

MEETING
STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
PROPOSITION 65
DEVELOPMENTAL AND REPRODUCTIVE TOXICANT
IDENTIFICATION COMMITTEE

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A P P E A R A N C E S

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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
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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

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1 P R O C E E D I N G S

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

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

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

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

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

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

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

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

9 (Laughter.)

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

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

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

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

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

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

25 But essentially, for all of these chemicals, you

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

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

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

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

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

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

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

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

25 (Thereupon an overhead presentation was

1 presented as follows.)

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

8 Why don't we skip to the next slide.

9 --o0o--

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

20 Next slide.

21 --o0o--

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

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

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

15 Were you here, Dr. Luderer?

16 COMMITTEE MEMBER LUDERER: I wasn't.

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

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

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

23 So the legal background -- next slide.

24 --o0o--

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

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

8 Next slide.

9 --o0o--

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

22 Next slide.

23 --o0o--

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

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

8 So it changed after that. That case is still in
9 effect. However, after 2012, the only part of the
10 decision that really relates now to our listing decisions
11 is the first one, which still requires us to list
12 chemicals that are identified by reference under the Labor
13 Code. That, right now, is limited essentially to
14 chemicals that are identified by the International Agency
15 for Research on Cancer. And so those are the chemicals
16 that we're identifying listing at this time. So the TLVs
17 are no longer a definitive source for listing under Prop
18 65.

19 Next slide.

20 --o0o--

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

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

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

10 So next steps. Next slide.

11 --o0o--

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

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

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

1 (Thereupon an overhead presentation was
2 presented as follows.)

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

5 --o0o--

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

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

21 Could I have the next slide, please?

22 --o0o--

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

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

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

14 CHAIRPERSON GOLD: Move on.

15 --o0o--

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

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

1 exposure, and one by the inhalation route.

2 --o0o--

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

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

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

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

4 --o0o--

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

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

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

1 for the mid- and high-dose groups. This was an eight or
2 14 percent reduction relative to the controls
3 respectively, but it was not clear from the paper whether
4 the weights were adjusted for the weight of uterine
5 contents, or in other words, reduced numbers of fetuses
6 and reduced weights of the fetuses might explain the
7 differences between the groups.

8 --o0o--

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

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

18 I just want to check.

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

23 --o0o--

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

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

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

15 --o0o--

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

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

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

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

10 --o0o--

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

21 --o0o--

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

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

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

10 Let's see. And the range-finding study found
11 maternal mortality was 100 percent at the concentration of
12 60 ppm, 67 percent at 30 ppm. So for the full teratology
13 study, they went with doses of 0.1, one, or seven ppm. In
14 the full teratology study, they found no effects on
15 maternal body weight, adjusted weight change, or food
16 consumption. They did find increased absolute and
17 relative liver weights at one and seven ppm.

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

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

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

6 --o0o--

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

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

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

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

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

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

12 --o0o--

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

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

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

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

7 --o0o--

8 DR. CAMPBELL: Moving on to the next study, Lee
9 and Gilles, same group, 1984. Dermal application of 13,
10 39, or 130 milligrams per kilogram per day HFA daily for
11 14 days. Control rats were dosed with water and pair fed
12 to treated rats. Ten animals per group and sacrificed at
13 24 hours following the last dose. The testes were
14 examined grossly and prepared for light microscopy.
15 Testes from the high dose group in this study were
16 prepared for electron microscopy, so they took a closer
17 look.

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

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

4 --o0o--

5 DR. CAMPBELL: And again, here's a picture. The
6 upper two, the left-hand side is the normal seminiferous
7 tubules at a magnification of 80, and on the right-hand
8 upper panel shows degenerative tubules following a dose of
9 130 milligrams per kilogram per day, the same
10 magnification.

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

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

20 --o0o--

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

1 130 milligrams per kilogram per day daily for 14 days,
2 seven exposed and eight controls. And they did testicular
3 weights, histology, hormone levels, and uptake of
4 radiolabeled acetate and mevalonate.

