that in the past the other chemicals were identified in the notices as a mixture or tobacco smoke or whatever so that folks would have that knowledge in advance.

One of the ways to address that, of course, would be to defer a decision today and say that you'd like to take it up at another meeting with an additional notice saying that you're considering -- you know, it's not a qualified listing, so much it's just a listing of a different -- it's a mixture or combination or something.

CHAIRPERSON GOLD: Part of the reason I'm asking the question is your comment, but also at the last meeting when we took up Xylene, some of the studies were dealing with mixtures where some of them were dealing with Xylene exclusively. I got the sense the Committee was focusing on the ones where it was the exclusive compound. So you're saying an option for us is to defer and consider Deltamethrin mixtures or products in which Deltamethrin appears, something like that?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think so. What you might be able to do for us is give us an idea of the kinds of -- may be the way that you would be comfortable considering a chemical mixture so we can put

that specifically in a notice so that there is a public notice saying these are the kinds of things that you're considering.

What I would not recommend is that you consider listing a proprietary named product for a number of reasons that it should be probably obvious. So it would be more like a description of what it is that you want to consider, if that makes sense.

CHAIRPERSON GOLD: That's helpful. Thank you. Any other questions about this? Dr. Rocca

COMMITTEE MEMBER ROCCA: So for today, should we considering just Deltamethrin and we can decide whether at future times to take up the mixtures and what other data might be available out there?

CHAIRPERSON GOLD: Correct me if I'm wrong, but it seems to me one option would be to say we want to defer this and at a later date consider Deltamethrin mixtures, however we word that.

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

CHAIRPERSON GOLD: That's one option. The other option is to vote on what we have today, but where it's not stated as a mixture. We are just saying we're voting on Deltamethrin. Are those our options?

CHIEF COUNSEL MONAHAN-CUMMINGS: You could. But the third option is you could vote today on the

Deltamethrin, which was the chemical that was noticed, and ask for -- to consider the other mixtures or whatever at a later meeting, if that -- I mean, if that's what you want. So it's not exclusive.

CHAIRPERSON GOLD: Should I be taking a straw poll or getting consensus here?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think you can discuss this among yourselves and kind of get a feeling whether or not the people are comfortable with actually taking a vote today.

One thing I was going to mention just in general on voting is that what we do for the DART Committee is a little bit different than what we do for the Carcinogen Committee, because you have the potential for three different end points. You have male, female, and developmental end points.

So the Chair will poll you basically on each one of those end points and then ask you whether or not the chemical has met the standard that we've talked about today of clearly shown by scientifically valid evidence, et cetera.

What happens under Prop. 65 is that the decision of this Committee actually has to be a majority of the appointed members of the Committee. So it's not going to be a majority of those present. It's the majority of the

appointed members. At this point, we have nine appointed members. So there would have to be five affirmative votes. And that means that the two members that aren't present are essentially no votes. Anybody that abstains is essentially a no vote, that sort of thing. So I just wanted to let you know if you do take a vote, that it would require five in order to make a decision one way or the other.

CHAIRPERSON GOLD: Thank you.

CHAIRPERSON ALEXEEFF: I'll just mention one thing. I think it was two, three years ago -- I'm sure Dr. Donald will remember -- the Committee voted, was looking at a mixture of like brominated and chlorinated solvents, looking at a mixture of that and did not vote to list. But then asked us to look at them individually.

So, I mean, there is -- but that was -- in one sense, it would make sense to -- if you're ready, to make a decision based upon what the item that is before you, which is the chemical Deltamethrin, and then decide if there is anything else you'd like the staff to prepare or any future thing you'd like to consider. That might be the most orderly way of proceeding.

COMMITTEE MEMBER BASKIN: One question I have to the material that was put together by the office. Is there anything more you think you're going to be able to

get? In other words, the searches I think were done in a way to get this chemical and all mixtures of this chemical. So I don't know if any more information is going to be brought to this Committee that's going to be relevant.

DR. DONALD: Our intent us to be as complete as possible in the materials we provide to you. We are not aware at this time of any other relevant materials. We are not aware of any other way of finding other relevant materials, which is not to say they don't exist.

COMMITTEE MEMBER BASKIN: I would interpret that if we came back you would say -- put your hands up and say, "We gave it to you."

DR. DONALD: Unless something turns up that we are currently not aware of. Yes, that's what we would have to tell you.

CHAIRPERSON GOLD: One item that has been raised though is the opportunity for -- I don't know if this is possible. I'm asking the question. For the authors of these papers to respond to some of the criticisms. Would that be useful for the Committee and is it possible?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: It would be useful to hear. Some of the --

CHAIRPERSON GOLD: I'll point out some of them

are old.

COMMITTEE MEMBER WOODRUFF: When I'm looking at what we have in terms of the synthesis of the evidence, it seems like the most -- a lot of the studies have been focusing on the effects on sperm, but there's also been some questions about the exposure to whether the chemical mixture -- there's some studies exposed to the formulation and some that are actual studies just by Deltamethrin itself. But there's also been some criticism raised of some of these studies, and that would be helpful I know to me to get clarity on those in this section, the male reproductive effects.

CHAIRPERSON GOLD: When you say clarity on the criticism. In what form? From the staff? From the authors? What do you mean?

COMMITTEE MEMBER WOODRUFF: When you said that it sounded like a good idea, but now that you're saying it --

CHAIRPERSON GOLD: I didn't mean the authors are old. The papers are old.

COMMITTEE MEMBER BASKIN: These papers have been through the peer review process. I think it's personally my job -- I won't speak for anybody else on the panel to make an assessment whether I think they're valid or not as an independent scientist. So I don't see the utility in that, to be honest.

CHAIRPERSON GOLD: Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I might agree that contacting authors at this point after the peer review process after a publication might be opening up a complicated can of worms.

CHAIRPERSON GOLD: George, do you want to say again what you thought the options might be?

CHAIRPERSON ALEXEEFF: Well, I think the only option for voting before the Committee is on Deltamethrin today.

And the reason I say that is if there's something else you want to vote on, there has to be a public process prior to that voting. So I think that's why, in my mind, the first thing is we decide whether or not you're ready to vote on Deltamethrin today or not, and then you can decide what other steps.

It could be that you don't want to vote it on until you've had a chance or see if staff can contact somebody, which is an option. We've done that kind of thing before. But in terms of actually making a decision, it could only be on Deltamethrin today.

