MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

WEDNESDAY, MAY 21, 2014

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

COMMITTEE MEMBERS:

Ellen B. Gold, Ph.D., Chairperson

Laurence Baskin, M.D.

Ulrike Luderer, M.D., Ph.D.

Isaac Pessah, Ph.D.

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

STAFF:

Dr. George Alexeeff, Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

Dr. Marlissa Campbell, Reproductive Toxicology and Epidemiology Section

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

Dr. Poorni Iyer, Reproductive Toxicology and Epidemiology Section

Ms. Cynthia Oshita, Proposition 65 Implementation

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

Dr. Lily Wu, Reproductive Toxicology and Epidemiology Section

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

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

ALSO PRESENT:

Dr. Michael Battalora, DuPont Crop Protection

Dr. Arthur Lawyer, Technology Sciences Group

I N D E X

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

P R O C E E D I N G S

DIRECTOR ALEXEEFF: Good morning. I'm George Alexeeff, Director of the Office of Environmental Health Hazard Assessment. And I guess everyone here -- most everyone here is a regular, because all of a sudden the room went quiet at around five minutes after 10:00. Everybody saw the Panel members are here. We're all in place, so I didn't even have to call it to order.

So first of all -- so I want to welcome everyone to the meeting of the Developmental and Reproductive Toxicology Identification Committee or Toxicity Identification Committee. And let me first mention just some of the information about evacuation and housekeeping. So first of all, I want you all to notice the exit signs around you, in case we have to leave quickly. And in the event of a fire alarm, or any other reason to evacuate this room, please leave by those lighted exit doors, and then take the steps down and outside. And then we'll relocate at a site across the street.

So also there's a couple housekeeping issues. So in terms of drinking fountains and restrooms, out the door, kind of big left turn and then way at the end of the hallway there. And then there's food downstairs in the cafeteria, and you can take the stairs there. And then also we have -- we encourage recycling of all materials.

So we have a lot of recycling bins and containers throughout, so -- and please turn off your cell phones. I must say I had forgotten to turn it off and -- during a budget hearing, and I was reminded of that during the budget hearing. So please turn off your cell phones.

So I want to welcome the members here. First of all, I realize it's a lot of effort for them to come here and give us their advice, take time of out their busy schedules to come here. And so I want to, first of all, thank them for their attendance. And directly on my left is Dr. Ellen Gold, professor and Chair of the Department of Public Health Sciences at UC Davis. And then to her left is Dr. Ulrike Luderer, associate professor in the Department of Medicine, Division of Occupational and Environmental Medicine at UC Irvine. And then to her left is Dr. Laurence Baskin, who is the Chief Pediatric and Urologist, professor of urology and pediatrics and surgeon scientist at UC San Francisco.

Now, on my right -- directly on my right is Dr. Tracey Woodruff, who's a professor in the Department of Obstetricians, Gynecology, and Reproductive Sciences at UC San Francisco, and Dr. Isaac Pessah, professor and Chair of the Department of Molecular Sciences at UC Davis.

So I also want to introduce the staff who will be involved in this presentation today. I'll just start. We

have Allan Hirsch our Chief -- our Chief Director -- Deputy Director, and then Carol Monahan-Cummings, who is our Chief Counsel, and then next to her is Lauren Zeise our Deputy Director for Scientific Affairs, and next to her Martha Sandy who's our Chief of our Reproductive and Cancer Hazard Assessment Section, and then Jim Donald, who is our -- the Chief of our Reproductive, Toxicity and Assessment Section, something of that nature. Anyway.

(Laughter.)

DIRECTOR ALEXEEFF: Too many titles. I'm going to stop adding all these titles. Anyway. And then Dr. Marlissa Campbell, one of our toxicologists, Dr. Lily Wu over here, and then Dr. Poorni Iyer. And then also I want to thank Cynthia Oshita for helping out here. She'll have a presentation later. So I think those are all of the introductions. I also want to turn it over now to Dr. Ellen Gold.

CHAIRPERSON GOLD: Okay. Well, I just want to say welcome as well. We are short a couple people for various reasons, illness and other commitments, but we do have a quorum. And so I welcome all the members of the Committee. And I want to thank in advance the hard work of the staff, which made our job easier.

And I think next on the agenda is for our counsel to make some statements.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. Good morning. First I wanted to make some general comments that I always make at the meetings. And then following that, I've got a presentation -- a brief presentation on the reasons that some of the chemicals are in front of you today. I know some of the members have heard this more than once maybe. The people on the website haven't or others, and so I just want to cover that again.

So a couple of things. One is that when you're speaking, if you could identify yourself each time that you speak, because this meeting is being webcast, and so people may not know who you are, particularly our staff, where our name tags are not necessarily visible. And the same thing for anybody that's speaking from the audience, if you could go ahead and give your name and affiliation.

I wanted to give just a couple of comments in terms of some of the comments that we get. And I didn't review all of the comments that we received in writing. But at meetings sometimes, we hear comments about whether or not a chemical has been clearly shown to meet the standard for this Committee to keep it on the list or to list it. All of the chemicals you're looking at today have to do with whether or not they should remain on the list. They've already been listed.

But essentially, for all of these chemicals, you

need to apply your clearly shown standard, the scientific standard that you have. It's not a legal standard, per se. It is a legal -- it has legal effect, but you're not attorneys and you weren't appointed to be attorneys to this Committee. You were appointed because you're excellent scientific experts. And so that's what we're asking you to do is apply your scientific expertise.

You also, as you know, have a guidance document that this -- a version that this Committee developed several years ago that are in your materials. That should be able to guide you in terms of some of the scientific issues that can come up as you're considering a chemical for listing or delisting.

Another thing that comes up sometimes is what the consequence of a listing or delisting may be for a given chemical, industry, or particular uses in a product. And as you know, that's not really within the purview of this Committee. You're looking at the question of whether or not a chemical presents a hazard, not whether or not that chemical requires a warning or is at a level currently that would cause human harm.

Okay. Also -- and along with that, of course, the exposure issues -- human exposure issues are important, but they generally aren't addressed here with the exception of whether or not the scientific studies

that you're looking at would apply to potential human exposures to the chemicals. We do adopt safe harbor levels for many of the chemicals that are listed, and those safe harbor levels actually are run past you as the Committee members when we're proposing them in the regulatory process. And so issues you may have with the way we approach those numbers should be addressed during that process, assuming a chemical is listed or remains on the list.

So I think that is all the general -- oh, one more comment. We encourage the Committee members to ask questions of our staff. And that has to do -- you know, you can ask questions on a legal nature from me, scientific nature from our staff here, who have spent a lot of time looking at the data and issues that are related to that. They are excellent scientists and they can help sort things out for you. And you can also ask follow-up questions after you hear comments from the public, if -- of our staff, if that's something that would be helpful to you.

Okay. Any questions on that general speech? You've heard it before.

Okay. So just briefly, if you could put up the slides, Cindy.

(Thereupon an overhead presentation was

presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: I just wanted to very briefly give you the background on why the -- two of the chemicals are in front of you today. Hexafluoroacetone and phenylphosphine are in front of you today, because of some changes to the federal Hazard Communication Standard.

Why don't we skip to the next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: In 2012, which is a couple years ago now, the federal OSHA made some changes to the federal Hazard Communication Standard, which our office uses to identify certain chemicals for listing under Prop 65. And based on those changes, we have determined that the chemicals that we've been bringing to you over the last year or so don't meet the criteria for listing under an authoritative body or Labor Code or formerly required mechanism, which are the other listing mechanisms for chemicals under Prop 65.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So our process is that when a chemical doesn't meet the -- no longer meets the criteria for any of our administrative listings, we present those chemicals to you as there -- our

scientific experts, so that you can consider the chemicals de novo, based on the currently available information. And so we have done that, as I mentioned, over the last year or so of meetings.

And you'll be happy to know that we only have a couple left after today. But just as background, the four chemicals that are on the left-hand side of this slide that are in color, are the ones that you have determined that should be retained on the list. And on the right-hand side, the white section of this slide, are the chemicals that you've determined should be removed from the list, and, in fact, these have been removed.

So next slide

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CHIEF COUNSEL MONAHAN-CUMMINGS: The chemicals that you're going to be considering today, as I mentioned, there's two of them. I probably ought not to try and pronounce them twice. So those are on the left here in the purple. And the two that are remaining for a future meeting are on the right. So we're down to the last four, out of a -- quite a number of chemicals that you've already considered.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So the

chemicals that you're considering today, of course, you need to provide -- or apply your own criteria for, and that's the clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity standard, which is in the statute. You don't need to worry about what the standard was under the other listing mechanism, because this is essentially a de novo review of current information.

Now, in the past, I have given you some additional legal background for why these chemicals were listed in the first place, and why they came -- they're coming forward for you to consider. I'm not sure whether or not you want to hear that again. So it's entirely up to you whether I go through that.

Were you here, Dr. Luderer?

COMMITTEE MEMBER LUDERER: I wasn't.

CHIEF COUNSEL MONAHAN-CUMMINGS: Do you want me to just run through it quickly?

COMMITTEE MEMBER LUDERER: That would be great, a brief summary.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Well, I'll be as brief as I can.

So the legal background -- next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: -- is that, as I

mentioned, there are four listing mechanisms under Prop 65. One of them is called the Labor Code listing mechanism, which relies on certain subsections of the California Labor Code, which in turn one of those incorporates certain provisions -- regulatory provisions under the federal Hazard Communication Standard, which is part of the regulations that federal OSHA adopt.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: And so up until March of 2012, the Hazard Communication Standard regulations specifically referred to the American Conference of Governmental Industrial Hygienists, or ACGIH. They publish a list of threshold limit values for chemicals that are present in the workplace. And so what the federal regulation did is define those TLVs as a definitive source for identifying chemical hazards. We used that list as a way to identify chemicals that cause reproductive or developmental effects. And so the chemicals that we've been going through recently had been identified that way and listed that way.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So just a summary here, there was a court decision that was entered

prior to the changes under the federal communication standard. And that case, *Chamber of Commerce versus Brown*, made it clear that we do have to use the Labor Code mechanism to add chemicals to the Prop 65 list. And at that time, it also affirmed that OEHHA must use the ACGIH TLVs and the subpart (z) of the federal regulations to list chemicals.

So it changed after that. That case is still in effect. However, after 2012, the only part of the decision that really relates now to our listing decisions is the first one, which still requires us to list chemicals that are identified by reference under the Labor Code. That, right now, is limited essentially to chemicals that are identified by the International Agency for Research on Cancer. And so those are the chemicals that we're identifying listing at this time. So the TLVs are no longer a definitive source for listing under Prop 65.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So then what we did after that -- the changes in the federal standard, we looked at all of the chemicals that had been listed under the Labor Code. We identified those that might be subject to listing under other administrative processes, like the

authoritative bodies or formerly required listings. And we did identify some chemicals that could be listed that way, and so we did change the basis for some chemicals.

And so what you have before you today are the remaining chemicals that we found that did not meet the basis for any of the three administrative listing mechanisms. And so they're in front of you for, as I mentioned, a de novo review of the current information that's available.

So next steps. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The Committee would today decide whether or not the two chemicals that are before you that are related to this issue do or don't meet your criteria for listing, or you have the choice to defer either one or both of the chemicals to another meeting, if you have questions that the staff can't answer for you today.

And then, as I mentioned, the last two chemicals that are in this particular posture are going to be presented to you at a later meeting. We don't have a particular date set for that meeting. So any questions on that?

Okay. So I think I'm done speaking for a while. So the next person to speak will be Dr. James Donald.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Good morning. Could I have the next slide, please.

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DR. DONALD: So as Carol has said, three chemicals are being presented today for you to determine whether they've been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity. Carol has described the basis for two of the chemicals being presented. I will describe the basis for the third chemical chlorsulfuron immediately before we present the summary on that chemical.

So consistent with the way we've presented chemicals for the last several meetings, we've provided the relevant data to you in a hazard identification document in the form of summary tables. And in this case, we were able to provide all of the original study reports and published papers that were summarized in those tables.

Could I have the next slide, please?

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DR. DONALD: And again, as has been our practice, we have identified publications through literature searches that covered the three major reproductive

toxicity endpoints, which are, of course, developmental toxicity, male reproductive toxicity, and reproductive toxicity. And those searches were conducted through a contract with the Public Health Library at the University of California at Berkeley following the search protocol described in the hazard identification document as Appendix A.

In this case, for chlorsulfuron, as you already know, the data, were proprietary data, which were provided to us by DuPont Crop Protection and forwarded to you. And unless you have any questions on that, I will now ask Dr. Marlissa Campbell to present a summary of the information on phenylphosphine -- excuse me, hexafluoroacetone.

CHAIRPERSON GOLD: Move on.

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DR. CAMPBELL: A comprehensive literature search resulted in eight references with data on the potential reproductive toxicity of hexafluoroacetone, or HFA in rats. Four of these references concern the potential developmental toxicity of HFA, three of them were conducted by the dermal route of exposure, and one by the inhalation route of exposure.

Four references -- additional references concern the potential male reproductive toxicity of HFA, and three of these also were conducted by the dermal route of

exposure, and one by the inhalation route.

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DR. CAMPBELL: The first study under discussion is by Britelli et al., 1979. This was done in two parts with a range-finding study, and a full teratology study. And the first experiment or range-finding study, these are conducted in order to establish the range -- appropriate range of doses to use in a more detailed full-scale study. And the aim is to find three test doses, the lowest of which ideally would be a no effect level, and the highest dose would provide some evidence of toxicity, if not in the offspring, then at least in the dams, so you know that you got a level in them that had some biological effect. And then ideally the mid-dose would help establish a dose-response relationship between the two.

In this case, for the range-finding study, they took 15 total pregnant female rats divided them among 10 doses, which ranged from 2.3 to 90 milligrams per kilogram per day. And these were compared to vehicle controls. Exposure was daily on gestation day six through 15, with HFA rubbed into a shaved area of the skin on the back of each animal. And they were evaluated simply for viability and gross malformations in the offspring.

For the full-scale teratology study groups of 14 animals were treated with the finally elected doses of

zero controls, one, five, or 25 milligrams per kilogram per day. And all of these doses were prepared to a volume of approximately 0.1 milliliter per rat.

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DR. CAMPBELL: Data were not shown for the range-finding study and descriptions of what happened were not particularly detailed. What they noted was that at 90 milligrams per kilogram per day the dams were described as showing perineal staining and weight loss. The paper also states that the range-finding study found doses at or above 40 milligrams per kilogram per day were almost entirely feto-lethal and that any litters that did have live fetuses had a very high percentage of abnormal fetuses, but there were no details provided on the nature of those abnormalities.

The full teratology study identified adverse effects on viability, growth, and frequencies of anatomical abnormalities and variations as listed here, anasarca or generalized edema, anophthalmia(no eyes), hydronephrosis, cleft palate, small kidneys, bipartite vertebral centra, and unossified carpals and/or tarsals as well as scoliosis of the spine.

Effects increased in frequency and severity with increasing dose. And I also wanted to mention that significantly lower final maternal body weights were found

for the mid- and high-dose groups. This was an eight or 14 percent reduction relative to the controls respectively, but it was not clear from the paper whether the weights were adjusted for the weight of uterine contents, or in other words, reduced numbers of fetuses and reduced weights of the fetuses might explain the differences between the groups.

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DR. CAMPBELL: The next study was conducted by -- I'm not sure if it's Becci(Bek-ee) or Becci(Bes-ee) 1982. In these experiments, HFA served as a positive control for teratogenic effects by the dermal route of exposure. The compound under study in the paper was actually n-methylpyrrolidone, but I'm not going to talk about that.

The range-finding study compared 0.5 milligram per kilogram per day dose of HFA to a wide range of doses for the compound under study.

I just want to check.

As you'll see from the next slide, that 0.5 milligrams per kilogram dose of HFA was ineffective. So for the full teratology study they used ten milligrams per kilogram per day HFA as a positive control.

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DR. CAMPBELL: No effects were observed on pregnancy rate or gestational weight again in either the

range-finding study or the teratology study. In the range-finding study, there were no significant differences from controls and live litter size implantation frequency, resorption frequency, or mean fetal weight. Again, they really didn't find anything.

At the ten milligram per kilogram per day dose used in the full teratology study, they did find increased mean resorption frequency per litter, decreased mean fetal weight, increased frequencies of certain skeletal defects, missing sternebrae, wavy ribs, rudimentary ribs, extra ribs, incompletely ossified vertebrae, incomplete closing of the skull, incomplete ossification of extremities, and missing or incomplete hyoid bones. And each of these effects was significant at the P less than 0.05 level.