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

9 In vivo, they found no effect on final body
10 weight or serum levels of LH or testosterone. There was a
11 48 percent increase in serum FSH. There was a 43 percent
12 reduction in testicular weights, and a 50 percent
13 reduction in testicular testosterone. Degenerative
14 changes were observed in spermatocytes, and there was
15 inhibition of Leydig cell C₁₉ steroidogenesis. They
16 didn't find any changes in the in vitro study.

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

19 --o0o--

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

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

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

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

11 --o0o--

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

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

25 At 12 ppm with 30 days exposure, they saw

1 testicular atrophy and oligospermia or aspermia with
2 effects on spermatids and spermatocytes. At 12 ppm with
3 90 days of exposure, there was severe testicular atrophy,
4 disappearance of mature and immature spermatids from the
5 seminiferous tubules, and spermatozoa were absent from the
6 epididymal tubules.

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

11 --o0o--

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

23 --o0o--

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

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

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

15 --o0o--

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

1 And that completes my presentation.

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

5 Hearing none. Do we have any public comments?

6 No.

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

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

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

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

1 really intended to study the teratogenicity of that
2 compound.

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

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

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

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

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

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

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

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

18 COMMITTEE MEMBER LUDERER: Nobody knows where it
19 is?

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

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

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

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

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

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

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

10 Okay. Dr. Baskin, male reproductive toxicity.

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

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

25 The pros to the study is that the science is

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

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

9 Developmental?

10 Are we ready to vote?

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

13 CHAIRPERSON GOLD: No female data on this, right.

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

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

21 I assume then we're ready to vote?

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

1 toxicity?

2 If you believe yes, please raise your hand.

3 (Hands raised.)

4 CHAIRPERSON GOLD: I see five.

5 Any noes?

6 (No hands raised.)

7 CHAIRPERSON GOLD: Okay. Any abstentions?

8 (No hands raised.)

9 CHAIRPERSON GOLD: No.

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

15 (No hands raised.)

16 CHAIRPERSON GOLD: I see none.

17 If you believe no, please raise your hand.

18 (Hands raised.)

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

20 Any abstentions?

21 (No hands raised.)

22 CHAIRPERSON GOLD: None.

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

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

3 (Hands raised.)

4 CHAIRPERSON GOLD: I see five.

5 If you believe no.

6 (No hands raised.)

7 CHAIRPERSON GOLD: Abstentions?

8 (No hands raised.)

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

14 Anything further?

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

18 DR. CAMPBELL: Oh, thank you.

19 --o0o--

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

25 Both of these reports are actually general

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

7 --o0o--

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

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

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

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

1 0.6 ppm and two out of four dogs at 2.2 ppm. They
2 described that the effects were similar to what was seen
3 in rats, but not as severe. Spermatogenesis was affected,
4 but it was -- continued to be maintained.

5 --o0o--

6 DR. CAMPBELL: And then onto the published study
7 by Waritz and Brown, which is from 1975. The acute
8 protocol consisted of four hours exposure to either 0, 19,
9 32, or 42 ppm. Six animals per group with two rats per
10 group sacrificed at each of days one, two, and seven --
11 oh, and -- one and two, and seven post-exposure to 19 ppm.
12 Two rats per group sacrificed at 14 days post-exposure to
13 44 ppm, and then they just did gross pathology.

