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CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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ORIGINAL

PUBLIC FORUM

MEETING OF THE DEVELOPMENTAL AND REPRODUCTIVE TOXICANT IDENTIFICATION COMMITTEE

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MONDAY, DECEMBER 13, 1999

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HELD AT:

2020 L STREET
AIR RESOURCES BOARD, BOARD ROOM LOWER LEVEL
SACRAMENTO, CA

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REPORTED BY:

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DR. JIM MORGAN, OEHHA

WINSTON HICKOX, OEHHA Secretary
CYNTHIA OSHITA, Proposition 65 Implementation

AGENDA

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SACRAMENTO, CALIFORNIA

MONDAY, DECEMBER 13, 1999

DR. BURK: Good morning, everyone. I'd like to call the meeting to order. This is the meeting of the DART Identification Committee. And I will introduce first, Dr. Joan Denton, Director of OEHHA, the Office of Environmental Health Hazard Assessment.

DR. DENTON: Good morning to you all. I wanted to take a moment to introduce to you the members of the Committee. And we have two new members of the DART Committee who have joined us. This is their first meeting, and I wanted to say a couple of things about them. So I'll just go around the table, here.

Of course, Dr. Burk, who is acting Chair. We had heard someone said that they thought that you were a new Chair. But I said, "No. Dr. Hendricks could not attend the meeting today, so Dr. Burk graciously, I guess, accepted the challenge of chairing the Committee.

To her right is Dr. Carl Keen, Dr. Linda Roberts, our new -- one of our new members, Dr. Hillary Klonoff-Cohen, and then Dr.

Kenneth Jones, who's on the very end.

To my left, Dr. Marion Miller, our new -- the other new person on the Committee, Dr. Pat Shiono, and then Dr. Steve Samuels rounds out the Committee.

I just want to say a couple of things about our new members. Both of our new members are epidemiologists.

And I will start with you, Dr. Shiono. Dr. Shiono is an epidemiologist who earned a degree in -- a Ph.D. in epidemiology, and an M.S. in biostatistics. As part of the -- of her curriculum vitae, she was a senior epidemiologist at the National Institutes of Health, where she studied the causes of low birthweight, pre-term, infant mortality, and congenital malformations. She also conducted epidemiology research on things such as cigarette smoke, alcohol, caffeine, and cocaine on birth outcomes.

After that, she was a founding member and director of research and grants for epidemiology at the Center for the Future of Children at the David and Lucille Packard Foundation. And in this capacity, she not

only managed research grants, but also did epidemiology research in pregnancy and birth outcomes in child health.

She has published the results of her work in numerous scientific journals, and has authored medical textbook chapters and also serves as a consulting reviewer and editor to several medical journals.

So we're very glad to have you, Dr. Shiono.

Then on my right, Dr. Klonoff-Cohen received her Ph.D. from the University of North Carolina at Chapel Hill in 1987. And she is a reproductive epidemiologist.

Currently, she is an Associate Professor at UC San Diego, and teaches -- there, she teaches medical and doctoral students. But also, she has conducted and is conducting research on causes of reproductive cancers and obstetrical and pediatric diseases.

Dr. Klonoff-Cohen has also published widely, and is the reviewer/editor for numerous first-authored publications, and is a member of several committees at the university, state, and local levels.

So again, we're very glad to have you. I would also like to mention that we have the privilege of another distinguished guest in the audience, our agency secretary, Winston Hickox.

Winston, I don't think I can give such a thorough background as I gave for the others, but we're very glad that, that you're here.

This is the first DART Committee meeting of 1999. And Winston came by as the, you know, as our first meeting to be introduced to the Committee members.

We also would like, if, if you'd like, Winston, to say a few words to the Committee. And this is the podium up here.

MR. HICKOX: Thanks, Joan. I really had not intended to speak formally, but given the chance to put a microphone in front of me, why not?

First of all, let me welcome you here today. This is your first meeting under a new administration. Many of you have served under two prior administrations. This administration, the Gray Davis administration, equally embraces the importance of this

Committee and its duties and responsibilities.