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DR. CAMPBELL: Okay. Just to do a little explanation here, the final two developmental toxicity studies on hexafluoroacetone were not available in the form of peer reviewed published literature or as submissions to U.S. EPA under the rule-making provisions of the Toxic Substances Control Act, or TSCA.

What they are is 8(e) is a mandatory provision of TSCA, which pertains to manufacturers, importers, processors, and distributors of chemical products, and requires them to submit to EPA any evidence that they

might have that their product could hold a risk of harm.

The FYI program is quite similar, and it just encourages data submissions by parties, which are not subject to mandatory reporting. Both of these types of submissions are screened by U.S. EPA, but they may or may not be reviewed in detail for incorporation into specific regulatory actions. And it's because these kinds of reports don't necessarily comply with EPA test guidelines or GLP guidelines and the reporting may be incomplete.

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DR. CAMPBELL: So the first one of these that was a submission by -- under the 8(e) program by Hoechst Celanese Corporation. It was not immediately obvious, because the data is prevented -- presented quite differently. They didn't include the range-finding study. It wasn't immediately obvious that this was, in fact, the same data that was reported in the study that was published many years earlier by Britelli et al., in 1979. So I'm not going to say anymore about that one. We'll just move on.

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DR. CAMPBELL: The other one was a submission under the FYI program. This is the only inhalation developmental -- or rat teratology study in this group, and that was provided to EPA by Haskell Laboratories. The

reporting is quite abbreviated and the full teratology study was only described in a two-page letter, but what they do tell you is that the range-finding study at ten ppm, two of the surviving fetuses were described as malformed and the third as having a developmental variation.

And you can see the methods. This was pregnant rats, inhalation, six hours per day daily for gestation day seven through 16 with evaluation on gestation day 22.

Let's see. And the range-finding study found maternal mortality was 100 percent at the concentration of 60 ppm, 67 percent at 30 ppm. So for the full teratology study, they went with doses of 0.1, one, or seven ppm. In the full teratology study, they found no effects on maternal body weight, adjusted weight change, or food consumption. They did find increased absolute and relative liver weights at one and seven ppm.

I just want to see if I've left anything out.

Yeah. The reduction in absolute gestational weight gain was due to reduced fetal weight. So once that was adjusted for the weight of the uterine contents, you don't see the effect on maternal weight. The malformations seen at seven ppm, included anasarca and/or cleft soft palates. The variations reported at one and seven ppm were primarily retarded ossification of various

skeletal elements. This is the last development -- of the developmental toxicity studies on HFA, and the next four slides will cover male reproductive toxicity. Three of these also conducted by the dermal route and only one by inhalation.

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DR. CAMPBELL: And most of them came from the same laboratory, so it's a various combination of not sure if it's Gilles(Jill-ees) or Gilles(Gill-ees) and Lee. The first one in 1983. This was dermal application of 13, 39, or 130 milligrams per kilogram per day daily for 14 days. Each doses group had its own control group, and the control rats in each of these groups was pair fed to their corresponding treated group. Eight animals per group sacrificed 24 hours following the last dose.

The right testis from each of these rats was prepared for light microscopy and the left testis was incubated with radiolabeled glucose and acetate for biochemical studies.

They found decrease in weight gain with increasing dose. Chromodacryorrhea, or bloody tears, were observed at 39 and 130 milligrams per kilogram. It was mild and temporary at the lower dose.

Severe testicular atrophy was reported for all of the high-dose group animals, and half of the mid-dose

group developed, what was described as, mild testicular atrophy. Spermatids in the maturing stages of development were found to be most vulnerable to HFA toxicity. There -- with the radiolabeled studies, there was increased incorporation of both labeled compounds into triacylglycerol and phospholipids at 39 and 130 milligrams per kilogram per day, and decreased incorporation of labeled acetate into sterols.

Vitamin A and zinc levels were checked to investigate any possible relationship to testicular atrophy. And no changes in either of these were found.

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DR. CAMPBELL: And just because picture is worth a thousand words, these are light microscopic sections of a normal or control on the top, and an atrophic testis from a rat treated with 130 milligrams per kilogram per day HFA, both seen at a magnification of 245 times.

As is the accepted practice for histological data, the adverse effects are described and then examples presented, rather than giving a statistical analysis. Now, let me see if I can bring up just to make these easier to see.

Okay. The S indicates a relatively thick layer of spermatocytes and spermatogonia at B, which is the basement membrane. The asterisks mark the most severely

damaged tubules, which are lined with a single cell layer, consisting of intact spermatogonia and Sertoli cells. The lumina, the central Lumina, contain the cytoplasmic processes of Sertoli cells. The ones labeled A are considered to be moderately atrophic tubules lined mainly with spermatocytes and devoid of spermatids.

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DR. CAMPBELL: Moving on to the next study, Lee and Gilles, same group, 1984. Dermal application of 13, 39, or 130 milligrams per kilogram per day HFA daily for 14 days. Control rats were dosed with water and pair fed to treated rats. Ten animals per group and sacrificed at 24 hours following the last dose. The testes were examined grossly and prepared for light microscopy. Testes from the high dose group in this study were prepared for electron microscopy, so they took a closer look.

There was no discussion of systemic toxicity, body weights, or organ weights. Testicular atrophy was a slight in 50 percent of the rats at 39 milligrams per kilogram per day, and severe in all rats at 130 milligrams per kilogram per day. At the light level, they describe effects on spermatids and spermatocytes and no effects were noted on a spermatogonia, Sertoli cells, or Leydig cells.

At the EM level, there were increased lipid droplets in the Sertoli cells and ultrastructural changes observed in Leydig cells.

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DR. CAMPBELL: And again, here's a picture. The upper two, the left-hand side is the normal seminiferous tubules at a magnification of 80, and on the right-hand upper panel shows degenerative tubules following a dose of 130 milligrams per kilogram per day, the same magnification.

The bottom panel is the EM level showing spermatids and Sertoli cells, and that's at magnification of 4,200. And let's -- woops -- go back. Everything is lit up.

What I really wanted to point out here in the EM view are the large vacuoles in early stages of degeneration, and those are marked by the V. And the P are phagosomes of Sertoli cells filled with cellular debris.

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DR. CAMPBELL: The next study in 1985, there were two experiments in this study. There was one conducted in vivo and the other in vitro. And actually the in vivo experiment also did have an in vitro component. The in vivo study involved dermal application of either zero or

130 milligrams per kilogram per day daily for 14 days, seven exposed and eight controls. And they did testicular weights, histology, hormone levels, and uptake of radiolabeled acetate and mevalonate.

The in vitro study, they actually took testicular fractions from untreated rats and incubated them with HFA and labeled acetate at the same time for three hours at 37 degrees -- 37.5 degrees centigrade.

In vivo, they found no effect on final body weight or serum levels of LH or testosterone. There was a 48 percent increase in serum FSH. There was a 43 percent reduction in testicular weights, and a 50 percent reduction in testicular testosterone. Degenerative changes were observed in spermatocytes, and there was inhibition of Leydig cell C_{19} steroidogenesis. They didn't find any changes in the in vitro study.

So let me see if I've left anything out. No, I think we've gotten all of it.

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DR. CAMPBELL: So here's the pictures. I'm just going to light these up. I've got the arrows.

Okay. The left-hand side shows normal seminiferous tubules from an untreated animal with a higher magnification in the bottom photo. Just to point out that M is the spermatid -- what they describe as the

spermatid maturation stage. The lower panels are closer magnification. In here, what's labeled as SC, that's a spermatocyte, and S is the Sertoli cell. So those are just some structures of note.

On the right-hand side, you can see what they look like, the seminiferous tubules, after 14 days of HFA exposure. Again, the higher magnification in the bottom view. S marks the Sertoli cells, and those arrows point to eosinophilic globules containing basophilic nuclear material.

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DR. CAMPBELL: The last of the studies Lee and Kennedy, 1991. This is the only inhalation male reproductive study of HFA. They used inhalation exposure to 0, 0.1, 1, or 12 ppm, six hours a day, five days a week for 90 days. The animals were sacrificed after either 30 or 90 days exposure, or at 28 or 84 days post-exposure, or PE. There were 40 animals per group, daily clinical observations, weekly weigh-ins, testes and epididymides were weighed and prepared for light microscopy.

And what they found was for 12 ppm at all of the time points they evaluated, body weights were decreased, there were certain clinical symptoms, and decreased absolute testes weights.

At 12 ppm with 30 days exposure, they saw

testicular atrophy and oligospermia or aspermia with effects on spermatids and spermatocytes. At 12 ppm with 90 days of exposure, there was severe testicular atrophy, disappearance of mature and immature spermatids from the seminiferous tubules, and spermatozoa were absent from the epidiymal tubules.

At 12 ppm 28 days post-exposure, there was evidence of variable regeneration. At 12 ppm by 84 days post-exposure, there was some partial restoration of spermatogenesis.

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DR. CAMPBELL: Here's the picture. What else? We have the arrows. Okay. The upper panel is a seminiferous tubule at Stage 4 in a control testis. The Mst marks mature spermatids. And you can see the tails pointing into the lumen. The lower panel shows the seminiferous tubule at Stage 4. That's from a treated animal at 12 ppm for 28 days. Both of these are at a magnification of 400. I wanted to point out the luminal surface shows fragmented tails of mature spermatids, and that's what the arrows are pointing to. And then just to summarize for both of these endpoints.

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DR. CAMPBELL: Turning back to the developmental toxicity data, you can just see these are the studies that

were available. The upper table shows results from the dermal developmental toxicology studies in rats. Findings, that all of which, were statistically significant, reduced viability, reduced growth of surviving fetuses, increased soft tissue, skeletal anomalies, and the dose range in which they saw those effects. And that there was evidence of increasing severity in frequency with increasing dose.

The lower panel shows the results of the inhalation study. Again, decreased viability, reduced weights of surviving fetuses, increased soft tissue and skeletal anomalies, and then the concentration range that you can see. Increasing severity of effects with increasing dose or concentration.

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DR. CAMPBELL: And then finally, this is just a summary slide of the male reproductive toxicity data that we just looked at. And you can see the upper table are the dermal studies, testicular atrophy, damaged spermatids and spermatocytes, effects observed at the EM level on Sertoli and Leydig cells, hormonal changes, increased serum FSH, reduced testicular weights, degenerative spermatocytes. And you can see the dose ranges that those effects were observed in 39, 140, 130 milligrams per kilogram per day are in the inhalation study at 12 ppm.

And that completes my presentation.

CHAIRPERSON GOLD: Thank you, Dr. Campbell. Does the Panel have any questions for Dr. Campbell before we go to public comments?

Hearing none. Do we have any public comments?

No.

Okay. So we have divided up the Committee discussion for Dr. Baskin to -- sorry -- to lead the male reproductive component and Dr. Luderer to review the developmental piece.

I don't know if it matters which goes first. Do you -- Dr. Luderer, are you okay with going first on developmental?

COMMITTEE MEMBER LUDERER: Okay. Since we already had such an excellent summary of the details of these studies, I just wanted to maybe start out by going through the studies that were presented that looked at developmental toxicity endpoints of the hexafluoroacetone, and maybe sort of highlight what are some of the positives and negatives of those studies, in terms of their design, et cetera.

So the Becci(Bek-ee) or Becci(Bech-ee), et al. study, that was the study where the HFA was used as a positive control. So one of the cons for that study was really there was only one dose level, because it wasn't

really intended to study the teratogenicity of that compound.

On the plus side, there was a large N. It was -- there was an N of 25 for that -- the teratology portion of that study. The range finding was a smaller N and a lower dose of the HFA used. They also examined all the fetuses from each litter, and I think the litter was the experimental unit, which was an appropriate analysis.

They shaved the skin for the dermal application. They also used collars to prevent licking. On the negative side or something one would have liked to see, but wasn't presented or discussed, was whether or not the animals were randomized to treatment groups, and whether there was blinding of the individuals who were evaluating the endpoints.

So then the Britelli study from 1979, in that study again another rat dermal application study. Some of the pluses for that study, again, they had range finding this time for HFA. They used multiple doses in the teratogenicity study. The data were analyzed with the litter as an experimental unit. The N was a bit smaller. It was 14 -- I think it was 14 per group, yeah.

And they -- also, the on negative side, they didn't mention randomization or blinding either for -- in that study, whether or not they did it. They described

shaving the skin. They didn't do any measures to prevent licking, but they did rub the material until dry, and they said there really wasn't -- once that was done, there wasn't any left on the skin to be able to be licked off by the animals.

For the Haskell study, this was again a rat study. This was the inhalation study with HFA. And again, there was a range finding study, and then a teratogenicity study with three different dose levels. The N was 24 per group. There was a reasonable N. There were, again, no -- this was not a detailed report, so there was kind of even less information about how they conducted the study.

And I actually did have one question. Did you try -- was there -- did you try to get a detailed report or is it just no longer existent?

DR. CAMPBELL: It's so old, it -- you know, 1988.

COMMITTEE MEMBER LUDERER: Nobody knows where it is?

DR. CAMPBELL: I don't even -- yeah -- wouldn't even know where to start to track it down.

COMMITTEE MEMBER LUDERER: Okay. And again, there was no mention of randomization or blinding and other details were missing there.

So again -- just to kind of summarize then, so

there were no human studies available for the developmental toxicity of hexafluoroacetone. I would say that for two of the three animal studies for which there were the detailed reports available, the Becci and Britelli hook study. I would say that there's high confidence in those studies. There's controlled exposure, individual level outcome data, appropriate control groups. As I mentioned already, my confidence would be tempered a bit by the lack of information on randomization and blinding, which potentially can introduce risk of bias, and that there was only one species studied. Albeit, there were two different strains of rat, and there were two different routes of exposure.

So the confidence is increased by consistency among these three independent studies I think, and between the two dose routes. The findings were similar between the dermal and inhalation exposure. So both of these showed increased resorptions, decreased fetal weights, increased malformations, including similar malformations among the studies, hemorrhages, pale fetuses, anasarca, cleft palate, various skeletal anomalies. And there were relatively large magnitudes for some of these effects, particularly the resorptions, fetal weights. And there was a dose response in the two of the three studies that actually had more than one dose.

So I think that, taken together, the weight of the experimental animal evidence supports that hexafluoroacetone is a developmental toxicant. Even though there are no human studies of the developmental toxicity, I think that the animal data are relevant to humans and strong.

CHAIRPERSON GOLD: Okay. Thank you. Any questions for Dr. Luderer or further discussion on the developmental toxicity?

Okay. Dr. Baskin, male reproductive toxicity.

COMMITTEE MEMBER BASKIN: Thank you. Again, very elegant presentation, and actually not much to add. You're always concerned when one of the papers in the development section has the chemical at hand as a positive control.

So the four papers that were presented for male reproductive toxicity again were all animal studies, three had dermal application, one had an inhalation application, if I'm not mistaken, and they were in rodents. And I think kind of the bottom line in summary, looking at standards of science, they, in my opinion, did meet them with very good histologic and figures of testes abnormalities in three out of the four papers, which looked actually reasonably definitive.

The pros to the study is that the science is

good, but it's really from one group where all the data is from, and it is what it is. So I would basically summarize that this is a concerning chemical with excellent scientific evidence that it affects male reproductivity and leave it at that.

CHAIRPERSON GOLD: Thank you. Any further discussion by the Committee with regard to male reproductive toxicity?

Developmental?

Are we ready to vote?

COMMITTEE MEMBER BASKIN: And there was no female data that was reviewed or in the literature.

CHAIRPERSON GOLD: No female data on this, right.

COMMITTEE MEMBER LUDERER: Yeah. I would maybe just add that for male reproductive toxicity the fact that even after 84 days there was still very severe effects in quite a few of the animals, so that it really didn't seem to be reversible, adds to the concern.

CHAIRPERSON GOLD: Okay. Thank you. Anymore comments, questions?

I assume then we're ready to vote?

Okay. So we'll vote separately on each endpoint. So, first of all, has hexafluoroacetone been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental

toxicity?

If you believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see five.

Any noes?

(No hands raised.)

CHAIRPERSON GOLD: Okay. Any abstentions?

(No hands raised.)

CHAIRPERSON GOLD: No.

Okay. Second, has hexafluoroacetone been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity? If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see none.

If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Okay. That's five of us.

Any abstentions?

(No hands raised.)

CHAIRPERSON GOLD: None.

And then finally, has hexafluoroacetone been clearly shown, through scientifically valid testing, according to generally accepted principles to cause male

reproductive toxicity? If you believe yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see five.

If you believe no.

(No hands raised.)

CHAIRPERSON GOLD: Abstentions?

(No hands raised.)