CHAIRPERSON GOLD: Did you want to say something?

COMMITTEE MEMBER BASKIN: I thought that is what we were asked to do and not anything more or less. Is that correct?

CHAIRPERSON GOLD: That is correct. But an option is to defer and not vote at this time. And it sounds like another option is to see if you want in the future to consider Deltamethrin mixtures, for lack of a better term. So I think what I'd like to do --

COMMITTEE MEMBER WOODRUFF: I will say one thing that was raised in some of the discussions, and I went back to check some of the papers, which is this issue about purity of the test compound.

I'm more in agreement with Dr. Baskin if they say that's what they exposed the animals to, that seems like that's relevant in the study.

My only question was whether that was -- in my mind, not question to other people -- whether it would be useful to go back and get clarity on that particular point. But I feel comfortable with voting I guess today.

CHAIRPERSON GOLD: So maybe I'm just going to ask each of the members if they're comfortable with voting on Deltamethrin with regard to the three end points that we consider. I'll sort with Dr. VandeVoort.

So the option is to be able to vote on the three end points with regard to Deltamethrin; defer, in which case you have to tell us what you would like to see in addition.

COMMITTEE MEMBER VANDEVOORT: I'm comfortable

with voting on Deltamethrin alone today, and I would like to see a deferral on formulations.

CHAIRPERSON GOLD: Dr. Nazmi?

COMMITTEE MEMBER NAZMI: I'm comfortable voting today on Deltamethrin.

CHAIRPERSON GOLD: Dr. Woodruff?

COMMITTEE MEMBER WOODRUFF: I'm comfortable voting today on Deltamethrin.

CHAIRPERSON GOLD: Dr. Rocca?

COMMITTEE MEMBER ROCCA: I'm also comfortable to vote today.

CHAIRPERSON GOLD: Dr. Pessah?

COMMITTEE MEMBER PESSAH: I can vote on Deltamethrin today.

CHAIRPERSON GOLD: Dr. Baskin?

COMMITTEE MEMBER BASKIN: Yes.

CHAIRPERSON GOLD: Okay. So I think we are ready to vote. I think we have a majority.

So question before you is: Has Deltamethrin been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity?

All those voting yes, please raise your hand.

COMMITTEE MEMBER WOODRUFF: Developmental or reproductive? Are we --

CHAIRPERSON GOLD: We're starting with developmental.

COMMITTEE MEMBER WOODRUFF: Okay. Thank you.

CHAIRPERSON GOLD: All those voting yes, please raise your hand. One.

All those voting no for developmental toxicity. Five.

No abstentions.

CHAIRPERSON ALEXEEFF: So are you voting now?

CHAIRPERSON GOLD: I voted.

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

All those voting yes, please raise your hand. I see none.

All those voting no, please raise your hand. I see seven.

Has Deltamethrin been clearly shown through scientifically valid testing according to generally accepted principles to cause male reproductive toxicity?

All those voting yes, please raise your hand.

All those voting no, please raise your hand. Five.

Okay. I see the result as for developmental toxicity one yes, six nos. No abstentions.

For female reproductive toxicity zero yeses, seven nos, and no abstentions.

For male reproductive toxicity, two yeses, five nos, and no abstentions. Thank you.

Is it appropriate to ask if the panel wants to review mixtures or? Can I hear from the panel on that issue? Dr. Rocca?

COMMITTEE MEMBER ROCCA: I would have a question whether or not this was considered part of the pesticide regulation review or part of the EPA review. If those are available publicly, they may have been reviewed based upon the actual chemical that's applied. I would want to know that.

CHAIRPERSON GOLD: So perhaps we can get some information on that before we decide if we want to review the mixture? I don't know the answer to the question.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm not sure we understand the question.

CHAIRPERSON ALEXEEFF: Dr. Shreider, do you have any comment on that? Dr. Shreider is with the Department of Pesticide Regulation.

MR. SHREIDER: I'm Jay Schreider. I'm a toxicologist with the Department of Pesticide Regulation.

We did a risk assessment on Deltamethrin approximately ten years ago.

It's not on?

Jay Shreider. I am a toxicologist in charge of risk assessment with Department of Pesticide Regulations. Risk assessment on Deltamethrin was done approximately ten years ago. And the major driver for that risk assessment was a neurotoxicity. So that's what really drove our review.

We reviewed the same FIFRA studies, came to the same general conclusion that the FIFRA studies did not indicate developmental or reproductive toxicity. The studies themselves are done on the active ingredient. There is limited information of those types of long-term studies on what would go into the formulated product. So even on the formulated product, the risk assessment would look at the amount of active ingredient in the formulated product, although we would also look at the acute toxicity studies.

There are some comments that were made in the document itself, some of the formulations. But the risk assessment itself was primarily concerned with the active ingredient and the development toxicity. Can't speak to on U.S. EPA's risk assessment.

The other complication in the formulated product comes with identifying when you have 50 percent as an naptha-based hydrocarbon, identifying what's in there.

That may change from batch to batch, depending on where it's purchased from. So starting to track that down becomes very problematic. And you could, in fact, have different hydrocarbon solvents and different -- the same product, but with different types of formulations.

I'm not sure if that's helpful or not.

COMMITTEE MEMBER ROCCA: Yes. Thank you.

CHAIRPERSON GOLD: I'm not sure I'm hearing a groundswell for looking at mixtures, but now would be the time to speak up if you want to. Okay.

So I believe we're back to our agenda then. And Ms. Monahan-Cummings is going to speak about the overview of the process for providing peer review of OEHHA proposed maximum allowable dose levels, along with Dr. Donald.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: We're switching gears entirely now, and we're going to start talking about a process that OEHHA goes through after a chemical is listed or sometimes at the same time as a chemical is proposed for listing.

And so next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: As you may recall from last month's meeting, the statute, Prop. 65

requires two things. One is that people that are being exposed to a chemical be provided with a clear and reasonable warning, where a person that's subject to the law knowingly and intentionally exposes that person to a listed chemical. It also prohibits the discharge of a listed chemical into sources of drinking water.

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CHIEF COUNSEL MONAHAN-CUMMINGS: There is an exception in the statute that says that warning is not required and a discharge is not prohibited if the exposure would have no observable effect, assuming exposure at 1,000 times the level in question. That only has to do with reproductive toxicants.