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

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

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

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

11 CHAIRPERSON GOLD: Thank you. Is that all?

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

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

18 On the other hand, they gave these
19 chemicals -- well, the other negatives are, there's no
20 histology, which always really bothers me. You know, when
21 you have a beautiful picture that was shown from the
22 previous chemical, that there's, you know, clear
23 abnormalities in the testes, and you take the study out to
24 90 days or 150 days or a year, then reversibility is also
25 addressed quite nicely. And this study didn't really

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

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

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

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

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

25 CHAIRPERSON GOLD: Do you care to comment on the

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

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

7 CHAIRPERSON GOLD: Dr. Woodruff.

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

13 DR. CAMPBELL: Which one are you looking at?

14 COMMITTEE MEMBER WOODRUFF: Table I.

15 DR. CAMPBELL: In which --

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

20 DR. CAMPBELL: Which table?

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

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

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

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

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

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

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

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

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

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

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

7 COMMITTEE MEMBER LUDERER: Can I make a comment?

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

11 COMMITTEE MEMBER WOODRUFF: Yes.

12 COMMITTEE MEMBER LUDERER: Okay.

13 COMMITTEE MEMBER WOODRUFF: And it's 3.66, 2.95,
14 1.42. That just was my question about that.

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

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

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

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

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

10 COMMITTEE MEMBER BASKIN: (Shakes head.)

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

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

15 CHAIRPERSON GOLD: Weights.

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

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

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

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

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

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

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

16 CHAIRPERSON GOLD: Dr. Woodruff.

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

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

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

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

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

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

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

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

15 COMMITTEE MEMBER BASKIN: No.

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

18 COMMITTEE MEMBER LUDERER: I think it would be
19 helpful.

20 CHAIRPERSON GOLD: Dr. Woodruff?

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

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

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

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

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

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

13 (Laughter.)

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

16 DR. DONALD: No.

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

21 CHAIRPERSON GOLD: Page 54.

22 COMMITTEE MEMBER WOODRUFF: Page 54.

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

25 COMMITTEE MEMBER WOODRUFF: Right. The three

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

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

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

9 (Laughter.)

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

12 COMMITTEE MEMBER LUDERER: (Shakes head.)

13 CHAIRPERSON GOLD: No. So the question is --

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

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

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

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

25 CHAIRPERSON GOLD: And is this something you

1 think you could accomplish today or --

2 DR. ZEISE: (Nods head.)

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

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

8 COMMITTEE MEMBER BASKIN: I mean --

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

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

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

18 DR. DONALD: Yes, we saw the graphs.

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

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

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

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

1 I believe.

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

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

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

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

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

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

25 COMMITTEE MEMBER WOODRUFF: Okay. That's useful

1 too.

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

4 (Laughter.)

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

7 (Laughter.)

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

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

14 COMMITTEE MEMBER WOODRUFF: At 90 days right.

15 COMMITTEE MEMBER PESSAH: Yeah.

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

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

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

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

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

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

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

13 CHAIRPERSON GOLD: Right.

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

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

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

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

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

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

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

9 COMMITTEE MEMBER WOODRUFF: Yes, I like breaks.
10 (Laughter.)

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

16 No public comments.

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

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

25 CHIEF COUNSEL MONAHAN-CUMMINGS: If I could make

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

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

8 (Laughter.)

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

12 CHAIRPERSON GOLD: All right.

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

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

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

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

1 able to do.

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

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

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

13 Okay. Thank you.

14 (Off record: 11:23 AM)

15 (Thereupon a lunch break was taken.)
16
17
18
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25

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

2 (On record: 12:30 PM)

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

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

9 CHIEF DEPUTY DIRECTOR HIRSCH: I'm not George.

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

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

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

1 to provide you with all the information that you requested

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

5 COMMITTEE MEMBER WOODRUFF: Yes, I am.

6 CHAIRPERSON GOLD: Okay. Thank you very much.
7 So we will move on then to chlorsulfuron,
8 correct, and have the staff presentation first. And we
9 welcome back Dr. Alexeeff.

10 (Thereupon an overhead presentation was
11 presented as follows.)

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

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

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

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

1 identifying reproductive toxins.