CHAIRPERSON GOLD: Okay. So the result is that five of our five members have found hexafluoroacetone to be a development toxicant. None have found it to be a female reproductive toxicant. And all five found it to be a male reproductive toxicant.

Anything further?

Okay. Onward. So our second chemical that we'll be considering is phenylphosphine. And Dr. Campbell, you'll also be making this presentation?

DR. CAMPBELL: Oh, thank you.

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DR. CAMPBELL: Two reports were identified as having information relevant to the potential reproductive toxicity of phenylphosphine. Waritz and Brown published a journal article and the DuPont report was submitted to U.S. EPA under the provisions of TSCA 8(e).

Both of these reports are actually general

toxicity studies were conducted by the inhalation route of exposure and were of less than chronic duration. Each of the reports discusses two separate experiments. The DuPont report covers 90-day toxicity studies in rats and in Beagle dogs. And the Waritz and Brown conducted both acute and subacute studies both types in rats.

--o0o--

DR. CAMPBELL: So this one shows the DuPont study submitted to EPA under 8(e). And this is the rat data. Their methods were to treat by inhalation six hours a day, five days a week for 59 exposures, which I know it doesn't add up to 90 days, and they don't offer any explanation about that arithmetic. So it's called a 90-day study and then this was the exposure scenario.

Also, both male and female rats were exposed, but they didn't report anything about effects on female reproductive organs. So we're just going to be discussing the male.

Sacrifices were sequentially five animals per sex per group at test days 30 and 90, and then again at 28 days post-exposure. And then the remaining animals were sacrificed 65 days following the end of exposure.

Systemic effects at 2.2 ppm were described as clinical, and neurological effects consisting of hypersensitivity to touch and sound, as well as decreased

body weight and weight gain. And the symptoms were considered to resolve during the post-exposure period.

Reproductive effects consisted of irreversible severe testicular degeneration at terminal sacrifice in five out of five males at the 2.2 ppm group. And unfortunately, there's no pretty pictures with this one.

--o0o--

DR. CAMPBELL: So I'll just go to the next slide, which is basically the same study, same doses, done in dogs. In this, they did the same kind of thing, four animals per group, 0, 0.6, 2.2 ppm was considered to be the average exposure -- average per exposure. Sacrifices, two dogs per group at test day 90, and then the remainder at 28 days post-exposure. Systemic effects at 0.6 ppm. Clinical symptoms during treatment, which resolved post-exposure.

At 2.2 ppm more severe clinical symptoms. Decreased hematological values and evidence of moderate anemia starting at one month of exposure and resolving post-exposure. Reproductive effects described as testicular degeneration, which was described as focal in one out of four control animals and in one out of four animals at the 0.6 ppm level, and as diffuse degeneration in three out of four dogs at 2.2 ppm.

Oligospermia occurred in one out of four dogs at

0.6 ppm and two out of four dogs at 2.2 ppm. They described that the effects were similar to what was seen in rats, but not as severe. Spermatogenesis was affected, but it was -- continued to be maintained.

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DR. CAMPBELL: And then onto the published study by Waritz and Brown, which is from 1975. The acute protocol consisted of four hours exposure to either 0, 19, 32, or 42 ppm. Six animals per group with two rats per group sacrificed at each of days one, two, and seven -- oh, and -- one and two, and seven post-exposure to 19 ppm. Two rats per group sacrificed at 14 days post-exposure to 44 ppm, and then they just did gross pathology.

The subacute study was four hours a day for 10 days with exposure to, what they gave as, 0.31 µM per liter. So Jim actually calculated that to be 6.8 ppm. Three rats per group were sacrificed immediately post-exposure, and the remaining at 14 days post-exposure. And again, it was just gross pathology.

The acute study they reported respiratory irritation during actual exposure with no other evidence of toxicity reported. In the subacute study, there was respiratory irritation during exposure, temporary dermatitis, foci of red blood cell formation in the spleen and decreased weight gain.

No reproductive effects were reported from the acute study. In the subacute study, they described mild depression of spermatogenesis in two out of three rats immediately post-exposure, and in one out of three rats at 14 days post-exposure.

--o0o--

DR. CAMPBELL: And just to summarize what you just heard, all of these studies were conducted by the inhalation route. One was -- one was a 90-day study in dogs and all the others used rats.

While none of these were specifically designed as studies of male reproductive toxicity, all of them evaluated and reported at least basic data on male reproductive organs.

And that concludes my presentation.

CHAIRPERSON GOLD: Thank you, Dr. Campbell. Any questions for Dr. Campbell?

Okay. Then Dr. Pessah and Dr. Baskin were going to review these studies. So, Dr. Pessah, you want to start?

COMMITTEE MEMBER PESSAH: Yeah. Thank you. So the data for phenylphosphine is actually very -- there's not a lot of data. And the numbers in each of the studies are rather small. And there was really no details as to how the animals were assigned to groups, or randomized.

Although, the numbers were so small, that one would expect that if this was a random effect, then you wouldn't see consistent sperm effects across the species and across the treatment -- the high treatment groups.

The reproductive effects seem to be pronounced more severe in rats than in canine. But then the small N's are really troubling to me, and so I'd have to defer to an expert on how severe these effects are and whether they arise in control groups, if larger numbers were examined.

CHAIRPERSON GOLD: Thank you. Is that all?

So, Dr. Baskin, our resident male reproductive expert, maybe you can respond to that.

COMMITTEE MEMBER BASKIN: I'm not sure I'm the resident expert, but I completely agree that with N of 3 and 4, it's very difficult to make really any intense determination.

On the other hand, they gave these chemicals -- well, the other negatives are, there's no histology, which always really bothers me. You know, when you have a beautiful picture that was shown from the previous chemical, that there's, you know, clear abnormalities in the testes, and you take the study out to 90 days or 150 days or a year, then reversibility is also addressed quite nicely. And this study didn't really

address all of those. So the limitations were no histology, very small numbers, and the studies weren't carried out for an extended period.

On the other hand, these are two inhalation studies. And the one from DuPont in particular showed by their wording -- you know, we don't have the histologic data -- that there were changes in the testes which are very concerning. And based on that, I wouldn't take this chemical myself.

So we're really stuck with two studies that weren't focused on this issue, but as a by-product showed concern, and I would kind of look at these as pilot studies. You know, concerning enough that I think that there is concern for male reproductive toxicity. And that's basically all we can say with, you know, somewhat marginal data.

A specific example of that, at the low dose in the DuPont study, one of the controls was described as having focal degeneration. So what does that mean? However, in the higher dose, three out of the four animals had focal degeneration, so that's kind of a quasi dose response curve that was positive.

But, boy, this is not the way that you would ideally design and look at this.

CHAIRPERSON GOLD: Do you care to comment on the

scientifically valid testing portion of the vote that we're going to have to --

COMMITTEE MEMBER BASKIN: I mean, this is ambiguous. There's just not much else to say. I mean, I would lean toward concern in male reproductivity. Unfortunately, we have to say either yes or no.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Cause I'm looking at the data from the -- in the back, and they do have -- I know this is a very crude marker for effects on testes, but they have testes weights. Did you guys graph those weights and look and see if they were --

DR. CAMPBELL: Which one are you looking at?

COMMITTEE MEMBER WOODRUFF: Table I.

DR. CAMPBELL: In which --

COMMITTEE MEMBER WOODRUFF: Oh, the DuPont study. Sorry. The '92 study. Am I looking at this right? Not the other one. Not the peer-reviewed article. Not the published one.

DR. CAMPBELL: Which table?

COMMITTEE MEMBER WOODRUFF: It's at the very end. It says just Table 1. It's on page 53.

CHIEF COUNSEL MONAHAN-CUMMINGS: Could you -- Dr. Campbell, could you turn on your mic.

DR. CAMPBELL: Oh, sorry. I'm looking.

DR. DONALD: The short answer is, no, we did not graph the data.

DR. CAMPBELL: Well, and yeah, you see what they did. They've just kind of scored them, so it's not --

COMMITTEE MEMBER WOODRUFF: Right, no I'm not talking about -- right, I see that they scored them, which there's no back-up on that. I'm just wondering about the weights, because that's more --

COMMITTEE MEMBER BASKIN: They all look kind of to be around the same.

COMMITTEE MEMBER WOODRUFF: Well, if you look at the average --

COMMITTEE MEMBER BASKIN: Sorry. The weights to me look to be pretty close to the same, and there's only, you know, what, ten total? So again, you're going to have -- you're going to have limited statistical abilities here.

COMMITTEE MEMBER WOODRUFF: Right. I was looking at the average weights, because it's -- I mean, I think the one thing that's hard to tell with some of these studies is sometimes there's a trend in the weights, but any individual dose may not be significant, because, like you're saying, there's limited numbers. So I think it's helpful to have, at the these presentations, if there's some of these numerical scores, particularly something

like this, which is, I assume, it's -- since it's not done visually, it's done with a -- right, they weigh it with a scale, that it has less risk of bias in terms of evaluating the endpoint. It's more objective that that might be useful information to see that. I mean, I agree, there's like very small numbers in these studies.

COMMITTEE MEMBER LUDERER: Can I make a comment?

Am I looking at the same table. The testis weight, the mean for the controls, is 3.66 and it's 1.42 for the high dose.

COMMITTEE MEMBER WOODRUFF: Yes.

COMMITTEE MEMBER LUDERER: Okay.

COMMITTEE MEMBER WOODRUFF: And it's 3.66, 2.95, 1.42. That just was my question about that.

COMMITTEE MEMBER LUDERER: I mean, I think that the -- you know, there's more than -- I mean, the mean is half the -- you know, there's more than a 50 percent decrease in the mean testis weight. And although they don't show images of the testicular histopathology, I mean, you know, it's severe -- described as severe degeneration in five out of five that persisted until the terminal sacrifice that was 65 days post-exposure.

I think even though the N is very low, these data are still quite -- are compelling regarding male reproductive tox, particularly given that the -- we're

seeing that these findings in five out of five of the animals with persistence.

COMMITTEE MEMBER PESSAH: My question on that was that this is a relatively high dose where the animals actually did show acute toxicity during the exposure period. And whether this would influence the weights? So were those normalized to body weight or not?

CHAIRPERSON GOLD: Dr. Baskin, you want to comment?

COMMITTEE MEMBER BASKIN: (Shakes head.)

CHAIRPERSON GOLD: No. So, Dr. Campbell, do you have anything, or Dr. Donald, do you have anything?

DR. CAMPBELL: I think this table is just showing absolute --

CHAIRPERSON GOLD: Weights.

DR. CAMPBELL: I imagine the body weights are somewhere in here, but they're not on the same table, so, yeah.

COMMITTEE MEMBER WOODRUFF: Right. This table just has the testicular weights that they weighed, however many there were.

COMMITTEE MEMBER PESSAH: They did report a decrease in body weight and weight gain.

DR. CAMPBELL: Ideally, one wants to look at both absolute and relative.

DR. DONALD: If you would find it helpful, we can look at these data -- we can analyze these data for trend and report back to you later today whether or not there is any significant effect.

COMMITTEE MEMBER BASKIN: I mean, I think -- I mean, that's potentially useful, but I mean, I'm going to have to make a decision, like everybody else, based on two papers, one 1975, one 1992, which weren't directly looking at this issue, with lack of histology and small numbers, with, I think, some concerning findings.

And that's kind of how we have -- that's all we're going to have. So, I mean, I think you can dissect this up and down and reanalyze it, but we're still going to end up with the same decision -- or have to make the same decision based on that.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah. I mean, I agree there's a lack of histology, but if we have weights, that's a more objective measure than histology, right? So I think that would be useful information. I mean, we are going to decide today either way, right, is that what you're suggesting?

DR. DONALD: Well, you always have the option of deferring a decision which you did at the last meeting.

COMMITTEE MEMBER WOODRUFF: Well, I don't want to

defer that long, but you offered to do it today, so I was like, oh, okay, well.

DR. DONALD: Yeah. We -- yes, if you would like us to do it today, we can do that, and report back to you later in the day what the result is.

CHAIRPERSON GOLD: So question to the Committee is would that be helpful in your decision making?

COMMITTEE MEMBER PESSAH: With the small number, I think I'd still have questions, but I think it would at least give me a quantitative basis as opposed to what appears to be a very qualitative basis, at this point, because just testicular weight isn't going to do it for me.

CHAIRPERSON GOLD: Dr. Baskin, would it help you?

COMMITTEE MEMBER BASKIN: No.

CHAIRPERSON GOLD: Dr. Luderer, would it help you?

COMMITTEE MEMBER LUDERER: I think it would be helpful.

CHAIRPERSON GOLD: Dr. Woodruff?

COMMITTEE MEMBER WOODRUFF: I'd like to see it.

CHAIRPERSON GOLD: Okay. So we're about half and half. The question is how much time would you require? Because we can defer till later today or we could defer to another meeting.

COMMITTEE MEMBER BASKIN: If I'm reading this right, we have a summary of the mean weight.

CHAIRPERSON GOLD: I'd like to be clear on what we're asking the staff to do and then how long it -- they think it will take them to do it. So something about weights I heard. So, Dr. Woodruff, would like to state what you'd like?

COMMITTEE MEMBER WOODRUFF: They offered to look at the individual -- to graph -- you have the -- yes, did you want to say something?

CHIEF COUNSEL MONAHAN-CUMMINGS: No, I just want them to hear what you're asking.

(Laughter.)

COMMITTEE MEMBER WOODRUFF: Oh, sorry. No. No. Go ahead. Did you want to say something?

DR. DONALD: No.

COMMITTEE MEMBER WOODRUFF: Oh, okay. So in the table at the end on the testicular weights, you have the testicular weights from each of the animals, right? Those are -- or the groups on page 57 -- page 54.

CHAIRPERSON GOLD: Page 54.

COMMITTEE MEMBER WOODRUFF: Page 54.

COMMITTEE MEMBER LUDERER: Actually, there's three tables.

COMMITTEE MEMBER WOODRUFF: Right. The three

tables, so you can look at the mean, the trend across the doses, and accounting for the body weights, which was the other concern, right?

DR. DONALD: Okay. So you would like us to look at pairwise comparisons and trends for both absolute and relative testis weight, is that correct?

COMMITTEE MEMBER WOODRUFF: Oh, yeah, that's good. Yeah, that's what I said.

(Laughter.)

CHAIRPERSON GOLD: Dr. Luderer, did you want anything else besides that?

COMMITTEE MEMBER LUDERER: (Shakes head.)

CHAIRPERSON GOLD: No. So the question is --

DR. DONALD: Okay. The one proviso is that we haven't yet found the individual animal body weights, so we may not be able to calculate the relative testis weights.

COMMITTEE MEMBER BASKIN: Yeah, I don't think it's there.

DR. DONALD: But if we can, then we'll do it.

COMMITTEE MEMBER WOODRUFF: Okay. That's fine. You can come back and tell us if they're there. I'm not going to push it, but if, you offered, and it's available, I think it would be informative, so...

CHAIRPERSON GOLD: And is this something you

think you could accomplish today or --

DR. ZEISE: (Nods head.)

DR. DONALD: Yes. If we can defer the decision until the end of the meeting, we should be able to provide that.

CHAIRPERSON GOLD: Okay. So let's defer the vote on this chemical until after the next chemical.

COMMITTEE MEMBER BASKIN: I mean --

CHIEF COUNSEL MONAHAN-CUMMINGS: Could I just mention also, Dr. Gold, that didn't ask for public comment yet.

CHAIRPERSON GOLD: Oh, good point. Thank you. No, I thought we did. Well, I apologize. We can certainly do that now.

COMMITTEE MEMBER WOODRUFF: Oh, by the way, the -- it looks like the weights might be on page 20, but they're graphed.

DR. DONALD: Yes, we saw the graphs.

COMMITTEE MEMBER WOODRUFF: We can use that little, you know, program to --

DR. DONALD: We're hoping that somewhere they're also tabulated, but we haven't been able to find that yet.

COMMITTEE MEMBER BASKIN: So, I mean, when you look at the table, we're looking at Table 1, correct?

CHAIRPERSON GOLD: Well, it also goes on Table 3,

I believe.

COMMITTEE MEMBER BASKIN: I mean, it gives the average of each group. It's kind of already there. So how is a graphic form going to help us?

CHAIRPERSON GOLD: Right. So within each dosage group, there's a mean testicular weight on Table 1.

DR. DONALD: Table 11 on page 54 gives the individual animal testes weights, so we could use those data.

CHAIRPERSON GOLD: Right. I think the question is whether using those would give you more information than you have by the means that are already in the tables?

COMMITTEE MEMBER WOODRUFF: Well, I think graphs are always visually useful, so -- but I think then we'd have -- it's true, you have four -- the four animals. So in this case, you'd have the means and the error bars and then we would be able to see how they look across the dose response. I think that could be -- I think just generally those are very helpful for us to see as a Committee.