So the statute itself includes this 1,000 times what we call kind of a safety factor or something. It was established in the law, and it doesn't -- it's not known exactly where that thousand came from. But it is in statute.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So shortly after the law was passed in 1987, the office adopted some regulations to interpret what the statute meant in terms of how to identify what this warning level or discharge level would be. And we call them maximum allowable dose

levels. Not daily. Dose levels. And you also can often hear of them as safe harbor levels.

We have established how to calculate these levels, and that includes the 1,000 times multiplier for the level in question. You'll see that as we discuss these and go along.

So it is a little different than most of your more common risk assessment methodologies where you might be able to apply a different safety factor, for example. But in context of Prop. 65, it has to be a thousand.

We adopt these levels, although we're not required to do so by the statute. We adopt levels for chemicals or that are listed. The reason we do that is to aid businesses in complying with Prop. 65 and also to help the public know when they're being exposed to a significant amount of a listed chemical.

In order to adopt these levels, we actually are required to follow the State process for adopting a regulation. So the process is different than what we use for listing chemicals, because we have an exception in the law for listing chemicals where we don't have to follow the regulatory process.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So when we talk

about safe harbors, this is the reason. In our regulations, we establish some guidance and methodologies for calculating a level. Our office will calculate levels, and we also have guidance there for someone else to calculate their own level where we don't have one or where they might disagree with ours. So it's considered a safe harbor because a business doesn't have to use that level. They can disagree with us and say the level needs to be higher. And they can establish that in a court proceeding that the level should be higher.

So essentially what this does is let somebody use our level so they don't have to go through the process of developing their own. But it's not a mandatory requirement.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the piece of this process that we wanted to talk to you about is that under a different statute in Health and Safety Code, it requires any agency within the Environmental Protection Agency that is adopting a regulation, that has a scientific basis, that we are required to obtain peer review of the scientific basis of that regulation.

And so since OEHHA is developing the MADLs and we are within Cal/EPA, our MADLs or at least the risk

assessments that support them have to be scientifically peer reviewed.

There is a separate process that we use for other kinds of scientific basis for regulations throughout the agency. And that is to contract through the President of the U.C. and they identify peer reviewers ad hoc for the various documents. And instead of using that process, we have an exemption from that part of the statute, and we've decided to use our expert panels because you all are much more familiar with what we do at OEHHA and the listing of the chemicals. So we use this panel as a peer reviewer for our safe harbor levels.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So these are the various steps in the process for adopting a safe harbor.

Click it.

Actually, the first box here is that the chemical is identified. And generally, that means the chemical has been listed.

I didn't mention that once the chemical is listed under Prop. 65, there is a twelve-month -- essentially a grace period before any kind of warning is required. And there is also 20 month grace period before discharges of the chemical to the drinking water are prohibited.

So during that period, we generally try to at least get out a draft safe harbor level for chemicals that we're listing. But in recent years especially when we are dealing with chemicals that have to do with food that are either in food or in food contact materials, we will sometimes propose a safe harbor level at the same time as we propose the listing, although we wouldn't proceed to adopt the level obviously if we don't end up listing the chemical.

So what we do -- and Dr. Donald is going to go over the details of this and how the MADLs get established. But as I mentioned, we do have to propose them as a regulation. So when you get the documents -- and I'm pretty sure all of you have already received one of these packages of documents for the chemical Bisphenol A, what you'll get is this document that's called an Initial Statement of Reasons. And that document contains the scientific basis for the regulation. You'll also get a copy of the public notice. And if you request, we can get you copies of the references that support the scientific evaluation.

We give you all of those documents just for context. The part of the document that we're asking you to review is usually only about three to five pages. And that consists of the actual scientific piece that's

supporting the regulatory number.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So as I mentioned, there is a regulatory package that we send to you, each of the members of the Committee. We're only asking you to peer review the scientific piece of that. The rest of the materials are just included for your information. You can be compensated for your time in reviewing the document. Although I'm aware the compensation isn't the greatest, but you can ask for compensation the same way that you do for your travel expenses and your time preparing for these meetings and attendance at these meetings.

You are requested to send your comments individually. This isn't a function where you have to reach a consensus in a public meeting. We're asking you as individuals to peer review the documents. You are not required to give us peer reviewed comments, but our request is that if you decide you don't have any comments, that you send us an e-mail or something to that effect saying that you don't have comments so that we're aware and we're not expecting those from you.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Just so you know, any of the comments that you make will obviously be

part of the administrative record. And that means they're public. So they would be included, and we will respond to those at the time that we adopt the MADL.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Starting from here, we'll have Dr. Donald talk to you about the more technical aspects of the document.

DR. DONALD: Thank you, Carol.

And please feel free to ask questions as I go along. I'll go through this fairly quickly.

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DR. DONALD: As Carol said, we have implementing regulations for the statute and the maximum allowable dose level is defined in the regulations. A level of exposure that causes no observable effect, assuming exposure at one thousand times the level in question, is derived using the assessment methodology laid out in the regulation.

And that maximum dose level that has no observable effect or the NOEL is divided by one thousand, that mandatory factor that Carol mentioned to arrive at the maximum allowable dose level.

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DR. DONALD: So to determine what the NOEL is and consequently the MADL, obviously we can use the data that formed the basis for listing the chemical. In addition to

that, if there were data that were not used in the listing process but which are considered to be of comparable scientific validity to the evidence and standards that form the basis for the listing, then we can use those data as the basis for the MADL.

If a chemical is listed for one reproductive effect, for example, developmental toxicity, then the MADL must be based on the reproductive effect for which the chemical is listed.

If the chemical is listed on the basis of more than one effect, some combination of developmental male reproductive and female reproductive toxicity, then we only develop one MADL, and we base it on the reproductive effect for which the studies produced the lowest NOEL.

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DR. DONALD: So some of the default parameters laid out or -- default definitions laid out in the regulation are that the NOEL is the highest dose level, which results in no observable reproductive effect. And that's expressed initially in milligrams of chemical per kilogram body weight per day. And we find that NOEL -- we base that NOEL on the most sensitive study that we consider to be of sufficient quality.

So the initial NOEL expressed in milligrams per kilogram per day is converted to a milligram per day dose

by multiplying by assumed body weight. For adult males, that's 70 kilograms. For adult females, 58 kilograms.