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

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

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

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

1 Okay. If not, then back to Jim.

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

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

12 --o0o--

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

20 --o0o--

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

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

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

23 --o0o--

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

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

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

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

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

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

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

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

8 --o0o--

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

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

22 --o0o--

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

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

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

13 --o0o--

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

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

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

4 --o0o--

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

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

21 --o0o--

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

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

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

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

19 --o0o--

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

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

5 --o0o--

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

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

21 --o0o--

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

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

3 --o0o--

4 DR. IYER: In this guideline two-generation
5 reproduction study in rats by Mylchreest -- reported by
6 Mylchreest in 2005, rats were exposed in the diet to 0,
7 100, 500, 2500, and 7500 ppm for two generations with one
8 litter per generation. And the test substance related
9 systemic effects on body weights and body weight gains
10 were noted at dose levels of 500 ppm and above, indicating
11 that the dose ranges were adequately selected to identify
12 effects. No adverse effects on reproduction was noted in
13 this study.

14 --o0o--

15 DR. IYER: In the study by Wood et al., in 1981,
16 there were two components, a two-year feeding study and a
17 three-generation reproduction study in rats. We will be
18 discussing the effects noted in the three-generation
19 reproduction study. The study was conducted according to
20 guidelines, and the animals were exposed for three
21 generations with two litters per generation to 0, 100,
22 500, and 2500 parts per million of chlorsulfuron in the
23 diet with two matings from each -- with two matings from
24 each second mating, such that animals from the F0
25 generation resulted in F1A and F1B litters. Animals from

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

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

9 --o0o--

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

19 --o0o--

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

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

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

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

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

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

3 --o0o--

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

15 When only the third generation was considered,
16 the mean ranged from 89.5 to 100 percent, whereas the
17 200 -- whereas, the 2500 part per million chlorsulfuron
18 group had a fertility index of 79 percent for the third
19 generation.

20 --o0o--

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

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

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

19 --o0o--

20 DR. IYER: Overall, summarizing the DART studies
21 for chlorsulfuron, the developmental toxicity studies in
22 the rabbit in, there were increased fetal resorptions at
23 75 mg/kg, 75 milligrams per kilogram per day in the
24 Hoberman study, and the supplements provided reanalysis of
25 these findings. In the Alvarez 1991 study, there were

1 multiple effects, which included fetal malformations,
2 minor fetal skeletal defects, reduced fetal body weights
3 400 milligram per kilogram per day, and decreased
4 sternebrae ossification at 1000 milligrams per kilogram
5 per day. And the supplements provided additional analysis
6 that my colleague just discussed earlier on.

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

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

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

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

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

1 So next slide.

2 --o0o--

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

13 --o0o--

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

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

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

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

12 Next slide.

13 --o0o--

14 DR. BATTALORA: There we go.

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

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

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

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

7 --o0o--

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

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

17 EPA eventually required a new study because the
18 1980 study was guideline deficient. They had a low number
19 of animals. The guideline calls for a minimum of about 20
20 animals per group with implantation sites at necropsy.
21 This study, starting with 16 or 17 does per group wound up
22 with only 12 to 13 in the high dose group and the control.

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

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

4 --o0o--

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

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

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

25 --o0o--

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

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

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

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

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

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

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

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

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

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

23 --o0o--

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

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

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

9 So what I've done at the first table there is I
10 have looked at the frequency of does with low food
11 intakes. And I defined it as zero to 20 grams per day.
12 And these animals typically might be eating about 100,
13 110, 120 grams per day, higher or lower. You know, of
14 course, it's a range.

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

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

1 at the high dose.

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

9 There was no dose response for resorptions in the
10 1980 study, as I showed you the jumpiness in the data. So
11 in terms of the resorptions at 75 mg/kg in the first
12 study, the 1980 study, it is influenced in part by a few
13 does with low numbers of implants. One of them had 100
14 percent resorptions, and there was another doe that only
15 had two implants, and one of the two resorbed. And it's
16 either a spurious finding or if it's test substance
17 related, it occurred in the presence of significant
18 maternal toxicity.