COMMITTEE MEMBER LUDERER: And we have them for three time points, so we have them in the two post-exposure time points as well, and it persists, the weight. So we're really talking about more animals per dose level.

COMMITTEE MEMBER WOODRUFF: Okay. That's useful

too.

DR. DONALD: Okay. We may need a little more time to do all of these things.

(Laughter.)

COMMITTEE MEMBER WOODRUFF: You want to reconsider your offer, is that what you're saying?

(Laughter.)

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

COMMITTEE MEMBER PESSAH: Okay. So again, my concern arose from the graph not the table, which shows that at the high dose, there's quite a retardation in body weight, and --

COMMITTEE MEMBER WOODRUFF: At 90 days right.

COMMITTEE MEMBER PESSAH: Yeah.

COMMITTEE MEMBER WOODRUFF: I'm wondering that the other ones said. They don't have the earlier time points, though. No, that's females.

DR. CAMPBELL: I mean, we could kind of super -- we could kind of superimpose the graph, so you could see if it's moving in the same direction.

CHAIRPERSON GOLD: Well, as I understand it, the testicular weights in the tables are for individual animals, and I'm not sure you can link the graph total weight, body weight to those individual testicular

weights. So getting a relative weight for each animal is not possible.

DR. DONALD: Well, yes, unless somewhere in the document the individual animal weights are also provided. But as I said, we haven't yet found that in the document.

CHAIRPERSON GOLD: Right. So we don't think that's possible. So I think we need to be clear on what we're asking the staff to do. Do you just want to graph the testicular mean to testicular weights by dose over time?

COMMITTEE MEMBER WOODRUFF: For the three -- there's three time points, right, that were evaluated?

CHAIRPERSON GOLD: Right.

COMMITTEE MEMBER WOODRUFF: Yes. So the -- did you see if they gave another body weight graph for the other time points that they measured in this study?

COMMITTEE MEMBER LUDERER: The graph covers the whole study, so it shows during exposure and post-exposure.

COMMITTEE MEMBER WOODRUFF: Oh, I'm sorry. I was confused. Yes.

DR. CAMPBELL: It's females. It's just females and males.

CHIEF COUNSEL MONAHAN-CUMMINGS: So, Dr. Gold, I wonder if I can make a suggestion, since we've -- we

probably need a break, at some point here, for the court reporter anyway, that maybe we take an early lunch break and -- because we have enough stuff where we're probably going to have to go past lunch anyway, and let the staff take a look at it and tell you either what they think they can do or they can bring back what they did.

CHAIRPERSON GOLD: That would be fine with me. Is that fine with the Committee?

COMMITTEE MEMBER WOODRUFF: Yes, I like breaks.

(Laughter.)

CHAIRPERSON GOLD: The question is whether we should take the break -- and so we will do that. We'll defer this and see what the staff comes back with, whether we want to start the -- first, let me ask if there any public comments on this chemical?

No public comments.

Okay. So we've taken care of that item. But we will defer the vote on this and see what the staff can come back with in terms of a little more data analysis, or if that's not possible. Either way, you'll let us know after the next chemical.

And then the question is whether we ought to take -- whether we want to take a break now or if we would like to at least start the explanation of chlorsulfuron.

CHIEF COUNSEL MONAHAN-CUMMINGS: If I could make

a suggestion on that. I believe that the conversation on that chemical is going to be a bit longer. We do expect public comments on it. And if you hear some before lunch, there's much more likelihood you're going to chat about it then.

CHAIRPERSON GOLD: Oh, I thought you were going to tell us we're more likely to forget.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: No, but also, you know, it's -- if you get to the restaurants and stuff earlier, you can get back faster.

CHAIRPERSON GOLD: All right.

DIRECTOR ALEXEEFF: Also, I think there's a number of -- this is George Alexeeff -- a number of nuances in the data, so I think it's probably better just to hear it all the way through as opposed to hearing some now and then trying to decide -- remember what you heard later.

CHAIRPERSON GOLD: All right. So if I don't hear any objections, we will now take a break. The question is for how long?

How long does the staff need to decide if they can do anything about this?

An hour. So let's reconvene at 12:30. And, at that time, you'll be prepared to tell us what you were

able to do.

DR. DONALD: Yes. We'll at least be able to tell you what we're working on and what we hope we can present after chlorsulfuron.

CHAIRPERSON GOLD: Okay. So hearing no objections -- no objections?

We'll take a break until 12:30 and reconvene, at least hear from the staff what they think they might be able to do, and then make a decision. If they've done some analyses, we'll present those and have a vote, if we feel we can vote. Otherwise, we'll go on to the next chemical and defer this one.

Okay. Thank you.

(Off record: 11:23 AM)

(Thereupon a lunch break was taken.)

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

(On record: 12:30 PM)

CHAIRPERSON GOLD: Okay. I think we're ready to reconvene post-lunch. And I think the first order of business is to hear from the staff what they have figured out while they were munching and looking at the same time.

COMMITTEE MEMBER WOODRUFF: Oh, yeah. Sorry about that. Wait a minute. You're not --

CHIEF DEPUTY DIRECTOR HIRSCH: I'm not George.

CHAIRPERSON GOLD: Dr. Alexeeff has taken a new form of Dr. Hirsch.

DR. DONALD: Okay. We have been attempting to calculate the various parameters that we were asked about before lunch. We have been able to calculate the -- we've been able to do a pairwise comparison of absolute testes weight. We are also calculating -- excuse me a pairwise comparison and trend test for absolute testes weight. We're doing pairwise comparisons and trend tests on an estimate of relative testes weight. We did not have the individual animal data, but we're making an estimate based on group means. And we're also working on preparing graphs of the testes weight data.

We're not quite finished yet, but -- so we would suggest that if you proceed with chlorsulfuron, by the time we're finished with that chemical, we should be able

to provide you with all the information that you requested

CHAIRPERSON GOLD: That's quite impressive. So is the Committee willing to wait until after we hear about the next chemical or do --

COMMITTEE MEMBER WOODRUFF: Yes, I am.

CHAIRPERSON GOLD: Okay. Thank you very much.

So we will move on then to chlorsulfuron, correct, and have the staff presentation first. And we welcome back Dr. Alexeeff.

(Thereupon an overhead presentation was presented as follows.)

CHAIRPERSON GOLD: So Dr. Wu and Dr. Iyer are going to make this.

CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me. I need to just take a -- one minute to just --

CHAIRPERSON GOLD: Oh, sorry. You have to explain why we're doing this.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- just to introduce the reason that the chemical is on -- is here for your discussion. Just briefly, this is a different route to get to this Committee. This chemical was listed back in 1999 based on a U.S. EPA identification. U.S. EPA is one of the authoritative bodies that are listed in our regulation that were actually identified by this Committee in a previous forum as authoritative for purposes of

identifying reproductive toxins.

U.S. EPA has recently changed their -- reached a different conclusion regarding the chemical. And so under our regulations, if the basis for listing for a chemical has changed, then we bring the chemical to you again for a de novo review.

In this particular case, DuPont Crop Protection has requested that the chemical be reconsidered, and we've agreed to present it to you today. One other reminder for you is that you did receive a couple of disks from DuPont, one of them that includes proprietary information on some studies. And you have already signed an agreement that you wouldn't use that for any purpose, other than for the meeting. And so this is just a reminder that you need to return those disks to us. You can do that at the end of the meeting today, if you want, and then we can get those back to DuPont.

For members of the public that want to have access to that same information, you're welcome to review it in the DPR, Department of Pesticide Regulation, Library here in this building. You just have to sign a form again attesting that you're only going to use it for a non-commercial purpose.

So if you guys have any questions on either one of those things?

Okay. If not, then back to Jim.

DR. DONALD: Well, actually, Carol just covered everything that I was -- thought I was supposed to cover, so I will pass it immediately on to Dr. Wu to present the summary on the rabbit studies on chlorsulfuron.

DR. WU: Thank you. A DART literature search of chlorsulfuron and proprietary studies provided by DuPont Crop Protection, a party requesting delisting of chlorsulfuron, produced developmental toxicity studies in rabbits and rats, and reproductive toxicity references in rats.

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DR. WU: First, I will be presenting summaries of two references and their related supplements pertaining to developmental toxicity in rabbits. Afterwards, my colleague, Dr. Iyer, will be presenting summaries of studies in rats, which include one developmental toxicity study and two summaries of references pertaining to reproductive toxicity.

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DR. WU: Hoberman completed a teratogenicity study in 1980, which was conducted on pregnant New Zealand white rabbits. Rabbits were divided into four groups which received 0, 10, 25, or 75 milligrams per kilogram per day on gestation day six to 19. Each group had 16 to

17 rabbits.

In the treated mothers, there was a dose-related decrease in mean weight change. Increased resorptions were reported at all dose levels, but the result was only significant in the 75 milligram per kilogram per day group. The exact P value was not reported. This study had three supplements which were subsequent reanalysis of the data.

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DR. WU: In 2010, a reanalysis of the Hoberman 1980 study was completed at the request of the original study sponsor. The 2010 interpretation of the 1980 fetal resorption data was provided by the original study author in the context of a broader historical control database compiled by the Middle Atlantic Reproduction and Teratology Association, known as MARTA.

The author stated the litters in which a single conceptus have -- the author stated that litters with a single conceptus have an insufficient number of implantations to support pregnancy in New Zealand white rabbits and end in reabsorption. Hoberman indicated that the 1980 study data were skewed by the inclusion of litters with 100 percent resorptions. Hence, pregnancies with 100 percent resorptions were excluded in the 2010 reanalysis.

In 2011, a revision to the Hoberman 2010 supplement was produced after a calculation error was discovered. In the original supplement, the mean percent -- mean percent resorptions per litter were calculated in two ways, either including or excluding the litters with total resorptions. The purpose of this 2011 supplement was to provide all data as individual animal data, and to correct a calculation error, and to present group means that both include and exclude animals with total resorptions.

A second revision of the first supplement by Hoberman was completed by Munley in 2014. This revision was done to correct calculations and table entries. Also, a literature reference was added to the first paragraph of their, "Reasons for Revision 1" section. In this revision, data from a group 3 female that was found dead on gestation day 18 was excluded from all litter mean calculations. Two females that were in group 4, one of which had uterine scars indicative of pregnancy at some prior unknown time and another that had been euthanized following clinical observations suggestive of an abortion recorded on gestation day 28 was also excluded.

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DR. WU: This table shows the percent resorptions reported in the 1980 Hoberman study as well as in the

reanalysis of the data presented in the three related supplements. OEHHA repeated the statistical analysis of the Hoberman data and related three supplements using the same methods described on page eight of the original 1980 Hoberman study to determine specific P values.

The Hoberman 1980 study showed percent resorption was higher in the 75 milligram per kilogram per day group compared with controls and was significant to the 0.01 level. The percent resorptions in the 2010 Hoberman supplement were called erroneous and the Hoberman 2011 supplement because of a calculation error.

The 2010 -- 2011 Hoberman supplement calculated percent resorption in two ways, one method included all pregnancies and the other excluded all 100-percent resorptions. In both cases, the percent resorption was higher in the 75 milligram per kilogram per day group compared with controls, and was significant to the 0.1 percent level when all pregnancies were included.

The significance of the percent resorption being higher in the 75 milligram per kilogram per day group compared with controls when 100 percent resorptions were excluded was 0.02.

In 2014, Munley corrected calculations to exclude females from groups 3 and 4 for the reasons stated previously, and reported the percent resorption was higher

in the 75 milligram per kilogram per day group compared with controls and was significant to the 0.01 level.

All of the supplements discussed in the reanalyzed percent resorptions data were in the context -- were discussed in the context of the range of control resorption rates reported in the MARTA database, which had a range from 0 to 29.2 percent.

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DR. WU: In 1991, Alvarez completed a teratogenicity study in New Zealand white rabbits. This study was done in two parts, a main study and a supplemental study. In the main study, 100 New Zealand white rabbits age 5 to 5 and a half months old were divided into groups of 20 and gavaged once a day on gestation day seven to 19, with 0, 25, 75, 200 or 400 milligrams per kilogram per day.

In the supplemental study, 60 New Zealand white rabbits aged five to five and a half months old were divided into groups of 20 and gavaged once a day on gestation day seven to 19 with 0, 400 or 1000 milligrams per kilogram per day.

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DR. WU: No maternal toxicity was reported in the main study. In the supplemental study, there was decreased mean maternal weight gain in the 400 milligram

per kilogram per day group. In the 1000 milligram per kilogram per day group, signs of maternal toxicity included a significant incidence of mortality, reduced maternal weight gain, and increased clinical signs.

Effects on the offspring included an increase in minor fetal skeletal detects and total fetal malformations in the 400 milligram per kilogram per day group, an increased incidence of unossified sternebra at the 1000 milligram per kilogram per day group, and reduced fetal weight at the 400 milligram per kilogram per day group. This study had three supplements which were additional analysis of this study data.

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DR. WU: In 2005, Mylchreest performed additional analysis of the 1991 Alvarez study at the request of the study sponsor to add a calculated parameter, percent resorptions per litter, to the reproductive outcomes tables for the main and supplemental studies.

In 2008, Lewis performed additional analysis of the 1991 Alvarez data in the context of historical control data for skeletal variation in fetal sternebra and fetal skull ossification for the relevant time period when the studies were performed. The historical control data that was chosen were DuPont Haskell historical control data from 1983 to 1994 for selected fetal sternebra findings in

rabbits and for selected fetal skull findings in rabbits.

The purpose of the 2012 supplemental report by Munley was to provide additional statistical analysis to support the interpretation of fetal body weight data from the original Alvarez study. This original offspring data were tabulated for both males and females, and then additional statistical analyses were performed and reported.

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DR. WU: The next few slides show the data from the Alvarez study and supplements. This slide shows Mylchreest data which added percent resorptions per litter as a parameter, and the results of which are shown here. There are no statistical significance between the treated and control groups.

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DR. WU: The incidence of skeletal variations are presented in the table on this slide. For example, unossified sternebrae were reported in one fetus of one litter in the 75 milligram per kilogram per day group. The incidences of partially ossified sternebrae and partially ossified skull bones are also reported and shown here. And most of the numbers that are outside of the parentheses are all the number of fetuses. And the number inside the parentheses showed the number of litters.

Whereas, the one exception is the partially ossified sternebrae showed the number of litters affected out of the total in parentheses. That's the one difference.

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DR. WU: This slide shows the incidence of fetal malformations. A significant increase in total fetal malformations was reported by Alvarez in the 400 milligram per kilogram per day group in the main study. There were five fetuses with malformations in five litters versus none in the control group. Three had visceral malformations: The gall bladder was absent in one, another had a doubled aorta, and the third had a ventricular septal defect. Hemivertebrae were also observed in two additional fetuses.

The increase in fetal malformations in the 400 milligram per kilogram per day dose group was reported by Alvarez as significant to the 0.05 level by pairwise comparison using the Fisher's Exact Test and with a significant dose related trend by the Cochran-Armitage test for trend.

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DR. WU: Fetal weight data are shown on this slide. For the main study, the 1991 Alvarez report noted statistically significant findings for reduced female weights in the 400 milligram per kilogram per day group,

and also a significant trend in females. For the supplemental study, the Alvarez report also noted significant affects in the 400 milligram per kilogram per day group for the male and female fetal groups combined, and for the female fetuses in the 1000 milligram per kilogram per day group.

The Munley reanalysis did not analyze the combined male and female data. Munley used analysis of covariance with litter size as a covariate to fetal weight to analyze the fetal weights for the sexes separately. Munley reported for female fetuses a significant difference in fetal weights in the 75 milligram per kilogram per day group in the main study, and a marginally significant difference in the 400 milligram per kilogram per day group in the main study.

And that concludes the information on the rabbit studies. Dr. Iyer will now present summaries of chlorsulfuron in rats.

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DR. IYER: Okay. This next slide presents the findings from a guideline teratogenicity study. And in this study, 25 mated female rats per group were exposed via oral gavage to 0, 55, 165, 500 or 1500 milligram per kilogram per day of chlorsulfuron. And like a typical guideline teratogenicity study, the endpoints that were

examined included clinical observations and food consumption and body weights of the maternal and fetal body weights as well. Fetuses were also examined for external, skeletal, and visceral abnormalities.

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DR. IYER: In this study, the maternal toxicity effects noted were increased vaginal discharge during treatment at dose levels of 500 and 1500 milligrams per kilogram per day, also reduced body weights and food consumption at 1500 milligrams per kilogram per day, which was statistically significant was noted, and less severe reduction in maternal body weight gain at 500 milligrams per kilogram per day was observed.