As many of you must know, in his prior statements, in occupying prior offices in California, and this year, as Governor, Governor Gray Davis has spoken often about his belief in the importance of sound science as the underpinning of the decisions that we make in our regulatory programs.

I'd share this with you, which I didn't have a chance to as we met earlier on a one-on-one basis: We have been engaged in an effort to re-think Cal/EPA as an organization structure. I don't really mean that as dramatically as that might sound, but the Governor and the legislature ask that we do that.

And in the course, I would share with you that the report that is the end result of that effort in draft form reached me on Friday. And nothing in that report does anything to diminish the importance of this Committee and this approach to the way in which we go about our regulatory functions in protection of the environment. In fact, if anything, it brings, I think, a clear focus to the need to be sure

that we adequately assess risk and separate that from risk mitigation responsibilities as part of the regulatory program here at Cal EPA.

I'm not going to be able to stay for your entire meeting today. I'm aware of some important subjects before you. I wish you well. I hope that the deliberation leads to a very defensible conclusion, that we find some way in all of this to find a path down the middle, if that's doable, in the arena of science and the finding of truth and the finding of the appropriate answers to specific questions.

This administration is, above all, about finding a course down the middle and using sound science as a basis for our decision. So Godspeed, good luck today, and thank you for the opportunity to meet you individually and to address you collectively.

Thanks, Joan.

DR. DENTON: Thank you, Winston. There are two items on the agenda that the Committee will be discussing today, quizalofop ethyl and fenbutatin oxide.

Before I turn it over to you, Dr. Burk, I wanted to mention that this -- the area around the building is notorious for giving people tickets if you run out of time on your meters. So I would just -- just wanted to advise you that if you are on timed meters, that you watch it carefully, because I, myself, have been the victim numerous times of the diligence of the meter people.

So with that, I will turn it over to you, Dr. Burk, for the meeting.

DR. BURK: Thank you, Joan. The first chemical that we are going to consider this morning is quizalofop ethyl. And I think first, we have a staff presentation by Dr. Jim Donald. Is that the plan?

MS. HECK: Yes. Dr. Burk? Colleen Heck, with OEHHA. We were going to have me just give a brief procedural statement before we turn it over to, to Jim Donald.

Thank you. Good morning. I wanted to give a brief background and procedural statement regarding these two chemicals, because this will be the first time that the DART Committee is being asked to consider a

chemical for listing that was previously under consideration for listing via the Authoritative Bodies mechanism.

Both quizalofop ethyl and fenbutatin oxide were formally identified by U.S. EPA as causing reproductive toxicity. On that basis, OEHHA issued a Data Callin Notice for each of these chemicals. OEHHA staff reviewed the information in the record at that time and determined there was a sufficient basis to move the chemical to the next stage in the listing process, the Notice of Intent To List.

Once both chemicals were in the Notice of Intent To List phase, the staff at OEHHA determined that the chemicals did not meet the regulatory criteria for listing or the Authoritative Bodies listing set forth in Section 12306 of the implementing regulations.

However, that same regulation mandates when such a determination is made at the Notice of Intent To List stage, that the chemical does not meet the listing criteria that it be referred to this Committee for its review.

And finally in this regard, the

regulation makes it clear what the standard is by which to review the chemical; it's the same standard you would use and do use for chemicals that come to you via the normal route, the non-Authoritative Bodies route.

So, that is, you are being asked to determine whether in your opinion the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. You're not sitting in review so much of the Authoritative Body as sitting in your normal role as Committee members serving as the Governor's State's qualified experts.

Thank you.

DR. DONALD: Good morning. My name is Jim Donald. I'm Chief of the Reproductive Toxicology Unit at OEHHA.

I'm going to make a couple of presentations on quizalofop ethyl. And normally, at this stage, we would give you just a brief overview presentation of the whole database for quizalofop. In this instance, we received on Thursday of last week a two-generation reproduction study on

quizalofop, which we had not previously been able to obtain. And in case you weren't -- you received copies of that this morning. In case you haven't yet been able to digest all five hundred-plus pages of the study, we thought we would give you a brief overview at this point.