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

23 --o0o--

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

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

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

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

13 --o0o--

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

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

1 I'll just go on to the next slide.

2 --o0o--

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

11 So based on today's standards, the findings at
12 1500's are considered overly toxic, not minimally. The
13 decrease in fetal body weight can clearly be attributed to
14 maternal toxicity. And, you know, we avoid doing anything
15 like this in modern day studies for animal welfare
16 purposes. And I think the 1998 guideline is reflecting
17 that in part.

18 Next slide.

19 --o0o--

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

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

4 --o0o--

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

8 --o0o--

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

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

22 Next slide.

23 --o0o--

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

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

6 --o0o--

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

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

24 --o0o--

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

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

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

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

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

18 CHAIRPERSON GOLD: Thank you.

19 Are there any questions from the Panel at this
20 time?

21 Yes, Dr. Pessah.

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

25 DR. BATTALORA: No, we did not.

1 CHAIRPERSON GOLD: Other questions?

2 Dr. Baskin.

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

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

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

14 Okay. Thank you very much.

15 No other public comments?

16 Going, going public comments.

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

20 Dr. Luderer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Let's see. I just lost my document.

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

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

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

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

25 So the effects on the offspring of the decreased

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

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

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

23 CHAIRPERSON GOLD: Okay. Thank you.

24 Dr. Woodruff.

25 COMMITTEE MEMBER WOODRUFF: Yes. Thank you.

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

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

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

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

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

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

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

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

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

17 DR. WU: In any of them.

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

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

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

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

24 DR. IYER: That's right.

25 COMMITTEE MEMBER WOODRUFF: Did you have any

1 thoughts as to why?

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

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

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

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

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

1 really provide any additional comment and --

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

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

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

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

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

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

12 COMMITTEE MEMBER WOODRUFF: Right, right.

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

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

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

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

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

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

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

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

23 COMMITTEE MEMBER WOODRUFF: This is on?

24 COMMITTEE MEMBER LUDERER: In the rat study.

25 DR. WU: Rabbit.

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

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

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

16 COMMITTEE MEMBER WOODRUFF: Table 5.

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

19 If you can help clarify, I'm hoping.

20 DR. BATTALORA: Yeah. I'm not going to say much
21 about the rabbit -- rat, because she just mentioned that
22 it was at the 1,500 where there was significant maternal
23 toxicity. And again, it wasn't significant by pairwise
24 for the rabbit on the screen right there, so OEHHA said at
25 400 there was an effect in one study, but note there's a

1 second study at 400. So what you saw at 400 in the first
2 study wasn't seen in the supplemental study at 400 or at
3 1000 mg/kg.

4 I just thought that was worth pointing out.

5 CHAIRPERSON GOLD: Thank you.

6 Dr. Pessah.

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

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

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

25 COMMITTEE MEMBER WOODRUFF: But we haven't seen

1 that, so --

2 CHAIRPERSON GOLD: Dr. Woodruff.

3 COMMITTEE MEMBER WOODRUFF: Sorry.

4 CHAIRPERSON GOLD: Use your microphone.

5 COMMITTEE MEMBER WOODRUFF: It's on.

6 CHAIRPERSON GOLD: Okay.

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

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

15 COMMITTEE MEMBER WOODRUFF: Right. Right. So --

16 CHAIRPERSON GOLD: Wait.

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

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

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

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

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

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

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

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

8 Any other comments?

9 Dr. Pessah.

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

17 CHAIRPERSON GOLD: Last time.

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

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

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

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

7 CHAIRPERSON GOLD: Okay. Thank you.

8 Dr. Donald.

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

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

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

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

1 Call the question to vote?

2 Do you need more time?

3 COMMITTEE MEMBER WOODRUFF: No, that's fine.

4 CHAIRPERSON GOLD: Okay.

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

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

12 COMMITTEE MEMBER WOODRUFF: Yes.

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

15 How about we reconvene at five minutes to 2:00

16 (Off record: 1:46 PM)

17 (Thereupon a recess was taken.)