Developmental toxicity effects were a significant reduction in fetal body weights at 1500 milligrams per kilogram per day, which was about ten percent less than the controls, and a less severe reduction in fetal body weight was noted at 500 milligrams per kilogram per day. And you can see that right here in the tables. I don't have a pointer. This one.

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DR. IYER: In the next set of slides, I'll present the findings from the multi-generation studies, which included a two-generation study with the one litter per generation, and a three-generation study with two

litters per generation, and two supplements that reanalyzed the findings from the three-generation study.

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DR. IYER: In this guideline two-generation reproduction study in rats by Mylchreest -- reported by Mylchreest in 2005, rats were exposed in the diet to 0, 100, 500, 2500, and 7500 ppm for two generations with one litter per generation. And the test substance related systemic effects on body weights and body weight gains were noted at dose levels of 500 ppm and above, indicating that the dose ranges were adequately selected to identify effects. No adverse effects on reproduction was noted in this study.

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DR. IYER: In the study by Wood et al., in 1981, there were two components, a two-year feeding study and a three-generation reproduction study in rats. We will be discussing the effects noted in the three-generation reproduction study. The study was conducted according to guidelines, and the animals were exposed for three generations with two litters per generation to 0, 100, 500, and 2500 parts per million of chlorsulfuron in the diet with two matings from each -- with two matings from each second mating, such that animals from the F0 generation resulted in F1A and F1B litters. Animals from

the F1B mating resulted in F2A and F2B litters. And animals from the F2B mating produced the F3A and F3B litters.

And there were 20 animals per sex per group. In addition, two supplements were provided, and these supplements provided analysis of the data from the original study, which will be discussed later on in the -- in today's presentation.

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DR. IYER: So in this three generation reproduction study by Wood, systemic toxicity results included a reduction in body weight and body weight gain in males at 2500 parts per million, and hematological effects were noted at dose levels of 500 ppm and higher. The reproductive toxicity results was decreased in fertility index at 2500 ppm for both F2 matings with 95 percent in controls versus 79 percent for both the F3A and F3B litters.

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DR. IYER: And here are the actual data. So this slide presents the mating success data for both matings of the F2B animals in the Wood multigeneration study, where both matings showed a decrease in fertility in the high dose group. The supplements. Munley in two supplements provided statistical analysis of these fertility data.

In the first supplement, Munley stated that there were -- there was no statistical significant -- there was no statistically significant lack of mating success in any treatment group by pairwise comparison. OEHHA agrees to this. We also did the calculation and we did not find any pairwise significance.

In Munley's first supplement, Cochran-Armitage trend test results were provided, both the asymptotic and exact test value. The second Munley supplement stated that the exact test calculations are more appropriate for this database. And OEHHA agrees and has therefore not presented the asymptotic values on the slide. OEHHA attempted to replicate the statistical analysis of Munley and did not find the same results however.

The Munley and OEHHA results are presented in the last column. Okay. It's presented in the last column of the slide. Based on the F3A and F3B litter data, the unadjusted Cochran-Armitage trend test indicated decreased fertility with increasing chlorsulfuron dose.

OEHHA tried to reproduce the adjusted trend test P values provided in the supplemental analysis. There were different ways to set up the trend test and adjust for multiple tests. This slide shows that OEHHA found a significant trend in all but the most conservative approach. And OEHHA statisticians can elaborate on the

results, if requested, or if the Committee has any questions.

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DR. IYER: Moving on. Also in the supplement by Munley in 2011, historical data -- historical control data from 1974 through 1983 were provided to aid in the interpretation of this fertility index data from the original study. Of the studies included in the historical database, only six of the 12 studies actually had a third generation. And so the authors compared the fertility index of the chlorsulfuron study to F1 to F3 values. Overall, the historical control data for fertility index ranged from 60 to 100 percent with the mean ranges from 82 to 95.

When only the third generation was considered, the mean ranged from 89.5 to 100 percent, whereas the 200 -- whereas, the 2500 part per million chlorsulfuron group had a fertility index of 79 percent for the third generation.

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DR. IYER: This slide presents the other issues addressed in the supplemental analysis. To aid in the interpretation of the findings for the third generation, the supplement also provided individual matings for F2B animals that produced the F3A and F3B litters.

Females unsuccessful in the first pairing were found to be successful in subsequent pairing. And for males, three individuals, one unsuccessful in both pairings. Additionally, the authors attempted to explain the problems in longevity and reproductive performance in Sprague-Dawley rats, as a result of inbreeding practices that were in place around the time of the conduct of the study.

As mentioned before, for males, three individuals were found to be unsuccessful in both pairings. Apparently, the study was conducted prior to the male proven breeder program possibly explaining the less than optimal fertility in the rats. The other issues addressed in the supplement is that no effects on fertility were evident in the subsequent multigeneration reproductive toxicity study by Mylchreest, which tested dietary concentrations of up to 7500 ppm, a dose that is three times higher than the highest dose in this 1981 study.

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DR. IYER: Overall, summarizing the DART studies for chlorsulfuron, the developmental toxicity studies in the rabbit in, there were increased fetal resorptions at 75 mg/kg, 75 milligrams per kilogram per day in the Hoberman study, and the supplements provided reanalysis of these findings. In the Alvarez 1991 study, there were

multiple effects, which included fetal malformations, minor fetal skeletal defects, reduced fetal body weights 400 milligram per kilogram per day, and decreased sternebrae ossification at 1000 milligrams per kilogram per day. And the supplements provided additional analysis that my colleague just discussed earlier on.

In the rat, reduced fetal body weights were noted at 1500 milligrams per kilogram per day with statistical significance in the Alvarez 1991 study. In the rat reproduction studies, the three-generation study by Wood noted a reduction in fertility index at 2500 parts per million in the third generation for both matings. And the supplements provided reanalysis of these findings.

The two-generation study in 2005 found no effects on fertility at dose levels as high as 7500 parts per million.

And those are all the findings that we have from the studies that were examined.

CHAIRPERSON GOLD: Thank you, both. First, are there any questions from the Panel of the staff presentation?

Okay. Hearing none. Then I believe we can move to public comments. I'm aware of one. So Michael Battalora -- sorry, if I mispronounced the name -- from DuPont.

And excuse me, so DuPont did request some extra time, and so we've granted 15 minutes for this presentation.

(Thereupon an overhead presentation was presented as follows.)

DR. BATTALORA: Good afternoon. My name is Michael Battalora from DuPont Crop Protection. And at first, I was a little bit daunted by just 15 minutes, but the OEHHA staff have done a good job at summarizing a lot of the data, but I'd like to emphasize a few points.

Thank you. That's the pointer for the screen.

Okay. And so if I could have the next slide.

Oh, I do it. Sorry. Oh, that's why you gave me this. Okay.

(Laughter.)

DR. BATTALORA: So where do I point?

DR. IYER: The right arrow.

DR. BATTALORA: The right arrow right here.

Oh, there. I need to point -- oh.

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DR. BATTALORA: Okay. I'll give you an overview of our developmental conclusions on the studies in the rabbits, and the rat as just previously described by OEHHA, and then I'll also talk about our reproduction conclusions.

So next slide.

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DR. BATTALORA: There we go. In terms of developmental toxicity conclusions, the original findings of increased resorptions in rabbits was not reproduced in a guideline study using a more robust design and higher dose levels. And then concerning the other studies, the effects observed in the replacement studies have been clarified to be the result of increases in offspring number influencing the weight of fetal rabbits, in one case, and then maternal toxicity effecting the fetal weights in the case of rats.

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DR. BATTALORA: Okay. You've just been given the details of this, so I'm going to try and go through it pretty quickly. There's the set-up of the study. And the first point -- and I'm going in a little bit different order. I'm going in the second rabbit study first, because, as I discuss the 1980 study, I keep referring back to it, so I figured I should go through this study first.

But anyway, the second bullet, there was no increase in resorptions at any dose, even at 1000 mg/kg. There was a slight decrease in fetal body weight at 400 mg/kg. It was not considered biologically significant by

the study director, since it was when the -- since it was within the laboratory's historical control range.

EPA noted the decrease in weight, and that it might be attributed to increase in offspring number. So we put this to test in a supplement to Alvarez, as we've referred to. And in that supplement, we did an analysis of covariance where we tested the contribution of fetal body weight and either dose or pup number. And in regard to that, the fetal body weight did not correlate with dose, and it did not correlate -- it did not correlate with dose, but it did correlate with a number of pups.

Next slide.

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DR. BATTALORA: There we go.

So the second -- oh, let me just mention before I go on. In this study by Alvarez, there were some things that OEHHA staff did bring up in terms of malformations, the low level of malformations. And as discussed in the study itself and in our comments in our letter to the Committee on April 28th, for example, if you see one of these findings of hemivertebrae at 400 mg/kg, it was also found in the concurrent control. And the other findings were not in the concurrent control, but they were in the historical control with the exception of one finding. I think it was the double aorta. So most of these findings

are within the historical control range of the study -- of the performing lab or the study.

Okay. And -- oh, yes, I should also mention that decreases in maternal body weight were the basis for the maternal no effect level by the U.S. EPA.

Okay. So now I'll go onto the next slide.

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DR. BATTALORA: Next slide gets into the 1980 study. And this is the original study that got us the TRI listing by EPA and that subsequently led to the Proposition 65 listing. Again, chlorsulfuron in corn oil, the dose is already presented -- the parameters of the study already presented.

The resorption rate at the top dose, as mentioned, was higher than the concurrent control and reported as test substance-related.

EPA eventually required a new study because the 1980 study was guideline deficient. They had a low number of animals. The guideline calls for a minimum of about 20 animals per group with implantation sites at necropsy. This study, starting with 16 or 17 does per group wound up with only 12 to 13 in the high dose group and the control.

So when the number of animals is low in a study, the historical control data becomes more critical. Hence, the supplements that were made. And unfortunately, as

OEHHA just presented, when we started making these supplements, we -- our original author was a bit hasty and made some mistakes and we've corrected those mistakes.

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DR. BATTALORA: Compared to the historical data in the MARTA database -- and the performing lab, by the way, contributed data to it. So we compared it to that data, and also we talked about the way to present the data with resorptions included or not included. And the reasoning behind that is because when the does have small numbers of implants, then there's lower hormones and less of a chance that the pregnancy will be brought to fullness.

So the MARTA database. As we surveyed laboratories, we found out that the practice in some laboratories is always to exclude the 100 percent resorbs groups and present it as a single -- and to present it as a separate parameter. And so the MARTA database likely contains a mixture of studies with and without 100 percent resorptions.

So on the next slide, I'll show you the impact of one doe in each of the ten milligrams per kilogram and one doe in the 75 milligram per kilogram with 100 percent resorptions.

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DR. BATTALORA: And this is a very busy slide. The data I'd like to emphasize for you is in blue. And there is the data that OEHHA already talked about the same parameter I guess on -- this doesn't show up. And you'd have to turn around to see it. But the line in blue I'm pointing out right here.

So at ten milligrams per kilogram we see that we have a percent resorptions per litter of 23.9, a very big standard deviation of 32, the number drops at 25, and then jumps back up at 75. And again, this number 33.7 is what finally was the final number corrected in Munley 2014, and again, a very big standard deviation.

Now, if you look at the next line that I have highlighted in blue, you'll see that the -- with the 100 percent resorbed doe excluded, you'll see now at 10 mg/kg the percent is up to 18 percent. There was no change in the set at 25 mg/kg, but then you see 28.2 is the number at 75 mg/kg.

So you look at the standard deviation, it's still big, but the standard deviation decreases a bit when we exclude the 100 percent resorptions. Why do that? Well, because the historical database is probably a mixture.

Now, when Munley made her last revision in February of this year, I believe it was, she used a high value -- sorry, her range of values from the MARTA

database went from zero to 29.2, because she picked the day 29 studies from the MARTA database. But, in fact, as I was preparing to -- as I was preparing this presentation, she pointed out to me that the 28-day studies had percent resorptions up to 43.7.

And so she made the point to me that we could have actually used the higher number to talk about the historical control range, because 28-day studies would be also considered in a study of duration of 29 days, but the reverse would not be true. So if the chlorsulfuron study was only 28 days long, we couldn't use the historical control data out to day 29. We would have only used the data out to day 28, because something could have happened in that last day.

So that's why in the -- my presentation here, I put up the 43.7 for the historical control range of the mean percent of resorptions, but down in the footnote, I refer to the day 29 high value of the range.

Okay. So next slide.

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DR. BATTALORA: Okay. So in terms of Hoberman, et al., the study did not clearly go into a description of maternal toxicity like you would normally see in a contemporary study. And so I pulled out some of the information. OEHHA talked about some of it, but I'll

emphasize some things in the data that might not jump out at you so dramatically.

First off, that there was one death at 25 mg/kg and two deaths at 75. And in the range finder, there was two of four animals that died at 100 mg/kg. So these deaths are dying at 75 mg/kg is an indication of maternal toxicity, because it was happening at a dose right near it in the range finder.

Then below that, you notice the bullet on the gross pathology changes. They increase with dose. And the most common findings were pale liver and kidney, and also nutmeg liver, which I've been told by pathologists is actually perhaps suggesting that that means hepatic congestion.

The rabbits were large suggesting that they may have been old, and that's not a maternal effect. It's just a comment that I didn't know where to put. But hence, age may have played a role in the data, although you can't be sure.

On the next slide, I'm going to talk about food consumption and weight changes that I just analyzed after I prepared the letter for the Committee in April.

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DR. BATTALORA: And the reason that I did this is, as I said, there was some indication of maternal

effects occurring, but it wasn't well characterized in the report. And so in this study design, they started dosing from gestation day six and stopped on day 19. And then the does actually had ten days to recover without dosing.

And so any findings on body weight might be kind of masked, because if you don't look at what's happening on the body weight during dosing, you're not seeing it during the most critical phase.

So what I've done at the first table there is I have looked at the frequency of does with low food intakes. And I defined it as zero to 20 grams per day. And these animals typically might be eating about 100, 110, 120 grams per day, higher or lower. You know, of course, it's a range.

And so what I've done is I've looked at for the groups with 16 animals over this 14-day range of dosing, that's about 240 days when you consider all the animals. I looked at the number of incidences of low intakes. So you can see at the control, we only have ten times when the intake was low. Whereas, if you go up to 25 mg/kg. It's up to about 30, which is three times the number of incidences -- three times the number of occurrences, and then at 75, you actually have 62 occurrences.

So this is interesting, because similar findings in the literature report a correlation between increased

resorption and decreased food intake. Now, in the literature, they may include -- they might have had a different number. I picked 20. Some studies talk about as high as just 60 grams a day, but I picked 20.

And the first article that I referred to also by the Matsuoka actually had picked 20 as their lowest to study. Then -- so low food consumption. Then what happens to the body weight. As I mentioned, if you look at body weight during the dosing, you can see that in eight does in the high dose group, they drop by greater than 300 grams during dosing. And of those eight, four of them actually drop by 400 grams or greater.

And so these marked weight decreases are not easily noted in the study because of the design, because the weights -- the final weights recovered.

So decreased food intake and body weight, along with deaths, demonstrate that 75 mg/kg was maternally toxic.

Next slide.

--o0o--

DR. BATTALORA: Okay. So a summary in terms of resorptions. The conclusions based on the top dose in both studies, the Alvarez and the Hoberman study, are difficult, the 1980 study, due to the design of low numbers, and in both studies, because there was mortality

at the high dose.

The mean percent resorptions was always within or slightly over the historical control range, and it was always within the range if you calculate it based on the mean number of resorptions. So there's different ways that reports are made, and some do this mean percent resorptions per litter, and some just use mean number of resorptions.

There was no dose response for resorptions in the 1980 study, as I showed you the jumpiness in the data. So in terms of the resorptions at 75 mg/kg in the first study, the 1980 study, it is influenced in part by a few does with low numbers of implants. One of them had 100 percent resorptions, and there was another doe that only had two implants, and one of the two resorbed. And it's either a spurious finding or if it's test substance related, it occurred in the presence of significant maternal toxicity.

There was no increase in resorptions in the 1991 study, the more robust study, as I mentioned. And increased resorptions by chlorsulfuron is no longer a relevant endpoint in EPA documents.

--o0o--

DR. BATTALORA: So in terms of teratogenicity study in rats, OEHHA has already given a good overview of

the study, but I wanted to talk about the study in terms of the issue of maternal toxicity. And I've got the 1991 guidelines on developmental toxicity assessment here. And I basically put that in there, because of the issue of describing minimal toxicity versus significant toxicity.