We provided a summary of the study in the same sort of format as we would have in the HID. And I'm just going to walk you through that. So if you'd like to turn to that in your binder, it's behind the quizalofop ethyl HID, behind the first blue divider, I think. Yeah, behind the first blue page. And copies of this are available at the table, at the entrance, to members of the audience.

The study appears to be a fairly standard, two-generation, four-litter reproduction study conducted in rats, a Sprague-Dawley derivative. Animals in the F-0 generation were exposed to quizalofop for 70 days before breeding beginning at age approximately 35 days.

In the second generation animals from the F-1A litter that we used for breeding were

exposed for 80 days prior to breeding beginning at, at weaning, so approximately age 21 days. The animals were exposed via diet. The concentrations in diet were zero for the control animals, 25, 100, or 400 parts per million. 23 males and 23 females were bred in the F-0 generation. And the same number from the F-1A generation were bred to produce the F-2 litters.

DR. SAMUELS: Excuse me, Jim. Could you please wait a second while we find --

DR. DONALD: I'm sorry. This, this --

DR. BURK: It's the last --

DR. DONALD: I'm sorry. I got my presentation mixed up. Okay.

DR. SAMUELS: Thank you.

DR. DONALD: Okay. So to hopefully put it into a little bit of perspective, the approximate intakes averaged over the entire exposure period or the secondary exposure period, as shown in the table, are given here.

I won't read all of them, but the approximate levels prior to gestation were on the order of 2 to 3 milligrams per kilogram in the low-dose group, around 10 to 13 milligrams

per kilogram in the mid-dose, a hundred parts per million group, and in the order of 40 to 50 or perhaps 40 to 60 milligrams per kilograms in the high-dose group. And during gestation, the intakes were around 2 milligrams per kilogram in the low-dose group, approximately 8 milligrams per kilogram in the mid-dose group, and 30 to 35 milligrams per kilogram in the high-dose group.

There were some effects on bodyweight in the parental rats. But these effects were not terribly consistent and did not show up in all of the periods of exposure for all the treatment groups. Specifically, the high-dose males were significantly lighter than controls during days zero/70 of treatment. And there was a -- reportedly, a significant trend for decreased bodyweight for the treatment groups.

During gestation, there were a couple of periods when the high-dose animals, the high-dose females, were significantly heavier than control animals, days 14 to 21 of gestation in the F-0 females during the second mating period, the mating -- the F1B generation, and also in the second matings of

the F1A females that produced the F2B generation. And in that generation also, the low-dose animals, the 25 parts per million animals, were also significantly heavier than the control animals.

With regard to indices of female fertility, there was a statistically significant effect on fertility index in the 25 part per million group, the low-dose group. This is Table 3 in your handout.

This effect, or -- a similar effect also showed up in second matings for the F1B generation, although that did not reach statistical significance. However, there was no statistically significant effect on fertility index in the higher-dose groups in either of these matings and no effects for the matings of the second generation animals.

There was a statistically significant decrease in the percentage of pups born alive to females in the 400 parts per million group in the first mating, the mating that produced the F1A generation. And there was also reportedly a statistically significant trend for decreased percentage of pups born alive

across the dose levels. And that mating -- this effect was not reported for any of the other matings.

With regard to male fertility, there was a corresponding decrease in fertility index for males in the 25 parts per million group. I apologize for this table. I realize that the dose levels are not identified. The dose levels are in decreasing order in the table. So the top value, the 95.7 percent, is for the control animals, and the 68.2 is for 25 parts per million, and so on down the table.

So in the F-0 matings, the males, in the 25 parts per million group, were significantly less fertile which corresponds to the significant effect on female fertility. And it's probably a couple-mediated effect. So there's really no way of telling whether it's primarily male or female. And again, this effect did not show up in the higher-dose groups or the second litter.