If the effect is on the developing conceptus, we also use the body weight of 58 kilograms since the exposure will be to the mother during gestation. And relatively recently, we have also adopted default body weights for reproductive effects in children. And I'll come back to that later.

The regulation does provide that if we have data on anatomic, physiologic, pharmacokinetic or metabolic considerations, that we consider to be reliable and we can take into account with confidence and we can use those to modify the MADL.

And if we only have data on levels of exposure that cause adverse effects, we can use the lowest observable effect level or LOEL and divide that by ten to establish a NOEL for purposes of this assessment.

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COMMITTEE MEMBER VANDEVOORT: Could I ask a question on that? Let me clarify that.

Did you say that if you -- if the studies have not identified the lowest dose -- so if all the studies show an effect, you just take the lowest dose and divide it by ten?

DR. DONALD: Yes. That's correct. So if every

experimental study had effects manifested, the lowest dose used in the study, we would use the lowest of those doses and divide it by ten.

COMMITTEE MEMBER VANDEVOORT: Is there some rationale -- I mean, why not divide it by 100?

DR. DONALD: Ten is the default value used by most regulatory agencies extrapolating from a LOEL to a NOEL. As I said, the regulation does provide that if we have a sufficient scientific basis for using some other factor, we would. But ten is the default.

COMMITTEE MEMBER ZEISE: I can clarify further. We did have a recent revision to the regulation as well that enables us to conduct a statistical analysis and establish a benchmark dose as an equivalent NOEL.

DR. DONALD: Right.

COMMITTEE MEMBER WOODRUFF: Can I ask a follow-up? The NOEL is not specified -- using the NOEL is not specified in the statute; is that right?

DR. DONALD: I can't hear you.

COMMITTEE MEMBER WOODRUFF: Using a NOEL, it just -- that's not -- what you used to specify the low dose -- lowest dose is not specified what you have to do in the statute, whether you use a NOEL approach or a benchmark dose approach.

DR. DONALD: Carol said what the provision of the

statute is and which the regulation is based. And that is in the statute you're exempted from the provisions that the warning requirements and the discharge prohibition if there would still be no observable given an exposure a thousand times the level in question.

So the implementing regulation kind of turns that around and says if you're trying to figure out at what level you have to provide a warning or what level discharge to associated drinking water is prohibited, you find the highest level that doesn't cause an adverse effect and divide that by a thousand to reach the maximum allowable dose level. So the regulation is an interpretation of the intent of the statute.

COMMITTEE MEMBER WOODRUFF: Okay. I'll save my questions until you're done

CHAIRPERSON ALEXEEFF: Just to clarify what Dr. Donald was saying is that the statute says there is no observable effect at 1,000 times the level.

COMMITTEE MEMBER WOODRUFF: 1,000 below.

CHAIRPERSON ALEXEEFF: It's 1,000 times that level. That's what -- it's basically NOEL with a thousand fold factor.

DR. DONALD: What we're saying, in effect, with the MADL is that if you expose someone at that level, you have to be able to demonstrate that at a thousand times

higher exposure, there would still be no observable adverse effect.

COMMITTEE MEMBER WOODRUFF: Right. I guess my question comes into when you look at NOELs that are in a lot of these toxicological studies, they're really not -- no observable -- there usually is an effect. It's often very small. And often it's not -- it's counted as a NOEL because it's not statistically significant, even though there may be an elevated effect. And that's why U.S. Environmental Protection Agency has been moving to a benchmark dose approach to find the low end of the dose response, whether it's a -- I say NOEL equivalent in the sense it's usually a one or five percent range response. And the LOEL is, in the ideal world, it's around a ten percent range response.

So it seems like I think we should just be careful to -- think people think NOEL means nothing has been observed. And that's not often the case in these studies -- and because they have low statistical power. So it would be something worth thinking about as moving all -- shifting all the low -- what your point of departure is, similar to what U.S. EPA has been doing.

DR. DONALD: And we have been thinking about that. The regulation was adopted more than 20 years ago, when the benchmark dose methodology wasn't really

established.

COMMITTEE MEMBER WOODRUFF: Right now you have a new opportunity.

DR. DONALD: In the last couple of years, we specifically adopted a provision for using the benchmark of dose methodology into the regulation.

The first example is for a listing methyl bromide is a structural fumigant. I can explain why we have that qualifier if anybody is interested later.

The listing is based on developmental toxicity. The route of exposure for humans that is of primary concern is inhalation exposure. We used a NOEL from a study in rabbits where there was no observable effect on exposure to 40 parts per million methyl bromide for six hours per day. So the first step is to convert the air concentration parts per million to milligrams per cubic meter. So we used a conversion factor of 3.89, which gave us a volume of 155.6 milligrams per cubic meter.

To convert that to a milligram -- excuse me -- we next converted that to an equivalent concentration that would result in an exposure over 24 hours or a daily exposure, which gave us a value of 38.9 milligrams per cubic meter. To calculate the NOEL expressed as milligrams per kilogram per day, we used the reported body

weight of 4.19 kilograms in pregnant rabbits exposed to 40 parts per million methyl bromide and used an inhalation rate of 1.512 cubic meters per day that we obtained from the literature. And that gave us a value of 14.04 milligrams per kilograms per day as the NOEL.

We converted that to a milligram per day value by multiplying by 58 kilograms, the assumed body weight for a pregnant woman, which gave us a value of 814.3 milligrams per day which, divided by the mandatory factor of 1,000, gave us a maximum allowable dose level for inhalation of methyl bromide as a structural fumigant of 814.3 micrograms per day, which following our usual procedure we rounded to two significant figures and adopted as 810 micrograms per day.

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DR. DONALD: So that was an example of deriving a model using essentially all of the default procedures specified in the regulation.

As Carol pointed out earlier, we're not required to follow -- necessarily to follow the default procedures. And the regulations specifically provides that we follow the default procedures in the absence of principles or assumptions scientifically more appropriate based on the available data.

So the second example I'm going to show you is

one where we varied from the default assumptions. And this is for Di(2-ethylhexyl)phthalate, DEHP, which is listed based on developmental and male reproductive toxicity.