CHAIRPERSON GOLD: Excuse me, if I can just interrupt for a minute. You have about two minutes left, but I notice you're about halfway through your slides, so maybe we'll give you five more minutes, but try and wrap it up in five minutes.

DR. BATTALORA: Okay. I'll go quick. All right. So you know this already. I'll go to the next slide.

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DR. BATTALORA: In terms of the maternal effects, it's already been described, but I'd like to mention that at 1500 mg/kg there were actually two treatment related deaths. And I would like to also emphasize these weight changes in the -- sorry, the food intake changes that were occurring. The adjusted final body weight was down, but look at the weight gain, down by 50 percent over gestation days seven to 17. The adjusted weight gain is significantly different, down by 30 percent.

So we have major weight changes that are occurring at the high dose group. Again, because of the design of the study -- well I, won't go into that. Okay.

I'll just go on to the next slide.

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DR. BATTALORA: So in contrast to the 1991 EPA criteria, I'd like to show you the 1998 criteria that they talk about maternal toxicity, and -- just to compare that. The highest dose should be chosen with the aim to induce some effects, but not death or severe suffering. And that it mentioned mortality not more than ten percent. And it says if you have higher levels of mortality, that you may invalidate the study.

So based on today's standards, the findings at 1500's are considered overly toxic, not minimally. The decrease in fetal body weight can clearly be attributed to maternal toxicity. And, you know, we avoid doing anything like this in modern day studies for animal welfare purposes. And I think the 1998 guideline is reflecting that in part.

Next slide.

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DR. BATTALORA: Okay. So the reproduction studies. I won't go into great detail here. We already talked about the fertility index being in the historical control range. The index was not statistically significant using the test that DuPont conducted, so we'll have to talk about that.

In the 2005 study, we already talked about the three-fold higher dose, and no test substance related changes.

--o0o--

DR. BATTALORA: And we already know what the study was that led to the listing. The EPA 1993 guideline was the statistical test that we used for the reanalysis.

--o0o--

DR. BATTALORA: So we also had the new study, as OEHHA described, the highest dose you know about it. It doesn't have three generation, it only has two. It's worth noting that no current guidelines tell you to go out to three generations. The only adverse effects were decreases in paranormal body weight, weight gain, and food efficiency. There was no test substance related changes on fertility or any reproductive parameters seen at the top dose or below that.

And remember, this study included a lot more robust design in terms of looking at reproductive parameters. We had things such as sperm mobility, estrous cyclicity. We did a lot of extensive histology.

Next slide.

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DR. BATTALORA: And this is an interesting slide. This is the data from the 2005 study, and I'd like to

point out to you in the F1 generation, that's the second line of numbers of fertility indexes, if you see the 81.5 percent fertility in this 2005 study in a control. And so that's essentially similar -- very similar to what you saw in the third generation in the 1981 study.

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DR. BATTALORA: So the revised study, the supplement to the 1981 study, as you know, we put it into the context of the historical control range. The historical control range they've already described -- woops, goodness -- they already described the range of it. There is very little data on a third generation. And so we thought that it was appropriate to compare it to the F2 -- the F1 offspring, and the F0 offspring.

And the data were not statistically significant by our statistician. Using EPA's test, I can give you details on that after today, if you would like that. The original study director did not have the advantage of the historical control data, and these statistical tools. And so I think that that's why they made their conclusion the way they did. Had they, I think they would have come to a different conclusion.

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DR. BATTALORA: The last slide, I believe I have

here, is the examination of two matings, as OEHHA described, showed that all females were fertile and that -- second bullet -- three males were unsuccessful in both F3 generations.

And after I submitted the letter in April, I teased some of the data of other studies. I didn't get through everything, but I actually found one of the 1983 studies at DuPont had four out of 20 control males that were infertile. And so that's a very similar scenario as our chlorsulfuron study.

And again, this is in line with the breeding problems that were reported to Charles River. Charles River developed this practice of proving fertility of males before they had released them. And again, it lead to the rederivation of the strain.

So I'm done with my comments and thank you for your time.

CHAIRPERSON GOLD: Thank you.

Are there any questions from the Panel at this time?

Yes, Dr. Pessah.

COMMITTEE MEMBER PESSAH: In the 2000 study, did you look for any differences in global methylation on DNA of the offspring?

DR. BATTALORA: No, we did not.

CHAIRPERSON GOLD: Other questions?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: So, in short, the Wood study from 1981, where there was decreased infertility at the high doses, in the more robust newer study, you didn't find that?

DR. BATTALORA: No, we didn't. And I didn't go into this for time, but we were actually told by EPA that that study was deficient. And they said if you want to keep up the registration, you need a new study, so that's why we did the new one.

CHAIRPERSON GOLD: Other questions or comments for Dr. Battalora?

Okay. Thank you very much.

No other public comments?

Going, going public comments.

Okay. Then we have two panel members to summarize and lead us in discussion. So Dr. Luderer and Dr. Woodruff, who wants to go first?

Dr. Luderer.

COMMITTEE MEMBER LUDERER: Sure. Okay. I want to thank the staff again for the excellent summaries and thank you also for that presentation.

So I wanted to just quickly again kind of maybe go through what I see as some of the strengths and

weaknesses of the different studies that form this database that we have here.

So the Hoberman 1980 study, so we have the -- you know, it's a controlled exposure study. They did randomize to treatment groups. The litter was the unit of analysis, so those are strengths. There was again no mention of blinding. You know, the N, particularly as was just pointed out in the high dose group because of the deaths in that group, was smaller than desirable.

And there were not -- the examinations of the fetuses were incomplete by today's standards, as was recording of food consumption after dosing ended. And the other -- so that was the first rabbit study. Then the Alvarez 1991 rabbit study, there -- like the Hoberman study, they used artificial insemination rather than natural mating, which it was argued in I think several of the supplements that this can lead to smaller litter sizes, which is a reason why adjustment for litter size is important. And also the small litters may have increased propensity to resorption as was also just mentioned.

And I wanted to say a little bit about the weight -- the effects on fetal weight in that Alvarez study, because there were so many supplemental analyses associated with that. And I agree that the initial analysis that was done in 1991 when the study was done,

they adjusted for litter by using litter means. And then the ANCOVA was done in the supplement that was presented to the -- in the materials we received, and also just again reviewed.

So in the ANCOVA, there were statistically significant effects of litter size, as was mentioned, but the effective dose was also statistically significant, as were expectedly the effects of sex. And then dose times study interactions, and the sex times dose interactions were also statistically significant.

Then when the pairwise controls were done, only the 75 milligram per kilogram females differed from the controls, but I think as properly mentioned by OEHHA, several of the pairwise comparisons approached significance. They were 0.07 to -- 0.06, 0.07, and that would be the 1000 milligram per kilogram females versus control, the 400, and also the 25, so -- but I think it's also important to note that there wasn't a -- the changes did not appear to be dose dependent, so there were some -- there was some up and down there in the fetal weight changes, but there were quite a few of the comparisons given in that ANCOVA analysis that approached significance.

In the Alvarez study, the rat study, so that's the second Alvarez study, there were decreased fetal body

weights again at 1500 milligrams, per kilogram. And there were also maternal body weight decreases, as has just been noted at 1500, as well as clinical signs at 1500, and then also maternal clinical signs at 500. So the fetal weight was observed at doses, which was -- that caused -- also caused maternal toxicity.

There was also the significant test for trend for litters with malformations in that study, but then there was no increase in malformations in any -- when their pairwise comparisons were made among the groups.

For the two -- the three- and two-generation studies, so the Wood study in 1981 and the Mylchreest study from 2005, it's already been noted that there were significant deficiencies in the Wood study. There weren't any histopathological examinations of parental animals, and no detailed reproductive assessments like estrous cycling or male reproductive performance. They didn't assess developmental landmarks, and they only examined the F3B offspring histopathologically. And so all those deficiencies were addressed in the Mylchreest study.

So in the Wood study, there was this decreased fertility only in the F3 mating, which we've just heard about, which was not reproduced in either the F -- in either of the generations in the Mylchreest study.

Let's see. I just lost my document.

And in the Mylchreest study with all these additional endpoints that were looked at, there were no indications of reproductive -- male or female reproductive toxicity.

So to kind of try to summarize, there -- first of all again, there are no human data available for chlorsulfuron. We have these -- we have the two -- we have well conducted animal developmental toxicity studies in two species, the two Alvarez studies, and the two-generation reproductive study in the one species that are -- that was conducted according to current guidelines.

And we have decreased dam weight in rabbits in both -- in the Alvarez study as well as decreased weight gain during gestation in the original Hoberman study in rabbits. And in the Alvarez study we also have increased abortions at the 1000 milligrams per kilogram group. And in rats, we also see decreased dam weight gain during dosing at the two highest doses and maternal mortality at the highest doses.

So we have this disputed evidence for increased resorptions in the Hoberman study, and no increased resorptions at higher doses in the same species by Alvarez with -- although there was a slightly different dosing window by one day between those two studies.

So the effects on the offspring of the decreased

fetal weights in particular were mostly seen at maternally toxic doses in the developmental toxicity study in the rats and the rabbits, with the exception that I had talked about in the Alvarez study with the reanalysis of the data, the female fetus weights at some of the lower doses, the 25 and 75 milligram per kilogram were significantly, or borderline significantly, decreased, but there was not a clear dose dependency to the effect on fetal weight in that study.

And there's no evidence for -- really for two -- in the two generation study for male or female reproductive toxicity, just these -- there is evidence for toxicity in the P1 and F1 males and females based on weight decreases. So I think overall the weight of the evidence, it does raise some concerns for developmental toxicity, but really most of the evidence is for at maternally toxic doses.

So this is one of those more I'd like to hear what the other Panel members have to say, but I think this is a -- because the effects were really only seen at maternally toxic doses, that leaves the question of, you know, how significant do we think they are?

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. Thank you.

That was a great summary of the studies. I would -- I just wanted to note that even though there was a lot of information given to us, there really is only a few studies with a lot of reanalysis of studies that were -- we didn't have any independent peer-reviewed studies. They're all industry laboratory studies, and they were in two species, as was noted by -- in rabbits and rats.

And I guess just to add a little bit to what you were saying, because I agreed with the comments, and had similar comments about the summaries, is that I did look at -- so there were three kind of main outcomes that were -- from the developmental toxicity studies that were evaluated. And that's the reabsorptions that were presented as well, the reabsorptions the fetal weight gain, or lower fetal weight, and the fetal malformations.

And so in terms of the resorptions, I mean, I agree that we did -- it wasn't -- there was two -- there's three studies, there's the Hoberman study, then the Alvarez reanalysis, and then this supplemental study that was done to look at the higher end-dose groups. And I just wanted to actually ask in terms of the -- this -- the graph that you presented, the chart on the percent reabsorptions per litter for the main study from the Alvarez, the Mylchreest, because the dose -- the other difference between those two studies is that there is no

dosing at the middle -- in the middle between the 2.5 -- the 25, 75, 200. The Mylchreest study only looks at 400 and 1000.

And did you say that there was no statistically significant comparisons between any of the dose groups in the control?

DR. WU: In the Mylchreest reanalysis, there was.

COMMITTEE MEMBER WOODRUFF: No, but what about the main study?

DR. WU: In the Hoberman study, there was statistical significance in the 75 milligram per kilogram per day group, but in the Alvarez supplement, which was done by Mylchreest in 2005, there was no statistical significance.

COMMITTEE MEMBER WOODRUFF: In the 400. Oh, you're -- oh this is in any of the groups, okay.

DR. WU: In any of them.

COMMITTEE MEMBER WOODRUFF: Okay. So I just noted that they're -- they're actually different. Well, I guess one of the things that I thought would have been helpful is to look at these comparisons, because you wouldn't always expect every time, given experimental studies, that they would always find the same thing. So it might have been useful to look at these outcomes together from the two studies in one chart.

And then in terms of the fetal weight -- reduction in the fetal weight, because I was very -- that was an interesting finding, because you saw, as you reported in the -- in the -- the test for trends for the fetal weight gain from the Munley and the Alvarez study that there was a significant test for trend in terms of fetal -- decreases in fetal weight.

And we saw decreases in fetal weight in the rabbits and the rat studies. And I just did a quick comparison that the weight reductions -- and this was, albeit, at the high dose was similar in terms of the percent reduction in weight for the mean weights, somewhere around between eight and nine percent.

So in terms of thinking about the relationship between the exposures, the dosing, and potential effects on fetal growth retardation, there was some consistencies, albeit, at these high doses -- higher doses, in terms of what we saw in the rabbits and the rats in terms of comparisons between the weight decreases. And then I had just a -- I was kind of struck by this graph that you presented on the fertility evaluation on the statistics. Did I hear that right that you tried to reconstruct these statistics but could not find the same results?

DR. IYER: That's right.

COMMITTEE MEMBER WOODRUFF: Did you have any

thoughts as to why?

DR. IYER: Well, you know, they can be done different ways. Our statisticians, who actually did the analysis are right here, and they can like elaborate in more detail if you need to get some more information. You have specific questions?

COMMITTEE MEMBER WOODRUFF: Well, I just think it just -- what gives me pause is that we have two studies -- two guideline studies and then a lot of reanalysis of those. And I just sort of feel like we should -- my feeling is that we should look at the original studies and the data they present, and I'm not -- I mean, I think that this calls into question the -- how much we should consider other people bringing in reanalysis to us when they haven't been independently verified by the State.

DR. DONALD: Well, the staff who performed the analysis for us are here and can explain it in further detail.

COMMITTEE MEMBER WOODRUFF: Oh, no, no. I'm saying I really value having you do this, because then it was like an independent verification of what had been presented in these other materials.

DR. DONALD: Right, but other than what was described in the study report, we have no independent knowledge of how the other analysis was done, so we can't

really provide any additional comment and --

COMMITTEE MEMBER WOODRUFF: Yeah. No, that's fine. It just makes me -- makes me think that this is a useful evaluation when we get these types of other evaluation of un -- of really existing -- primary literature that I think that we should have this kind of evaluation in the future, because it's clearly finding that there can be differences.

I am looking -- I don't -- I think the only other thing I wanted to comment was that I think it's a concern if we see 100 percent reabsorptions from a dose of a chemical. So I wasn't -- I guess I find that that is a more compelling -- that that is -- should be included with the other data in terms of reabsorptions. So those are all the comments I have about this.

Oh, I have one more thing. There is actually -- even though these tests focus on certain endpoints, there was also -- I thought there was a lack of evaluation of some endpoints, so -- and I just wanted to check this. The three-generation study, and looked at this, they didn't have things like did they measure the weights of the fetuses? I couldn't find anything like that.

DR. IYER: They did measure the weights of the fetuses. That was there. It's there in the actual study. I can show you which --

COMMITTEE MEMBER WOODRUFF: And did you guys evaluate at all?

DR. IYER: No, there wasn't -- you know, there were -- there was some in decline -- sporadic, but it wasn't -- you know, there wasn't any pattern that we could pick up on. The information is all there. It's just that these were done. The three-generation reproduction study was the old guidelines, wherein they didn't have to provide all this other information, which the current guidelines do ask for, which Dr. Ulrike just mentioned, you know, what the estrous cyclicity and all that.

COMMITTEE MEMBER WOODRUFF: Right, right.

DR. IYER: So that information was not there, because that was not part of the guidelines at the time which this study was conducted. So that information is not there, but they do have weights, and they do have other details, but there wasn't any pattern that -- you know, that didn't show up with any significant findings.

CHAIRPERSON GOLD: Any other comment by the panel or questions?

I don't know if you want to respond to anything that Dr. Woodruff brought up.

COMMITTEE MEMBER LUDERER: No. I mean, I think -- I mean, I think a lot of what we were saying kind of really did overlap, but there's -- we're both concerned

that even though some of these effects occurred at maternally toxic doses that there did seem to be the decreased fetal weight on several of the studies, as well as well -- well, I guess, I do have a question about the malformations, the test for trend.

I'm trying to remember which study that was. Yeah. It was in the Alvarez rat study 1991B. So there was a test for trend with a number of litters with malformations, but then when the pairwise comparisons were made, it wasn't significant.

I still -- you know, I think that that was concerning. I mean, given that some of these malformations may be rare maybe is important that the test for trend was significant even though the pairwise comparisons were not.

DR. DONALD: With regard to the incidence of fetal malformations in the Alvarez 1991A study, we'd actually report that there was a significant increase in the incidence of malformations in the 400 milligram per kilogram dose group, as a pairwise comparison, but there was also a significant dose related trend by the Cochran-Armitage test.

COMMITTEE MEMBER WOODRUFF: This is on?

COMMITTEE MEMBER LUDERER: In the rat study.

DR. WU: Rabbit.