In terms of developmental parameters, Table 5 shows information on live birth, bodyweight at birth, and apparently, postnatal bodyweight. This is up to four days

postnatal.

There was a significant effect, significant decrease in pup bodyweight at the high-dose group, 400 parts per million in the F1A generation. There was also reportedly a significant trend for decreasing birthweight across the groups, although the basis for that trend is not necessarily apparent.

In the F1B generation, there was also a significant decrease in pup birthweight at birth and significant trend for decreased birthweight across treatment groups. No significant effects on birthweight were reported in the second generation, the F2A or F2B litters.

At age 4 days postnatal, pup weights were significantly affected or significantly lower in the 400 parts per million group in the F1A and F1B litters, both pre- and post-culling to 8 pups per litter. In the F2A generation, there was a significant effect after the cull, but not prior to the cull.

There was also -- I believe there was a significant effect on number of pups born alive, but I don't believe that's reflected in

the table. Let me refer to my notes. Yes.

The mean number of pups born alive was significantly decreased in the 400 parts per million litter in the F2A generation, which is actually indicated, I believe, in the wrong place on the table. And this is somewhat consistent with the effect that decreased percentage of pups born alive in the F1A generation that was reported under indices of female reproductive toxicity.

Clinical observations were made on the pups after birth. A number of parameters were reported. The only one that was statistically significantly effected was the incidence of hematoma in pups. In the F1B generation, all of the dose groups at 25 and 100 and 400 parts per million dose groups had significantly higher incidence of hematoma in the pups. In the F2A generation, there was a significantly higher incidence of hematoma in pups in the 100 and 400 parts per million groups.

Turning to indices of male reproductive toxicity, testes weights are shown in Table 7. There were no significant effects on testes weight in any of the parental animals. One

pathological effect that was noted in the report was a single incidence of several foci of nodular hyperplasia of interstitial cells in both testes of one rat in the 400 parts per million group of the F1A generation.

Ten animals per group were assessed for pathological effects from those groups in that generation. This effect was noted to be of minimal severity, but it was pointed out in the report that this effect is not usually spontaneous in rats under one year of age.

Table 8 shows information on absolute and relative organ weights in the F2B weanlings. This was the only generation in which these parameters were assessed. A number of organs were significantly effected. Also, bodyweight was significantly effected in both male and female pups.

With regard to potential subsequent reproductive effects, the absolute weight of the testes was significantly lower in the 400 parts per million pups than in controls. And there was reported to be a statistically significant trend for decreased absolute testes weight. But bearing in mind that there

was also decreased body weight and a trend for decreased body weight, it's probably not surprising that the absolute organ weights were -- Excuse me. The relative testes weights were not decreased.

And finally, the last page is -- and this is not included in the document that you have -- but this is just a very brief summary of the effects that were noted by the study authors as being treatment related.

They considered the significant decrease in the percentage of F1A pups born alive and in the number of F2A pups born alive in the 400 parts per million group to be perhaps a minimal compound-related effect. They believed that significant and consistently lower weights of the pups in the 400 parts per million group were compound related.

And they also noted that decreased pup weights were not a secondary effect of decreased dam weights, since weights were of dams in the 400 parts per million group were comparable to those of the controls during pre-mating and gestation with the exception of the F2B litters.

And as I previously mentioned, they noted that the single incidence of nodular hyperplasia in both testes of one male rat in the 400 parts per million group was an effect that was not usually spontaneous in rats one year of age.

That concludes my presentation on that study. I'll be happy to try to answer any questions you have, but given the time we had to review the study, I'm not sure I will be able to provide all of the details.

DR. BURK: Oh. Linda. Could you please speak into the microphone? I will ask all of you to do that for the sake of our stenographer.

DR. ROBERTS: Did they describe the hematomas?

DR. DONALD: No, at least not that I could find in the report.

Okay. If there are no further questions, I'll move on to the general presentation on the HID, quizalofop.

There is a representative from DuPont in the audience, Dr. Ghantous, who may know more about the study than I do. So she might

possibly be able to answer questions.