This particular example is for the MADL we developed for oral exposure. This one is also route specific and based on a no observable effect level of 5.8 milligrams per kilograms per day found in rats. And that was based on rats fed a diet containing 100 parts per million DEHP. But in the study report the authors, based on body weight and food consumption, had converted that to a milligram per kilogram per day dose for us -- so calculating the NOEL for 70 kilogram man, you multiply 5.8 by 70 kilograms to give us a value of 4.6 milligrams per day, which divided by mandatory factor of a thousand gave us a MADL for adult oral exposures of 410 micrograms per day after rounding.

The main concern for DEHP is effects on the male reproductive system, resulting from early postnatal exposure. Because of the way Prop. 65 is interpreted, exposure during the early postnatal developmental period is not considered -- generally not considered evidence of developmental toxicity. But because the effects are on the male reproductive system, in this case, it is still considered evidence of male reproductive effects. So

using a body weight of 70 kilograms, the default in the regulation is obviously inappropriate for infants.

So for infants zero to two years of age, we used an average body weight of ten kilograms over this developmental period. That value had already been adopted into our parallel cancer regulations, but was not at that time among the default values in our regulations for developing MADLs but we have subsequently adopted that value into the regulations.

At the time we reviewed the available data, looked at particularly at the National Center for Health Statistics and concluded that ten kilograms was still a reasonable value to use. So multiplying the NOEL by ten kilograms gave us a value of 58 milligrams per day, divided by a thousand, gave us a MADL for instant oral exposure of DEHP of 58 micrograms per day.

There was also concern for exposure during the neonatal period the first 28 days postnatal. We had no default value even in the cancer regulations for that period, so we decided to use the 50th percentile birth weight for boys of that age derived from data from the National Center for Health Statistics.

So calculating the NOEL for 3.5 kilograms neonate gave it a value of 20.3 micrograms per day rounded and divided by a thousand gave us a MADL for oral exposure to

neonatal boys to 20 micrograms per day.

And I would be happy to take any other questions at this point.

CHAIRPERSON GOLD: Any questions about this process for Dr. Donald or Ms. Monahan-Cummings at this time?

CHIEF COUNSEL MONAHAN-CUMMINGS: Can I just mention to you, I have the envelopes here for you. This is another MADL we want you to review. This one for SO2. So before you leave today, I'll give you these.

And I mentioned earlier that there is -- that we adopt these through a regulatory process. And so there is a limit on the regulatory process. You have to adopt your regulation within one year from the time you propose it or you have to start the process over.

And so in terms of priority, we are hoping that the ones that -- the one we're giving you today would be the one you'd give priority to, because we have to adopt it within the next two months. Maybe three months.

But in any event, we'll give this to you. And if you could give us your comments within, say, the next 45 days, that would be wonderful. If you're not able to do that, like I said, you can send us a note and say you're not going to be able to give peer review comments. That's entirely fine. We just need to know that.

The other ones that you have, you have one for BPA. That chemical has not been listed yet. So you have -- that's the one you have the most time for. And then they'll be another one related to cyanide -- hydrogen cyanide you'll be getting shortly. So lucky you, you get three in a row.

COMMITTEE MEMBER ROCCA: I have a question about the comment period. For example, the comment period for BPA has been extended?

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

COMMITTEE MEMBER ROCCA: If we were doing things according to the way we would like to get them done, would you want the Committee comments in by that date as well?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. In a perfect world, that would be nice.

In the context of BPA, I don't think that's necessary at all, which you could bring into my next comment I was going to make in terms of the staff update, but do you have any other questions on the MADL process?

CHAIRPERSON ALEXEEFF: Just answer the question it's -- your comments are not considered part of the public comment period process. But we would like to have them early enough so that we could respond to them or make whatever necessary changes.

But what happens with the regulatory process, the

information -- there is one year to complete the process. But in that process, the regulation can change. And there is additional comment periods along the way if there is any changes made.

So the idea is that at some point if you could give us comments -- and we can give you a ballpark time line that would basically be helpful to us, getting it sooner than later. So if there was a dramatic change to be made and there would be adequate comment for -- again, the public would get the comment on the change, if we made a change.

COMMITTEE MEMBER ROCCA: So in this case, will we get to see all the public comments that are to be in before we would have to have our comments in?

CHIEF COUNSEL MONAHAN-CUMMINGS: Not normally. Normally, what we get is during the public comment period, we don't get any comments. We get them on the last day. And as soon as we receive the comments within a couple days, we post them on our website.

But if you were to make your peer review comments during the public comment period, you wouldn't have the benefit of those public comments unless they came in early. And we don't normally send the public comments to the Committee members. If you would like us to do that, we're happy to do it. But normally we just post them on

our website.

Do you have any questions?

COMMITTEE MEMBER WOODRUFF: I was wondering, you mentioned that you were going to be -- you're starting to modify how you're doing the MADLs when you use LOELs and you've been using benchmark dose evaluation. Will you be considering that, too, for the NOEL evaluations?

DR. DONALD: Sorry. I think we may have mislead you a little bit. We have specifically adopted the option of using the benchmark dose methodology into our regulation. We would use that in any instance where the benchmark dose methodology was preferable to the NOEL or LOEL approach.

COMMITTEE MEMBER WOODRUFF: I see. So in these new ones coming forward, you will show the benchmark dose calculations as well; is that right?

DR. DONALD: Well, it depends on the nature of the data that we have. If the data are amenable to benchmark dose approach, we're moving towards using that. But we have not yet put out any draft MADLs that are based on the benchmark dose approach.

CHAIRPERSON GOLD: I believe we're ready to move to the next agenda item. Ms. Monahan-Cummings is going to talk about Prop. 65 litigation updates.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. Since

we've only had a meeting a month ago, I'm not going to go into a lot of detail on our current litigation. But I did want to mention a couple things related to our conversation just now on maximum allowable dose levels.

There is an equivalent process for carcinogens where we establish no significant risk levels. Those don't include the thousand-fold factor we were talking about. But we do adopt safe harbors for our cancer chemicals also. And I think I mentioned last time -- maybe I didn't -- that we're currently in litigation with Syngenta Crop Protection regarding a no significant risk level that we adopted for chlorothalonil. That is listed as a carcinogen. And we had a pretty old safe harbor level for that, and we recently adopted a new one. And Syngenta has objected to that number. So we are in litigation in that case.