COMMITTEE MEMBER LUDERER: Oh, okay. I was talking about the rat study. I think in the study there was reportedly a test for trend that was --

DR. IYER: It's in the reproduction study. It was in the three generation.

COMMITTEE MEMBER LUDERER: Okay. I'll see if I can find it. Yes, it's in the Alvarez 1991B, the rat study. It said the number of litters affected showed a significant trend with 0.01, 0 and 3 affected litters in the different groups respectively, but they didn't detect the trend when the data from the high gross dose group was omitted, and that's on page, let's see, 19 of the report. And I think later on somewhere they said they also did pairwise comparisons. I think that might have been in the table.

COMMITTEE MEMBER WOODRUFF: Table 5.

CHAIRPERSON GOLD: I believe there's a public comment, if you can keep it brief. Yes, please.

If you can help clarify, I'm hoping.

DR. BATTALORA: Yeah. I'm not going to say much about the rabbit -- rat, because she just mentioned that it was at the 1,500 where there was significant maternal toxicity. And again, it wasn't significant by pairwise for the rabbit on the screen right there, so OEHHA said at 400 there was an effect in one study, but note there's a

second study at 400. So what you saw at 400 in the first study wasn't seen in the supplemental study at 400 or at 1000 mg/kg.

I just thought that was worth pointing out.

CHAIRPERSON GOLD: Thank you.

Dr. Pessah.

COMMITTEE MEMBER PESSAH: You know, I kind of can understand that these effects are only seen when you observe gross maternal effects, especially food intake, and body weight. But in the 2005 studies was any effort made to do developmental neurotoxicity testing at the lower levels in those offspring?

DR. BATTALORA: Sorry. Michael Battalora, DuPont Crop Protection again. Since there was no indication of any developmental neurotox -- since there was no indication of neurotoxicity in the whole database, we didn't do that, and we just -- you know, we haven't been requested that study from -- we haven't been asked to do any neurotoxicity studies by EPA, because the database is clean on sulfonylureas.

We have done it for other sulfonylureas, but because of that, the weight of evidence, they haven't requested it for other ones, so we've been able to waive it.

COMMITTEE MEMBER WOODRUFF: But we haven't seen

that, so --

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Sorry.

CHAIRPERSON GOLD: Use your microphone.

COMMITTEE MEMBER WOODRUFF: It's on.

CHAIRPERSON GOLD: Okay.

COMMITTEE MEMBER WOODRUFF: I was just saying I think your point is a good point. I think it's -- there's no data on this chemical about neurotoxicity -- adult neurotoxicity that I saw on here, so I'm not sure. You know, we don't know, right? That would be my --

COMMITTEE MEMBER PESSAH: Well, at least the databases I have access to, which is PubMed is clean because there are no studies reporting negative effects.

COMMITTEE MEMBER WOODRUFF: Right. Right. So --

CHAIRPERSON GOLD: Wait.

DR. BATTALORA: So there have been data call-ins for some sulfonylureas and those studies are clean. And so actually we've been able to -- EPA has basically said they don't want more of that for that class of chemistry.

CHAIRPERSON GOLD: Okay. Dr. Woodruff, do you have anything more?

COMMITTEE MEMBER WOODRUFF: Well, I just -- I agree that this -- I mean, I think this is a very -- it's hard to evaluate. My concern is that you're seeing these

indicators of different types of developmental effects that could really be a clustering of adverse outcomes, so skeletal malformations, reabsorptions, and fetal growth effects could just really, even though they're looked at independently together, could be an indicator of some type of treatment related effect. And so I think it's -- I agree that the studies are limited in some ways, but also they're indicative of something that might be happening here.

CHAIRPERSON GOLD: So ultimately, we have to make a decision based on whether these are scientifically valid approaches. And I just -- it's helpful in the back of our books to remind ourselves of what are considered sort of sufficient evidence. This might help. I'm not sure this is going to help, but it might help, that we consider the study designs, the number of animals, appropriate controls, appropriate route of administration that's relevant to human exposures, because we have no human studies, relevant periods of timing, the ability to look at stage of pregnancy, critical periods, et cetera, to have -- to be able to examine dose response, and consideration of maternal and systemic toxicity and differentiating effects of the agent from other things.

That we've seen -- that multiple species have been examined in these well-conducted studies, and that we

see some consistency, that it's consistent with metabolic and pharmacokinetic data, time course of events.

I'm not sure if this is helpful, but I just kind of wanted to review -- remind the Committee, because this is not straightforward, to sort of think about the gestalt of the design of the studies and what they're telling us, and see if that helps in the decision making.

Any other comments?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: The safety of this class of chemistry is based on their mode of action, which is targeting a system in the plant that doesn't actually exist in mammals or -- the question I have is why does 400 or 500 mg/kg per day produce these overt effects on maternal food intake, if the target isn't present? What are the off-target effects?

CHAIRPERSON GOLD: Last time.

DR. BATTALORA: One of the things that sulfonylureas do target is the hemolytic effects. And so at high dose levels, and I think -- I can't remember what slide, but somebody I think at OEHHA had presented that on one of the slides in the rat studies.

And so -- and I think that that was about at 100 mg/kg. The rat studies at 1500, we never looked at the effects on the red blood cells, but I could only imagine

at that high of a dose that you're starting to see effects on the red blood cells. So that's one thing.

As far as the decreased food, I can't explain why that happens, but that is one of the things that we see with most of the sulfonylureas is that we see weight changes.

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Donald.

DR. DONALD: As I'm sure the Committee members are well aware, your guidelines indicate that the relationship between maternal and developmental toxicity can be complex and should be assessed on a case-by-case basis. So I would just remind you that weight fluctuations in rabbit dams is not considered a good indicator of maternal toxicity.

In fact, to quote from U.S. EPA guidelines, body weights and changes in body weight are viewed collectively as indicators of maternal toxicity for most species. Although, these endpoints may not be as useful in rabbits because body weight changes are usually more variable.

So just one point to keep in mind as you deliberate.

CHAIRPERSON GOLD: Okay. Is the Panel ready to vote? I see one or two nods. What about at this end of the table?

Call the question to vote?

Do you need more time?

COMMITTEE MEMBER WOODRUFF: No, that's fine.

CHAIRPERSON GOLD: Okay.

COMMITTEE MEMBER WOODRUFF: I mean, I just -- this is sort of new information he brought up, and so now I'm like -- sorry. I did not know that piece of information, so now I'm like looking back to think about this.

CHAIRPERSON GOLD: Would it be helpful to the Panel if we took a five minute break --

COMMITTEE MEMBER WOODRUFF: Yes.

CHAIRPERSON GOLD: -- so you can mull it over a little bit?

How about we reconvene at five minutes to 2:00

(Off record: 1:46 PM)

(Thereupon a recess was taken.)

(On record: 1:54 PM)

CHAIRPERSON GOLD: All right. You have more questions. All right. Dr. Woodruff, you have questions.

DR. DONALD: If I might before --

COMMITTEE MEMBER WOODRUFF: Oh, okay.

DR. DONALD: -- you start, I was asked to clarify the quotation I read to you.

DIRECTOR ALEXEEFF: Can you speak into the mic.

DR. DONALD: I'm sorry. I was asked to clarify for the record that the quotation I read to you is from the U.S. EPA 1991 Guidelines for Developmental Toxicity Risk Assessment.

CHAIRPERSON GOLD: This is concerning rabbit weights?

DR. DONALD: Yes.

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

COMMITTEE MEMBER WOODRUFF: Yes. So one of the questions that came up was -- or issues that came up was maternal weight gain. And I'm looking at -- and maybe you could explain this -- Table 1 in the Alvarez 1991B study. It looks like -- while that it's true that on some gestational days the high dose group was maternal weight was lower, it also looks higher at the end, so --

DR. IYER: As far as the blood lead --

COMMITTEE MEMBER WOODRUFF: Well, then if there really wasn't -- and so -- and I'm just looking at this. They actually look fatter at the end of pregnancy in the high dose group, not thinner.

DR. IYER: I need to know which table you're talking about?

COMMITTEE MEMBER WOODRUFF: It's Table 1 under the -- on page 22 the in the Alvarez 1991B study.

DR. IYER: Page 22. Okay.

COMMITTEE MEMBER WOODRUFF: That's how much weight they gained over the...

DR. LAWYER: Can we comment one more time?

DR. IYER: So the comment is that they actually gained more weight.

COMMITTEE MEMBER WOODRUFF: Well, that's my question to you. Or anyway, it's not at every weight. There's not a difference among the group -- the dose groups for maternal weight gain or loss at every gestational day necessarily.

DR. BATTALORA: That's right.

COMMITTEE MEMBER WOODRUFF: So I think one of the questions was does maternal weight affect the outcome? But there's no consistent trend necessarily in the maternal weight in this study.

DR. IYER: Typically, maternal toxicity is evaluated by looking at either weight gain, or lack thereof, or clinical signs.

COMMITTEE MEMBER WOODRUFF: Right.

DR. IYER: And for the time of exposure or if it's a specific defect during the time of development of that particular organ system. So that's what you would want to look at. And I don't see any patterns specifically here telling you, one way or the other, that

it's -- that there is an effect.

What does happen, in this -- in the high dose group is that there was about a ten percent -- two animals died, I believe. And so I think that's -- that's, as far as what happened to the animals in the -- in this -- in the rat study.

CHAIRPERSON GOLD: Yes, Dr. Battalora.

DR. BATTALORA: Yeah. Just briefly. So in that table, the key thing is that during dosing the body weight gain changes were dramatic. That's where we had shown that the decrease from day seven to 17 was down by 50 percent. But you're right, by the end of the study, they've had time. They've had ten days to recover -- ten without dosing to recover.

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

COMMITTEE MEMBER PESSAH: Just one really quick question.

Thank you.

Chlorsulfuron is a benzoyl sulfonylurea, right?

It's well known that there are receptors for sulfonylureas. In fact, from a molecular perspective, they're involved in several really important human issues. Has it ever been screened, chlorsulfuron, for activity against sulfonylurea receptors?

DR. BATTALORA: The answer is no, but the ones that are used for -- well, I should say, I'm not aware of it. I don't know that.

It tends to be that the ones that are effective for herbicides are not effective as anti-diabetics.

COMMITTEE MEMBER PESSAH: They've never been screened?

DR. BATTALORA: I'm not aware of it being screened. I'm not saying that it hasn't been, but I'm just not aware of that. It's not a screen that we would typically do when we're looking for a herbicide.

CHAIRPERSON GOLD: Any other questions?

So we have the option to vote or to defer.

(Laughter.)

CHAIRPERSON GOLD: I'm not -- it is an option, if you feel that there would be good reason to defer, but I'm sensing it's time to vote, unless I hear any objections.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I'm not objecting to voting. I'm not -- that's not why I'm saying this. I wanted to just comment that -- cause I feel like we do get some of these chemicals like this. And I think that it's challenging to vote on it, because the data has some deficiencies in it, though there's indicators that it could be problematic. So I -- and I think that the

evaluation of the original data is most helpfully done by the staff, because I think that's -- brings clarity to some of the underlying issues.

I think that though any indication on the vote, which I would -- I'm going to say I probably would abstain, is not because I don't think this is a problem. I think it's because the data is weak. And we had this discussion at the last meeting about trying to have some of these chemicals -- putting them on whatever this list is to ask EPA to test them further, because I just don't feel that this necessarily has a clean slate in terms of what we know about it.

CHAIRPERSON GOLD: Perhaps it would be useful to be reminded what happens -- sorry, if we -- the majority votes for abstention.

CHIEF COUNSEL MONAHAN-CUMMINGS: If the majority abstains, then the chemical comes off the list. It's -- the abstention is basically a no vote.

CHAIRPERSON GOLD: Now, are we ready?

Okay. Has chlorsulfuron been clearly shown through scientifically valid testing, according to generally accept principles, to cause developmental toxicity? If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see none.

All those voting no, please raise your hand.
(Hand raised.)
CHAIRPERSON GOLD: I see one.
Those abstaining.
(Hands raised.)
CHAIRPERSON GOLD: Four.
Has chlorsulfuron been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? If you believe yes, please raise your hand.
(No hands raised.)
CHAIRPERSON GOLD: I see none.
Those who believe no, please raise your hand.
(Hands raised.)
CHAIRPERSON GOLD: Four.
Abstaining?
(Hand raised.)
CHAIRPERSON GOLD: One.
Has chlorsulfuron been clearly shown through scientifically valid testing according to generally accepted principles to cause male reproductive toxicity? If you believe yes, please raise your hand.
(No hands raised.)
CHAIRPERSON GOLD: I see none.
If you believe no, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Three.

If you're abstaining, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see two.

Okay. So the results are that for developmental toxicity, we have four abstaining and one voting no; for female reproductive toxicity, we have four voting no, one abstaining; and, for male reproductive toxicity, we have three voting no and two abstaining.

So now we're ready to hear from the staff about phenylphosphine and what they were able to produce during the break.

DR. DONALD: Thank you, Cindy.

So we have completed -- can you go back to the first slide, please.

Thank you.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Oh, I have the control. Sorry.

We have done a pairwise comparison of absolute testes weight and a trend test for absolute testes weight for the data from the DuPont 1992 study. We have also -- well, I'll talk about these first, and then I'll move on to the next one.

So we did the comparison at each time point. And as you can see, for each of the time points, the difference between the control group and the 0.6 parts per million group is not statistically significant. But again, for each of the three time points, the pairwise comparison between the controls and the 2.2 part per million group is strongly statistically significant at each time point. And there is a very strong trend for significant -- a strongly significant trend at each of the time points also.

And I would also remind the Committee that absolute testes weight is generally considered a more useful indicator of testicular toxicity than relative testis weight. But we did also do the comparisons for an estimate of relative testes weight. And we did not have the individual animal body weights, so we could not calculate the actual relative testes weight per animal, so we estimate an estimate for each animal based on the group mean body weights that we extracted as best we could from the graph in the study report.

So again, at each of the time points, there was no statistical difference between the control group and the 0.6 part per million group on a pairwise basis. But again, each of the time points at the end of treatment, the 29-day recovery period, and the 69-day recovery

period, there was a strongly significant pairwise effect between the controls and the 2.2 part per million group.

And as was with the absolute testes weights, there was also a strong -- a strongly significant trend for effect at each of the time points. And consistent with the request that we present these graphically, hopefully we're going to do that in just a moment.

COMMITTEE MEMBER WOODRUFF: Is that like magic.

(Laughter.)

DR. DONALD: Yes. You gave us just enough time to complete it.

(Laughter.)

DR. DONALD: Okay. So this shows the scatter plots. This shows the effects on absolute testicular weight on a per animal basis for the control group, the 0.6 part per million and the 22 part per million -- sorry, 2.2 part per million.

Again, showing it at the end of treatment after a 29-day recovery period, and after a 69-day recovery period.

--o0o--

DR. DONALD: And this shows the same data for the estimated relative testicular weights at end of treatment and after the two recovery periods.

--o0o--

DR. DONALD: And then we presented -- the same data presented in a slightly different form for absolute testicular weight.

--o0o--

DR. DONALD: And for estimated relative testes weight.

So would you like to see any of those again?

(Laughter.)

COMMITTEE MEMBER WOODRUFF: Because they were so awesome the first time, yeah.

CHAIRPERSON GOLD: That's very impressive. Thank you for doing this in such a short period of time.

So, Dr. Baskin and Dr. Pessah were the lead discussants. Did you have any questions or comments on the additional analyses?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: I have a general question on whether we ever make a recommendation or comment on a dose response, in other words, state that there's a safe level and an unsafe level, as opposed to listed or not listed?

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: What -- I think what Dr. Baskin was asking was whether or not you can

establish a level where you, as a group, feel that the chemical is safe versus a level where it's not safe. And what this Committee does is decide whether or not the chemical is clearly shown to cause reproductive effects -- or toxicity and then our office does the other piece where we determine what the no significant -- no observable effect level is. And then the law requires that, based on that, you multiply that by 1000 -- no, divide by 1000. Multiply, wooh.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: They'd all be happy.

But anyway, so we divide by 1000 and come up with a level where a warning is actually required. And so it's actually a lower -- it would be even more safe than safe, if that makes any sense, where the warning threshold is.

COMMITTEE MEMBER BASKIN: Thank you.

CHAIRPERSON GOLD: But the bottom line is the dosage piece of it is your job not our job.

DR. DONALD: Yeah, but just to add to that, we do send -- we make the calculations available for public comment and we specifically send them to the Committee members and solicit any comments you'd like to make.

CHAIRPERSON GOLD: Yes. Okay. Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So the relative

testicular weight takes into account the changes in the body weight, is that right?