DR. BURK: Does anyone on the Committee have any questions at this point? Well, perhaps we will later.

Maybe we should just continue with your report, Jim, and then we'll discuss everything.

DR. DONALD: Okay. Consistent with the guidance we've had from the Committee in the past, I'm only going to provide a very brief overview of the Hazard Identification Document.

Evidence on developmental reproductive toxicity of quizalofop ethyl: This document was released for review by the Committee and also public review approximately 3 months ago.

The next slide.

As has already been mentioned by Colleen Heck, quizalofop ethyl originally came under consideration for listing because of its formal identification by the U.S. Environmental Protection Agency as a chemical that caused reproductive toxicity, specifically identified testicular atrophy. So it was under consideration for male

reproductive toxicity. And subsequent to publication of a Notice of Intent to List, the chemical has been referred to this Committee because the data used by the Authoritative Body did not meet the criteria specified by the regulations.

Next slide, please.

Quizalofop ethyl is a propionic acid Ester, but the specific name I won't attempt to pronounce. And the chemical formula and molecular weight is shown.

Next slide, please.

It was formerly used as a herbicide on broadleaf crops in California, but has not been registered for use in California since 1993.

Next slide, please.

Turning to developmental -- potential Developmental effects of quizalofop ethyl, we were not able to identify any relevant human data. We're now aware of three studies in animals; one study in rabbits, two studies in rats. The rabbit studies consisted of typical developmental toxicity studies, with oral exposure on days 6 to 18 of

gestation. In this study, no adverse developmental effects were identified, and this included exposures of dams which were minimally toxic to the dams.

Next slide, please.

We have one developmental toxicity study

In rats where exposure was orally on days 6 to 15 of gestation. In this study, lower fetal survival at day 21 of gestation was reported in the highest dose tested. There was also a higher incidence of skeletal variations at the high dose and the mid dose, primarily manifested as a variation in the incidence of fourteenth rib.

Next slide, please.

Lower postnatal bodyweight and foodintake was reported in high-dose offspring between 1 -- at week 1 and 8 postnatal. And again, these were offspring that were exposed to quizalofop in utero but not postnatally. So it's lower absolute and relative uterine weight in the high-dose female offspring assessed at 8 weeks of age. And when offspring were assessed for reproductive function at age 10 weeks postnatally, there

was no indication of effect in reproductive function.

I probably should have said at the beginning that the study was conducted in two phases. Some of the animals were -- actually, some of the dams were sacrificed at age 21, and the uterine content assessed at that time. A subset of dams were allowed to deliver and rear their litter. That's why we have these two data sets from the study.

The next slide, please.

In the two-generation reproductive study which I've just described, we had a decreased percentage or number of pups born alive in the F1A and F2A high-dose litters, decreased birth weight in the high-dose litters of the F1A and F1B groups, decreased early postnatal weight in the high-dose litters in the F1A, F1B -- 2B groups.

Next slide, please.

And an increase incidence of hemangioma in all treatment groups in the F1B generation and in mid and high-dose groups in the F2A generation.

Next slide, please.

Moving on to potential female reproductive effects, again, we were unable to identify any relevant human data. In terms of animal data, we have two studies in rats, the multi-generation -- the multi-generation reproductive study I described prior to the presentation, and also the reproductive component of the study that I described under "Developmental Effects".

We also have five studies where the potential effects in reproductive organs, female reproductive organs, were assessed: Two studies in dogs, two studies in rats, one in rats -- excuse me, one in mice.

Next slide, please.

So as I mentioned earlier in the rat two-generation reproduction study, there was a significant decrease in the fertility index in low-dose dams in the F1A generation. However, there was no effect in the mid to high-dose dams in that generation, and no effect on any dose groups in other generations.

Next slide, please.

There are two subchronic studies in dogs reported in the literature. In this study,

uterine and ovarian weights varied from control values at the time points in those studies. But there were no apparent dose response relationships in those variations.

In rats, there are two studies, one subchronic and one chronic study. In neither of the studies was there any evidence of effects in female reproductive organs.