And then very recently, you may be interested in knowing that we were sued by the American Chemistry Council for the proposed listing of Bisphenol A. We're proposing that listing under the authoritative body listing mechanism based on a report from the NTP Center for the Evaluation of Human -- Risk to Human Reproduction, ERHR. And so in that case, it's very early in the process. They're asking for an injunction which would require us to stop the listing process.

One of the reasons I wanted to bring that up to you is, as I mentioned, you received a request to review the draft maximum allowable dose level for BPA. And that's one where we have proposed that concurrent with the proposal for listing the chemical.

So in the event the court prevents us to proceed with the listing, which I'm not saying the court is going to do that. We're hoping it doesn't. But if that happens, we'll advise you right away so that you don't spend time reviewing the safe harbor because, as court cases go, they usually take two or three years to resolve. And things could change by that time and we may want to look at a different MADL. So we will let you know on that one.

But as I mentioned, it shouldn't be the highest priority of the three that you're going to have in any event because it's concurrent with the proposal for listing. I have the one for SO2 today. And my understanding is you'll have the one for hydrogen cyanide shortly. Hydrogen cyanide is another one where we're proposing a draft concurrent with the listing. And so we will have some time for you to make your comments.

But so I know that you're all busy with other stuff, and we're certainly not requesting a volunteer panel throw everything aside and do this work for us. We

do appreciate it.

To the extent you can let us know if you're going to be able to do the peer review and how much time you need, that's helpful. If you're not going to be able to do it, if you could let us know that, too. Thank you.

COMMITTEE MEMBER ROCCA: I have a question about the peer review. So just want to be clear on the process. The process is that based upon the authoritative body, it's being listed and we're being asked to review the safe harbor.

CHIEF COUNSEL MONAHAN-CUMMINGS: For BPA?

COMMITTEE MEMBER ROCCA: We're just reviewing the safe harbor. We're not reviewing the listing, per se.

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct. And that's pretty much true on any of the MADLs that we would be providing to you. Even if it was -- I mean, sometimes we set them for chemicals that are listed by this Committee. Sometimes we set them for chemicals that are listed under our Labor Code process, whatever. So you're not being asked to peer review the basis for the listing. Just the basis for the safe harbor number, which we try to identify just the pages within the documents that we give you that actually require your review.

And you're also, as I mentioned, free to ask us to send you any of the references that we have that we

site in our document. We don't normally send those all to you. But we would be happy to provide any of them that you're interested in.

CHAIRPERSON ALEXEEFF: Just as a comment, although you're not being asked to review the listing, per se, it still applies that if, for example, the authoritative body listed on the male reproductive toxicity and we were basing the level on developmental toxicity, then you should let us know and call us on that. Because we should still be following the regulation about basing it on an end point that's consistent with the listing.

CHAIRPERSON GOLD: Next on the agenda is a general public comment period. I don't know that we have any. No public comments.

No. Then I'll turn to Dr. Alexeeff for a summary of the Committee actions.

CHAIRPERSON ALEXEEFF: Well, actually, I had some a couple questions to ask the Committee before I summarize the meeting.

First of all, I wanted to thank you again for your comments and your thoughtful deliberation process on Deltamethrin today and your attention with regard to the MADL process.

But I did want to talk a bit about the

presentation of materials to the Committee. I had mentioned in the beginning that basically we consider there are three basic sources of information that come to you as part of this process. One is some information that with specifically provide, like in this case we summarized the information in a document and then there is the public comments and then this meeting today and comments made at the meeting.

But we've developed -- the information we sent to you today has kind of changed over time. And based upon the previous Committees, we've tried to adjust it to provide the information that those committees wanted or that we interpreted that would be best suited for them to make their decision.

So part of the question that I have -- and this is can be an on going question -- doesn't have to be finished today -- is what types of information would be most helpful to the members of the Committee for their deliberation? And part of I think a little bit of it came up today, and I think just something that comes to my mind and Dr. Rocca's, it looked like you were reading off of a table. And we could summarize the information in a table, if that would be the way you would prefer to see it, as opposed to summarizing each individual study.

And that's the other question as to whether or

not that is helpful at all. In the appendix, we summarized each individual study.

And then in the document, we sort of try to summarize each end point, and then we had an executive summary. So you could comment -- any comments you have on any of those parts being helpful or not helpful -- for example, the executive summary, was it helpful?

Also over time, we've had comments, concerns raised from members of the public regarding the content of the information that we've provided to the Committee. And it seems to kind of go back and forth.

So the question is we are trying to -- in other documents that we develop, like for other programs, we actually either propose the level, make a decision, and then it goes out for either peer review or public comment.

In this case, we're trying to provide information for you to make the decision and for us not to be making the decision. So it's a very difficult fine line for us to provide you enough information, at the same time to not make it seem like we think the answer is A or B.

And sometimes it comes out that maybe we didn't say enough positive things about some study or enough negative things about another study. So any guidance you might have along those lines would be helpful for us. I realize it's hard and you're talking in general.

But you know, again so there is sort of how would you like the information presented. And what types of -- how would you like us to provide any sort of thoughts we have on the data that's before you?

CHAIRPERSON GOLD: Dr. Pessah first.

COMMITTEE MEMBER PESSAH: For me, it was kind of eye opening. I took it for granted that when the study gets published through peer review the appropriate controls are done.

I think what would really help me in at least the animal studies and perhaps there are some parallels in human studies that just list what the controls are. Don't evaluate them. But at least that would be very helpful.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I think it would be also helpful in the summary tables, there's some grouping by end points. But to have more grouping by within a particular group within end points that are a subset, like in the male reproductive health effects.

I would like to see effect sizes in here. So you have whether it increases or decreases. But that doesn't give a sense of the magnitude of the effect, even when it's not statistically significant, because sometimes a lot of these -- I actually wrote down how many numbers were done in each of these studies.

And actually, I would also say there has been a -- I think you were at SOT. There was a great presentation by Paul Foster who is head of the toxicology branch at NTP because they're re-doing how they're doing their developmental tox studies. And they have a whole new design that they're implementing, which is -- he has -- I thought he had very nice presentation about how it's an improvement of what EPA and OECD is doing, because they do longer length of testings, so it increases the power of their studies to see reproductive effects.

And he had a very nice summary about how a lot of the studies they had been doing and other guidelines -- not guidelines but studies that had been done by other sort of -- I don't want to say guidelines -- certain regulatory agencies actually had pretty low statistical power in order to see effects.