DR. DONALD: Yes.

COMMITTEE MEMBER WOODRUFF: Okay. Thank you. And my understanding is that we -- any dose as seen as harmful, that's part of our charge is to look at that issue. Okay. Thank you.

DIRECTOR ALEXEEFF: This is George Alexeeff. There's the other part, you know, in terms of acceptable scientific methods and stuff like that.

COMMITTEE MEMBER WOODRUFF: Right.

CHAIRPERSON GOLD: Okay. Time to vote. Everybody ready?

All right. I'm just -- give me one second. I have too many pieces. I'm sorry.

Okay. All right. So has phenylphosphine been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? If you believe yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see zero.

If you believe no, please raise your hand.

(Hand raised.)

CHAIRPERSON GOLD: I see zero.

DIRECTOR ALEXEEFF: I think there was one.
CHAIRPERSON GOLD: Did I miss one?
I'm sorry.
All those abstaining, raise your hand.
(Hands raised.)
CHAIRPERSON GOLD: Four.
Okay. Has phenylphosphine been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? If you believe yes, please raise your hand.
(No hands raised.)
CHAIRPERSON GOLD: I see zero.
All those voting no, please raise your hand.
(Hands raised.)
CHAIRPERSON GOLD: One.
I think I -- two. Those abstaining.
(Hands raised.)
CHAIRPERSON GOLD: Three.
Has phenylphosphine 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.
(Hands raised.)
CHAIRPERSON GOLD: Two, three, four, five.
All those voting no.

(No hands raised.)

CHAIRPERSON GOLD: I presume zero.

Abstaining?

(No hands raised.)

CHAIRPERSON GOLD: Zero.

So in summary, for developmental toxicity, we have one no vote and four abstaining. For female reproductive toxicity, we have two voting no, and three abstaining. And for male reproductive toxicity, we have five voting yes, no abstentions, and no no votes.

Okay. Thank you all for --

COMMITTEE MEMBER LUDERER: Can I just ask for a clarification? No means that there's evidence that it's not a female reproductive toxicant can't? Is that --

DR. DONALD: No.

CHAIRPERSON GOLD: It means that there's no evidence that --

COMMITTEE MEMBER LUDERER: There's no evidence. Okay.

DR. DONALD: A no vote means the chemical has not been clearly shown.

COMMITTEE MEMBER LUDERER: Okay. All right. Well, then I --

DR. DONALD: So it means even if there is evidence, it doesn't reach the level.

COMMITTEE MEMBER LUDERER: -- I would have voted no.

COMMITTEE MEMBER BASKIN: Yeah. I mean, that would include, since I'm the only one voting no on these things --

(Laughter.)

COMMITTEE MEMBER BASKIN: -- that it hasn't been studied.

COMMITTEE MEMBER BASKIN: You know, or published. We don't know the data. There's no data, so I think you have to vote no.

DR. DONALD: That's correct. A no vote encompasses any combination of evidence that does not rise to the level where you believe the chemical has been clearly shown to cause the effect. So that may include absolutely no evidence at all. It may include evidence for lack of effect or it may include evidence for effect that you do not believe constitutes it being clearly shown.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So just based on your comment, are you thinking that you need to revote?

COMMITTEE MEMBER LUDERER: Yes.

COMMITTEE MEMBER WOODRUFF: Can I ask a question?

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

COMMITTEE MEMBER WOODRUFF: So the definitions of these, are those in the statute or are they defined by the Committee?

CHIEF COUNSEL MONAHAN-CUMMINGS: The definition of the criteria?

COMMITTEE MEMBER WOODRUFF: Yeah, for no, yes, and abstentions.

CHIEF COUNSEL MONAHAN-CUMMINGS: The statute just says whether the Committee decides whether or not the chemical has been clearly shown through scientifically valid evidence to cause reproductive toxicity. There's also a provision in our regulations that talks about the only way that the Committee can take an affirmative action is when there's a majority of the appointed members that vote yes.

So the effect is that if a member votes either no or abstains, it's still a no vote, but you can certainly say I'm abstaining because I don't think there's enough data or something. It's just that when you vote no, that's -- really it can be the same thing.

DIRECTOR ALEXEEFF: This is George Alexeeff. Actually, we had a number of internal discussions when this Committee was appointed, not with the Committee, but amongst ourselves, as to whether we were -- whether we should rethink the way the questions are being asked. And

we decided to leave them as they were, just not to confuse the situation, in part because, you know, the statute refers to whether or not something has been shown to cause reproductive toxicity.

And these questions ask -- suggest additional information. You know, like if you vote no -- if you're voting no, then it sort of implies something else. So what you're suggesting is actually well, maybe we should be voting or have questions that basically have us sort of be able to articulate what we think the state of the evidence is about this chemical. Is that what you're suggesting?

COMMITTEE MEMBER PESSAH: That is especially relevant when there is zero evidence for or against. I mean, voting no in most sort of ways of interpreting a no means that you think it's not harmful. And when we're abstaining, we're actually saying there's virtually no evidence to make -- base a decision on. And so I think we need to define that.

CHAIRPERSON GOLD: This was all -- if we considered making this revision, it would also help inform the staff and other organizations that we think further work needs to be done, which is something that's been brought up a couple of times before. So I wonder -- I don't think we ought to do it for today necessarily, but

for the future to consider having a different category or an additional category is what I'm saying, and a clarification a little bit about what each of these votes means.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. That may not require a regulatory change, so much as an agreement among the Committee and maybe some addendum or whatever to your guidance that says, you know, this is what an abstention means or whatever. But it's entirely fine when you're voting to say I'm abstaining because I don't think there's any evidence one way or the other, because, you know, obviously that's different than saying I think it's safe.

And you all aren't trying to decide whether it's safe or not, but that may be the perception you want to avoid or whatever. So I still am wondering whether or not you want to revote.

CHAIRPERSON GOLD: I mean effectively it doesn't change the bottom line, but if the Committee wants to revote, I suppose we can. Is that permissible?

DIRECTOR ALEXEEFF: The other alternative, instead of revoting, is the Committee members can make a statement for the record as to why they voted whatever they voted. And that would at least provide more information than making a yes a no and, you know,

whatever.

CHAIRPERSON GOLD: That sounds fine. Okay. Why don't we just go down the line. I'll start with Dr. Pessah, if you want to say why you voted the way you did, or you don't have to if you don't want to.

(Laughter.)

COMMITTEE MEMBER PESSAH: I've abstained on two of those issues -- on two of those votes, because there is no evidence for or against phenylphosphine.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I also abstained because there's no evidence either way on the two outcomes that I abstained on, developmental and female reproductive effects.

CHAIRPERSON GOLD: All right. And I would agree with that. It wasn't really a statement that there's no -- that there is evidence that it's not a problem. It's just inadequate evidence.

COMMITTEE MEMBER LUDERER: And I abstained on the developmental and female reproductive toxicity for the same reasons, because there is no evidence either way.

CHAIRPERSON GOLD: Dr. Baskin.

COMMITTEE MEMBER BASKIN: It's my understanding I'm supposed to vote yes, if there is evidence. So therefore, I voted no, because there was no evidence.

CHAIRPERSON GOLD: Okay. Thank you all.

The next agenda item, I believe, unless I've completely lost track here, is that we have staff updates --

(Laughter.)

CHAIRPERSON GOLD: -- correct?

Ms. Oshita.

MS. OSHITA: Okay. Good afternoon. Okay. I'd just like to give you an update on the chemical listings. As you recall at your last meeting in March, I had mentioned that we expected to move forward with the listings of methyl isobutyl ketone as known to cause reproductive toxicity and megestrol acetate as known to cause cancer. We have done so. Both were listed on March 28th, 2014.

In addition, on April 18th, we added pulegone, pentosan polysulfate sodium, pioglitazone, and triamterene. And then on May 2nd, we have also added n,n-dimethyl-p-toluidine. Those were all added as known to cause cancer.

We've received comments on beta-myrcene, atrazine, propazine, simazine and their chlorometabolites, DACT, DEA and DIA. And we also received comments on nitrite in combination with amines and amides, which we are reviewing.

We issued a Notice of Intent to List for ethylene glycol. And we extended the comment period, which will now close on June 11th.

And then last, you'll probably be happy to hear that this will be your last meeting for 2014, and that we will be polling you for your availability in early 2015 very shortly here.

CHAIRPERSON GOLD: Thank you.

So, Ms. Monahan-Cummings, you have an update.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. This is the last time you're going to hear from me this year. Aren't you lucky?

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Awh.

I wanted to introduce our newest attorney. You want to stand and bow. This is Mario Fernandez. I've doubled my attorney staff. And so Mario is our newest attorney. Just started a couple weeks ago, and we're real excited to have him. He's going to primarily work on regulatory actions, but he is one of the backups for me, so you may well see him at one of your meetings. So I just wanted you to know who he is.

We won't ask him to make a speech.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: And then Cindy

mentioned that we had gotten comments on the proposed listing of the triazines. And I just wanted to mention that we also got a lawsuit based on our proposed listing of the triazines. This is the, what we're calling, Syngenta 2, because we've already got a case that was filed by Syngenta Crop Protection. And so we have Syngenta 1 and Syngenta 2.

And so it's an early filing, because we actually haven't made a decision whether or not to list, but it -- they're actually holding off until we make that decision and publish our responses to comments and then we'll find out what happens next in court.

And then just the other case that you -- that I've mentioned to you before, the American Chemistry Council versus OEHHA. It has to do with a brief listing of bisphenol A. And we're still in the early motion process in that case. Currently, ACC is asking for discovery, which we're opposing.

And then just a pitch again for our -- we've got a pretty large regulatory project going on right now that has to do with how to provide warnings for listed chemicals. And while I keep telling you that worrying about warnings is not within your expertise, I think you might be interested in some of the work we're doing on that. It doesn't have to do with any particular chemical,

but there is information available on our website, including webcast recordings of our pre-regulatory work. And so you're welcome to opine as an individual person.

But since it's not within the purview of this Committee, then you wouldn't be giving us advice at this point on it. And I think that's all, unless somebody has a question of legal import.

No.

CHAIRPERSON GOLD: Thank you. So our penultimate item is to see if there are any other public comments?

Yes, sir.

DR. LAWYER: Dr. Arthur Lawyer from the Technology Sciences Group in Davis. Just a comment and then two questions.

One, the comment is to staff. I mean, for those of us in the public that have to listen to the same thing that you do, but might look at it from a different vantage point, it's wonderful to see the neutrality that comes out with the staff presentations. So I wanted the Director and the Committee to know that we appreciate it too. It really does make a difference.

Two issues. One came up on the first two compounds. Those compounds both had studies, bigger studies. And what you had was the TSCA version of the studies, abbreviated versions of it. And I think what

you've learned from the third compound, which is a FIFRA regulated compound, is the pesticide folks that work with Proposition 65 have learned that there's a way to get those big studies to you within this world of proprietary costing stuff. It's not that we're trying to keep these studies from the public. It's this nuisance of having the cost and data compensation of these expensive studies get in the way of sharing them.

It seems to me that a lot of those studies might have been available, if those parts of even DuPont knew that there was a way to get it safely to this Committee. So maybe to the staff or the Director, I think -- I think we could -- maybe some of us in industry could help show them the way that we all learn through deltamethrin with this Committee a year ago. So that's comment number one.

And the second one is a question. This Committee was very instrumental in getting the tables set up for the data summaries, and we found them very helpful. And for the first time, we actually took then those tables and annotated them with a red type. We thought that was helpful in our concept of it, but it's really a question back. Did you find it helpful or was it annoying?

I just -- it's a new concept for us having those tables. Any comments on whether that part of the presentation that we put together was helpful to you?

CHAIRPERSON GOLD: Any Committee members have comments on the edited tables?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: I would prefer it without the red.

DR. LAWYER: Okay. Keeping it in a less bold way, but somehow so you could see it.

COMMITTEE MEMBER BASKIN: I mean, I would guess direct yourself to your first comment, they're unbiased, put together scientifically, and the red adds bias.

DR. LAWYER: Okay. Well, that's why -- that's part of the reason I wanted to ask the question. Sorry.

CHAIRPERSON GOLD: So you're not objecting to the additions or --

COMMITTEE MEMBER BASKIN: No, no. The tables are great.

CHAIRPERSON GOLD: No, but I mean his additions to the tables?

COMMITTEE MEMBER BASKIN: I like the tables that come from --

CHAIRPERSON GOLD: OEHHA.

COMMITTEE MEMBER BASKIN: Yeah. And I --

CHAIRPERSON GOLD: Unchanged.

COMMITTEE MEMBER BASKIN: Unchanged.

DR. LAWYER: Okay. That was the reason I asked.

The tables are a new phenomena, so are our red editing of it.

CHAIRPERSON GOLD: Anyone else want to comment on the revisions to the tables?

(Laughter.)

DR. LAWYER: Anyway, thank you very much.

CHAIRPERSON GOLD: Okay. Thank you. So I believe Dr. Alexeeff is going to summarize, correct, that's where we are?

DIRECTOR ALEXEEFF: Actually, before we're getting to the end, did you want to say something?

I think you have a --

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. I did want to say that -- I wanted to ask the staff about this, because the National Academy of Sciences just came out with a new report on how -- on recommendations to EPA on improvements to the IRIS program, which if people are familiar is the main program that does risk assessments at EPA for toxic chemicals. And they have recommended a number of improvements on how that process can work.

And I think it would be very useful to have some type of reflection here at this Committee about what that -- how that may be -- what kind of -- how OEHHA could take advantage of that -- those recommendations and what

IRIS is doing and the NAS recommended.

DR. ZEISE: Can I just follow up with a question. So when you say OEHHA, are you thinking about OEHHA in the context of Proposition 65 evaluations and the work for the Committee?

COMMITTEE MEMBER WOODRUFF: I really meant -- yes, I really meant the -- evaluating and presenting the data for this Committee in terms of developmental and reproductive toxicant evaluation.

DR. ZEISE: Well, as we move forward, we could certainly take a look at that and have some discussion with the Committee.

CHAIRPERSON GOLD: So if you feel it would be useful to maybe summarize what -- it keeps going off when I hit it. I'm sorry.

To summarize, what they've done at the National Academy of Sciences and then how it might apply to the business at hand here, and how it might be adapted for our purposes. If you have insights, that would be really helpful.

All right. Now, Dr. Alexeeff.

DIRECTOR ALEXEEFF: Yeah. Well, actually I wanted to acknowledge someone who asked me not to acknowledge her, so that's kind of the way that goes.

So, as you know, when we, you know, prepare these

reports, we make copies, we have postings on our website, we have to -- if there's a regulatory decision in terms of like a, what we call, a MADL or that kind of stuff has to go through a regulatory process. There's public comments. They have to be organized. They have to be posted, all this sort of stuff.

So we have, you know, a few people that help on that. And Cindy, of course, is one of them. The other person that we haven't seen -- you haven't seen too much is Sue Luong in the back. And she's actually retiring after doing this for 24 years. So she's been with this program doing this for -- since 1990. And I just want to acknowledge her, because it's been, you know, tremendous all the work that she's done, so I want to thank her.

(Applause.)

DIRECTOR ALEXEEFF: Okay. So the Committee considered three chemicals today. I guess it doesn't make a difference what order.

One chemical that was considered was chlorsulfuron. And that chemical was on the list. And the Committee decided, based upon looking at all endpoints, that it should not remain on the list. We had the votes mentioned earlier.

In terms of hexafluoroacetone, that chemical has been on the list. And the Committee voted to -- sorry --

and the Committee decided to retain it on the list for developmental and for male reproductive toxicity.

And final for phenylphosphine, which had -- the chemical which has been on the list, the Committee voted to retain it on the list for the endpoint of male reproductive toxicity.

So I wanted to thank the Panel again for taking time out of their busy schedules to be here. And I know -- the discussions I thought were very thoughtful, and very insightful. And I know that it was not necessarily your favorite kind of decision process trying to make a decision with incomplete information or where you felt that you wish you had more, but I do appreciate the thought and efforts you put into it.

And I also wanted to thank the staff for their preparations of the report, and the assistance in this meeting. And I also just want to thank also the recorder who's been our trusted recorder for many, many meetings, and also the people who have attended here, and either listened or asked questions and such. So thank you.

And I want to thank Dr. Gold specifically for running such a great meeting.

CHAIRPERSON GOLD: Thank you. And I think without further ado, we can -- if there's no further business, going, going, we can adjourn.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 2:33 p.m.)

C E R T I F I C A T E O F R E P O R T E R

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, Developmental and Reproductive Toxicant Identification Committee was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed under my direction, by computer-assisted transcription.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 3rd day of June, 2014.

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