Next slide, please.

In a chronic study in mice at the end of a 38-week exposure period, uterine and ovarian weights were increased at all the doses tested. And there was also an increased incidence of ovarian hemorrhage at the high dose tested.

Next slide, please.

Finally, for male reproductive effects, again, we have no human data. And again, for animal data, we have a two-generation reproduction study and a study with exposure during organogenesis and postnatal assessment of reproductive function. And then we have five studies of potential reproductive organ effects.

Next slide, please.

In the two-generation reproduction study, there was a significant decrease in fertility index in low-dose males of the F-0 generation, and again, no effect on the high-dose males in the generation -- in that generation or in the F1A generation. And there was a single incidence of focal hyperplasia of the testis in the high-dose male, in the single high-dose male in the F1A group.

Next slide, please.

Two subchronic studies in dogs: One study was of 6-months' duration. Testicular atrophy was reported at the high dose tested. And this study provided the basis for the Authoritative Body identification of reproductive toxicity.

However, there was also a 12-month study conducted in dogs with essentially the same design as the 6-month study. In this study, there was a more comprehensive assessment of testes made, and no testicular atrophy was identified.

Next slide, please.

Two studies in rats: A 13-week study reported a very high incidence of testicular

atrophy at the end of the treatment period. A subset of animals were also alive at the 6-week recovery period. And a high incidence of testicular atrophy was reported at the end of that period.

In a 2-year study, a 104-week study, there was no testicular atrophy reported after exposure to levels of quizalofop ethyl, the maximum level of which was approximately one-third the effective dose in the earlier study.

Next slide, please.

In a chronic study in mice at the end of the 78-week exposure period, there was reportedly increased incidence of testicular atrophy, with bilateral atrophy being increased in a dose-related manner at the two highest doses, and the combined incidence of unilateral and bilateral atrophy being increased at all doses.

The next slide, please.

So to summarize briefly, the evidence for developmental toxicity of quizalofop ethyl consists of data from a developmental toxicity study in rats, exposure on days 6 to 15 of

gestation, where there was lower fetal survival and higher incidence of skeletal variations.

Next slide, please.

And also, lower postnatal bodyweight and food intake and lower absolute and relative uterine weights at age 8 weeks of age in offspring exposed prenatally to quizalofop ethyl.

Next slide, please.

In the two-generation reproduction study in rats, we have reports of decreased live births, birthweights and early postnatal weights, and an increased incidence of hemangioma in pups.

Next slide, please.

Evidence for female reproductive toxicity consists of a report of increased ovarian weights and increased incidence of ovarian hemorrhage after 78 weeks exposure in mice.

Next slide, please.

And the evidence for male reproductive toxicity consists of a certain form of testicular atrophy in dogs exposed to quizalofop ethyl for 6 months, but it was not

replicated in a 12-month study with the same exposure parameters; increased incidence of testicular atrophy in rats exposed to quizalofop ethyl for 13 weeks.

Next slide, please.

Increased incidence in testicular atrophy in mice exposed for 78 weeks and isolated decrease in fertility index in low-dose males of the F-0 generation only in -- in the F-0 generation only, and a two-generation reproduction study, and a single incidence of focal hyperplasia of the testis in an F-1 rat from a two-generation reproduction study.

And that concludes the presentation. I'd be happy to take questions at this point.

DR. BURK: Steve, question for Jim?

DR. SAMUELS: Jim, if you would turn, please, page 25 in the September handout that's Table C.1.2.9.

DR. DONALD: Um-hum.

DR. SAMUELS: In the parentheses it states that chi-square tests for percentages were carried out. Where does that data come from? Could that be --

DR. DONALD: That was taken verbatim from

the study report, but no elaboration was provided.

DR. SAMUELS: Well, if it's so, then it's an improper test, since it used the pup or the fetus as the unit of analysis instead of the dam. So I doubt if these would be statistically significant variations if the proper analysis were used.