So I think -- so that was I kind of meandered off the point of the tables. I would ask him to give a presentation to this Committee, because I thought it was very effective in terms of what they're doing to upgrade their scientific testing to get more effective test regimes and to evaluate a fuller, more subtle range of end points.

Back to this table. So I think the effect sizes, even when we don't have statistical significant, is going

to be important, because there's still information in here that I felt we could use to give us more information about the relationship between exposures and response in the studies.

CHAIRPERSON GOLD: Dr. Rocca.

COMMITTEE MEMBER ROCCA: I was anticipating this question since last time we spoke you said you could be soliciting this.

So I actually prepared a list as I was setting up my things. Does this need to all be entered into the record? Or may I share with you the information?

Basically, what it talks about is what sort of methods would be important to understand about the test article and the route and frequency. Tables would be very nice and to organize the tables. And I also like to see things kind of by species and route. If there are two rat studies, I would like to see those listed together.

The other sorts of -- list all the end points that were evaluated someplace in a table. Because usually what you end up with is, oh well, these two were positive. You didn't see the other 20 that were negative. And frequently, you'll have things that correlate, like body weight and slower development, those sorts of things. So if we could have all of the end points and the ones that were effected.

And then, of course, the discussion of what parental toxicity there was. And very importantly after reviewing this one, I want to know what other scientific evaluations have been done that it was not called out in the document at all that quite a few authoritative bodies have already reviewed this. And I would have been interested to see their evaluations.

CHAIRPERSON GOLD: I would add from my perspective that in addition to the text, the summary tables are very helpful. But I think they could be a little bit expanded along the lines you've heard.

But also, for example, I couldn't tell sometimes if animals were randomly assigned to treatment groups. And when they did culling, I couldn't tell how that was done. Knowing the total sample size per group. I think the effect size is important, statistical significance alone is not. Knowing what the control was.

So just to add to the other comments that I think if you had a table that not only showed results, but made some comments about some of the strengths and some of the limitations, that would be helpful as well.

CHAIRPERSON GOLD: Other comments from the Committee? I think Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I have three comments.

First of all, I want to thank Dr. Donald and the

team, because I know it's difficult to put together this amount of information in one kind of cohesive document.

Second comment is regarding I guess organization. I find myself referring back to the original studies regularly. That sometimes precedes my use of the appendix. So I feel like if some of those tables could be maybe fused into the manuscript into the actual text, it might be a little bit more handy. Instead of flipping back and forth.

My final comment could be a very personal thing, but also could be a very practical consideration. My preference is spinal bound. I actually had this done, because it found it very difficult to maneuver the metal binding in terms of ease of reading on public transport or offices or something like that. But thanks once again to your team. In general, very nice presentations.

CHAIRPERSON GOLD: I would add one more comment that if a study is found to be extremely poor, I would still include it in the table with the comment about that.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I would also -- actually, I should have raised this -- that the National Toxicology Program has developed some new tools for extracting data from studies to put them all in the relevant data from studies and put them all on the same

basis so it's easier to see across them.

I think that is a very -- since they're also doing reproductive developmental -- evaluation of reproductive and developmental end points would be a very valuable tool that they are making available to other public -- other public, including public agencies. So I would recommend that as another way to lay out information in a systematic manner that captures the relevant information from the studies.

CHAIRPERSON ALEXEEFF: Well, first of all, I don't know if staff wants to ask any questions. This could affect your work.

Should we decrease the amount of text in terms of moving more toward tables? Is the executive summary helpful or not? It's kind of odd. Usually, the executive summaries sort of leads one to a conclusion. Since we are trying to not have a conclusion, it's actually kind of hard to write.

CHAIRPERSON GOLD: I think if the table are sufficiently detailed, the text could be reduced. But I'll ask my panel members how they feel about that.

COMMITTEE MEMBER BASKIN: This is a subtly different document than, for example, reading JAM or New England where they're going to give you a level of evidence and completely bias before you've read the

article. So I appreciate the way it's presented.

I like the text. And tables are fine. I think it's kind of the right amount. I think you're pretty much right on. There's supplementary your data. If you are an expert in an area, you don't need to go into it all of us aren't an expert in each specific chemical or field. So I think it's pretty right on kind of the way it is.

CHAIRPERSON ALEXEEFF: Let me ask one more alteration.

So in terms of, okay, the tables, if we were to expand the table. In the back, we have each individual study summarized. So we could include a lot of that information in the table instead. Would that be more helpful? Okay.

CHAIRPERSON GOLD: Dr. Rocca, you had another point?

COMMITTEE MEMBER ROCCA: Yes, I had a quick question on another topic that probably once again this is a legal question.

Knowing that we have authoritative bodies who we use to help us list chemicals, it appears we have authoritative bodies that reviewed this chemical and didn't list it. So how does that work? Do we only accept positive data from regulatory bodies? Or if they don't list it, do we also --

CHIEF COUNSEL MONAHAN-CUMMINGS: Let me start, and then Dr. Donald can add in.

First off, the majority of -- pretty much all the chemicals that come to this Committee are coming here because there hasn't been a conclusion by another authority that is recognized by Prop. 65 that there is a developmental reproductive toxicity for that chemical. So we're asking you to do an original review, for lack of a better word.

Also, under our regulations, this Committee, not this one in particular, but the overall Committee has identified those entities that it considers to be authoritative. So you can re-look at that list at any time, take things off, add things in. And so I know sometimes you get comments that, for example, Health Canada or the World Health Organization or the EU which, didn't even exist at the time that the regulation was adopted, have made a determination one way or the other. So you might want to consider whether you want to include some of those, federal OSHA or whomever.

So we do -- and Dr. Donald can talk about this. We do include information from other agencies as it's appropriate. But for the most part, I think we are just identifying studies. And they may have been submitted to a regulatory agency, but very few agencies actually list

chemicals. They may identify chemicals, but they don't list chemicals in the way we do.

COMMITTEE MEMBER WOODRUFF: Just a point of clarification. U.S. EPA doesn't list reproductive and developmental toxicants. They do risk assessments and hazard assessments. But they don't create a list. So I think that -- right? So that doesn't make -- they can't use them -- you can't use them as an authoritative body because they don't have a list.