18 (On record: 1:54 PM)

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

21 DR. DONALD: If I might before --

22 COMMITTEE MEMBER WOODRUFF: Oh, okay.

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

25 DIRECTOR ALEXEEFF: Can you speak into the mic.

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

5 CHAIRPERSON GOLD: This is concerning rabbit
6 weights?

7 DR. DONALD: Yes.

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

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

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

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

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

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

1 DR. IYER: Page 22. Okay.

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

4 DR. LAWYER: Can we comment one more time?

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

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

12 DR. BATTALORA: That's right.

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

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

20 COMMITTEE MEMBER WOODRUFF: Right.

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

1 it's -- that there is an effect.

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

7 CHAIRPERSON GOLD: Yes, Dr. Battalora.

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

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

17 COMMITTEE MEMBER PESSAH: Just one really quick
18 question.

19 Thank you.

20 Chlorsulfuron is a benzoyl sulfonylurea, right?

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

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

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

6 COMMITTEE MEMBER PESSAH: They've never been
7 screened?

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

12 CHAIRPERSON GOLD: Any other questions?

13 So we have the option to vote or to defer.

14 (Laughter.)

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

18 Dr. Woodruff.

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

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

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

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

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

19 CHAIRPERSON GOLD: Now, are we ready?

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

24 (No hands raised.)

25 CHAIRPERSON GOLD: I see none.

1 All those voting no, please raise your hand.

2 (Hand raised.)

3 CHAIRPERSON GOLD: I see one.

4 Those abstaining.

5 (Hands raised.)

6 CHAIRPERSON GOLD: Four.

7 Has chlorsulfuron been clearly shown through
8 scientifically valid testing, according to generally
9 accepted principles to cause female reproductive toxicity?
10 If you believe yes, please raise your hand.

11 (No hands raised.)

12 CHAIRPERSON GOLD: I see none.

13 Those who believe no, please raise your hand.

14 (Hands raised.)

15 CHAIRPERSON GOLD: Four.

16 Abstaining?

17 (Hand raised.)

18 CHAIRPERSON GOLD: One.

19 Has chlorsulfuron been clearly shown through
20 scientifically valid testing according to generally
21 accepted principles to cause male reproductive toxicity?
22 If you believe yes, please raise your hand.

23 (No hands raised.)

24 CHAIRPERSON GOLD: I see none.

25 If you believe no, please raise your hand.

1 (Hands raised.)

2 CHAIRPERSON GOLD: Three.

3 If you're abstaining, please raise your hand.

4 (Hands raised.)

5 CHAIRPERSON GOLD: I see two.

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

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

14 DR. DONALD: Thank you, Cindy.

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

17 Thank you.

18 (Thereupon an overhead presentation was
19 presented as follows.)

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

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

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

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

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

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

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

8 COMMITTEE MEMBER WOODRUFF: Is that like magic.

9 (Laughter.)

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

12 (Laughter.)

13 DR. DONALD: Okay. So this shows the scatter
14 plots. This shows the effects on absolute testicular
15 weight on a per animal basis for the control group, the
16 0.6 part per million and the 22 part per million -- sorry,
17 2.2 part per million.

18 Again, showing it at the end of treatment after a
19 29-day recovery period, and after a 69-day recovery
20 period.

21 --o0o--

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

25 --o0o--

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

4 --o0o--

5 DR. DONALD: And for estimated relative testes
6 weight.

7 So would you like to see any of those again?

8 (Laughter.)

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

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

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

16 Dr. Baskin.

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

22 CHIEF COUNSEL MONAHAN-CUMMINGS: No.

23 (Laughter.)

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

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

10 (Laughter.)

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

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

17 COMMITTEE MEMBER BASKIN: Thank you.

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

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

24 CHAIRPERSON GOLD: Yes. Okay. Dr. Woodruff.

25 COMMITTEE MEMBER WOODRUFF: So the relative

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

3 DR. DONALD: Yes.

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

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

11 COMMITTEE MEMBER WOODRUFF: Right.

12 CHAIRPERSON GOLD: Okay. Time to vote.

13 Everybody ready?

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

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

21 (No hands raised.)