DR. DONALD: There are three criteria for what constitutes formal identification by an authoritative body. One is that the authoritative body maintains a list of chemicals that are known to cause reproductive toxicity, and none of the authoritative bodies do that. So we've never actually used this criteria.

The second is that the chemical has been formerly identified in a report -- or actually identified in a report by the authoritative body that concludes that the chemical causes reproductive toxicity, which is the most usual criteria that we have used.

The third is that the authoritative body has otherwise identified the chemical as causing reproductive toxicity in a report that indicates it's a final action and we used that criteria on occasion. But it's not necessary that an authoritative body has its own list of

chemicals.

The other consideration is that, as you are well aware, Prop. 65 is very specific. Only considers two types of toxicity: Cancer and reproductive toxicity. It doesn't require -- at least for reproductive toxicity, it doesn't require that the reproductive toxicity be the most sensitive effect of the chemical. There may be other forms of toxicity that occurs at lower levels, but a chemical can still be added to the Proposition 65 list if the chemical is clearly shown to cause reproductive or developmental toxicity.

So in some instances, authoritative bodies may have regulated a chemical based on a different end point. And may also have identified reproductive or developmental toxicity or have concluded the chemical causes that effect. And in that case, we have a basis for proceeding with listing through the authoritative body mechanism.

If they identify a different end point as the most critical effect and don't draw a conclusion or otherwise identify the chemical as causing reproductive toxicity, perhaps because it is not a relevant consideration for them because they've already regulated a more sensitive end point, in that instance, the chemical may come before this Committee. And we don't see that as an inconsistency.

We do, in prioritizing chemicals for consideration by this Committee, we do consider whether there's been a recent evaluation by an authoritative body or whether there's likely to be an evaluation in the near future.

For Deltamethrin, I'm afraid we don't have the date immediately to hand. But we're not aware that there's been a recent evaluation by U.S. EPA and, for example, the evaluation by DPR, as you heard, was 13 years ago.

So we are cognizant of the parallel evaluations that sometimes exist and we try to adapt to them. But in this case, Deltamethrin came through our most recent iteration of our prioritization process and was recommended for consideration by the last iteration of this Committee. So it came before you on that basis.

CHAIRPERSON ALEXEEFF: I wanted to speak to the general question of how do chemicals come before you. And so we do have a prioritization process that Dr. Donald is referring to that we had brought to the previous Committee. And we have a screening procedure where we screen a large number of chemicals to see which ones are most likely to cause reproductive toxicity without going into great extent of reviewing every chemical, which would take too much time.

So we screened it and we bring to the Committee. And at that time, we bring a prioritization to the Committee, that is usually when we would let you know if there's been any other recent reviews and what they might have said and that kind of stuff.

And like for our Cancer Identification Committee, that is clearly something that's important to them as well, has there been a recent review and what have they found. That's one way a chemical comes to the Committee is through the prioritization process.

Another way is that if a chemical is already on the list, it was listed, let's say, in 1990, but for some reason there's new evidence -- and let's say it was listed by the authoritative body and there is new evidence the authoritative body has decided to change its mind and no longer considered, that chemical would come back to this Committee to look at to see, well, does the Committee want to keep it on the list. So there's that process as well.

And then there is also another process which states the prioritization that Committee members themselves can suggest chemicals for us to look at. And for example, that happened with the environmental tobacco smoke where it was considered once and then it was not listed, but then new information came out and it was suggested we look at it again. And then it was ultimately

listed.

So there's different ways it comes before you. But again, whatever information, you know, you'd like to have at your fingertips when you're looking at a chemical, we would be happy to provide it.

COMMITTEE MEMBER BASKIN: What happens if a chemical is on one list and not another? For example, on the carcinogen list, but it also may or allegedly causes developmental issues?

CHAIRPERSON ALEXEEFF: Sorry. What was your question?

COMMITTEE MEMBER BASKIN: The carcinogen list and the reproductive and developmental lists are two separate lists.

CHAIRPERSON ALEXEEFF: Correct. They're two separate lists. And I think, you know, may be Cindy could even summarize the list. There are a number of chemicals on the list. Or if not today then --

COMMITTEE MEMBER BASKIN: I was looking at the website. I'm assuming that's the list, the one on the website; right?

CHIEF COUNSEL MONAHAN-CUMMINGS: Actually, there's one list for developmental and reproductive toxicants. And so what it says on there is what the end point is. It could be cancer and developmental. It could

be just cancer. It could be just developmental. Could be just male repro, that sort of thing.

So the one you usually see on the website is in alphabetical order. But it will show like the CAS number and the end point there.

So because the chemical is listed as a carcinogen, for example, doesn't mean we can't bring it to this Committee or use another process for listing it as a developmental or reproductive toxicant. Does that make sense? Does that answer your question?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think the other list that Dr. Alexeeff is thinking of is a completely separate list that we talked about last time, last meeting, where it's the chemicals that haven't been adequately tested. That's a completely separate list.

CHAIRPERSON GOLD: So I think it's still you.

CHAIRPERSON ALEXEEFF: All right. Well, summary of the meeting. So today, the Committee considered Deltamethrin as a -- to determine whether or not it was clearly shown through scientifically valid testing according to generally-accepted principles to cause either developmental toxicity, female reproductive toxicity or male reproductive toxicity, and the Committee determined that it does not meet the standard for any of those toxicities.

CHAIRPERSON GOLD: Okay. Thank you.

And the only closing comments I would make is we'll be in discussions with agenda items concerning time limits and submission of web comments, perhaps revising the guidelines. I think that came up the last time at the last meeting. I think that was it for right now. Although voting procedures was also potentially mentioned. Anyway, so we'll be working together on future agendas where we might take up those items.

CHAIRPERSON ALEXEEFF: We do plan to have the next meeting but not next month. It would be in the fall sometime, either early or late fall.

CHAIRPERSON GOLD: So with that, I'd like to thank the staff for their hard work on this and for all the public comments and for the Committee's attention to detail and critical comments and thinking. Thank you all. And adjourn the meeting.

(Whereupon the hearing concluded at 3:31 p.m.)

CERTIFICATE OF REPORTER

I, TIFFANY C. KRAFT, 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 hearing was reported in shorthand by me, Tiffany C. Kraft, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

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

IN WITNESS WHEREOF, I have hereunto set my hand this 1st day of April, 2013.

TIFFANY C. KRAFT, CSR, RPR
Certified Shorthand Reporter
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