22 CHAIRPERSON GOLD: I see zero.

23 If you believe no, please raise your hand.

24 (Hand raised.)

25 CHAIRPERSON GOLD: I see zero.

1 DIRECTOR ALEXEEFF: I think there was one.

2 CHAIRPERSON GOLD: Did I miss one?

3 I'm sorry.

4 All those abstaining, raise your hand.

5 (Hands raised.)

6 CHAIRPERSON GOLD: Four.

7 Okay. Has phenylphosphine been clearly shown
8 through scientifically valid testing, according to
9 generally accepted principles to cause female reproductive
10 toxicity? If you believe yes, please raise your hand.

11 (No hands raised.)

12 CHAIRPERSON GOLD: I see zero.

13 All those voting no, please raise your hand.

14 (Hands raised.)

15 CHAIRPERSON GOLD: One.

16 I think I -- two. Those abstaining.

17 (Hands raised.)

18 CHAIRPERSON GOLD: Three.

19 Has phenylphosphine been clearly shown through
20 scientifically valid testing, according to generally
21 accepted principles to cause male reproductive toxicity?
22 All those voting yes, please raise your hand.

23 (Hands raised.)

24 CHAIRPERSON GOLD: Two, three, four, five.

25 All those voting no.

1 (No hands raised.)

2 CHAIRPERSON GOLD: I presume zero.

3 Abstaining?

4 (No hands raised.)

5 CHAIRPERSON GOLD: Zero.

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

11 Okay. Thank you all for --

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

15 DR. DONALD: No.

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

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

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

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

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

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

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

6 (Laughter.)

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

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

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

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

23 COMMITTEE MEMBER LUDERER: Yes.

24 COMMITTEE MEMBER WOODRUFF: Can I ask a question?

25 CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 whatever.

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

6 (Laughter.)

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

10 CHAIRPERSON GOLD: Dr. Woodruff.

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

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

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

22 CHAIRPERSON GOLD: Dr. Baskin.

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

1 CHAIRPERSON GOLD: Okay. Thank you all.

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

5 (Laughter.)

6 CHAIRPERSON GOLD: -- correct?

7 Ms. Oshita.

8 MS. OSHITA: Okay. Good afternoon. Okay. I'd
9 just like to give you an update on the chemical listings.
10 As you recall at your last meeting in March, I had
11 mentioned that we expected to move forward with the
12 listings of methyl isobutyl ketone as known to cause
13 reproductive toxicity and megestrol acetate as known to
14 cause cancer. We have done so. Both were listed on March
15 28th, 2014.

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

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

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

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

8 CHAIRPERSON GOLD: Thank you.

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

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

13 (Laughter.)

14 CHIEF COUNSEL MONAHAN-CUMMINGS: Awh.

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

23 We won't ask him to make a speech.

24 (Laughter.)

25 CHIEF COUNSEL MONAHAN-CUMMINGS: And then Cindy

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

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

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

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

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

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

8 No.

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

11 Yes, sir.

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

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

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

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

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

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

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

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

3 Dr. Baskin.

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

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

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

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

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

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

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

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

21 CHAIRPERSON GOLD: OEHHA.

22 COMMITTEE MEMBER BASKIN: Yeah. And I --

23 CHAIRPERSON GOLD: Unchanged.

24 COMMITTEE MEMBER BASKIN: Unchanged.

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

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

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

5 (Laughter.)

6 DR. LAWYER: Anyway, thank you very much.

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

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

12 I think you have a --

13 CHAIRPERSON GOLD: Dr. Woodruff.

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

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

1 IRIS is doing and the NAS recommended.

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

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

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

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

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

21 All right. Now, Dr. Alexeeff.

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

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

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

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

15 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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20 

21
22
23 JAMES F. PETERS, CSR, RPR
24 Certified Shorthand Reporter
25 License No. 10063