DR. BURK: Are there any other questions for Jim at this time? I know we can always get back to you.

The next thing I think we usually do, I think, is hear public comments, if there are any. I haven't received any cards. If anyone wants to speak, they should fill out a card.

Oh. Well, we have a card. Thank you. Hanan Ghantous, representing DuPont, will speak on quizalofop ethyl up here at the podium.

DR. GHANTOUS: Thank you, Jim, for the excellent presentation and the summary.

DR. BURK: Please speak right into the microphone.

DR. GHANTOUS: First, I would just like to apologize for not sending this

multi-generation study earlier. I know we had -- this has been issued since September, but like all other agchemical companies, we have been going through reorganization. And things just fell through the cracks. So I do apologize for that.

I have just few comments. I'm not going to talk about the summaries or the studies, just a few comments on these studies, the multi-generation study.

We think that no reproductive effects were seen in the study. The NOEL was 25 ppm, and that was based on liver effects. There were no compound-related testicular effects seen, except for the foci of hyperplasia that were observed in the testes of only F1A male in the 400 ppm group, which is the highest group.

And this effect was not substantiated by decreased fertility in the 400 ppm males or decreased testicular weights or abnormal testicular pathology in any other parenatal males examined. Also, no compound-related testicular effects were observed in the two-year study conducted at the same dietary

concentrations, which was reviewed by Jim.

The U.S. EPA has reviewed this multi-generation study and concluded that perinatal toxicity occurred at the 400 ppm dose level in male rats, as evidenced by findings of decreased body weights and pre-mating body weight gain in the F-0 and F1 groups. EPA also concluded that there were no reproductive effects observed.

For the developmental effects, the rabbit and the rat studies that were reviewed, in the developmental studies, there were no effects in the rabbit study, and the weight of evidence of positive and negative effects in the rat study shows that quizolofop ethyl does not have a developmental effect in the rat.

The low uterine weight in the offspring effect at age 8 weeks in the highest dose tested dams were not seen, and they are dams administered directly with quizalofop ethyl, and were not considered to have been induced by the effect of quiz (quizalofop ethyl).

The decrease in number of fetuses alive at the time of sacrifice of the dams on day 21 of gestation in the high dose and low

bodyweight of pups in the high dose group would be due to the significantly lower bodyweight gain and heat intake of the dams in the hundred and 300 kilograms per day group at various points of gestation and lactation.

For the reproductive effects in males and females -- in assessing the reproductive toxicity on males and females, there were no effects on the ovaries or uterus in dogs, rats, or mice, other than an increase in ovarian weight in the mouse. But no other clear evident effects on the ovaries (inaudible) in the mouse. Changes in ovarian weight in dosed females occurred because of the presence of ovarian cysts and consequent trimming difficulties. There were findings of testicular atrophy in male dogs and rats at the highest concentration tested. However, other studies with longer duration and similar concentration in the dog and much longer duration with lower concentration in the rat did not show any evidence of testicular atrophy.

Testicular atrophy was seen in the mouse after exposure of 78 weeks. However, that was

seen at the highest dose, which has reached or exceeded the MTD in that study.

I would just like to remind the Committee that for listing -- for Prop 65, the criteria state that the chemical must clearly show through scientifically valid testing according to generally accepted principles to cause reproductive toxicity.

Also, the regulations require that sufficient evidence exists. Sufficient exists -- sufficient evidence is defined to mean that there is sufficient data which take into account the adequacy of experimental design, including duration of the exposure and other specified parameters indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

Weight of evidence approach will be used to evaluate the body of information available for a given chemical. To do so means that all positive and negative data will be considered.

Thank you very much.

DR. BURK: Thank you.

MS. HECK: Dr. Burk, if I could just

briefly respond to one point. The comments were made -- there was a reference to the Sufficiency of the Evidence standard in the regulation, but as I pointed out, you're not sitting directly in review of what the Authoritative Body did. OEHHA Staff have already done that and looked at the regulatory criteria. You now sit, as you always do, as a committee looking at the entire body of evidence in determining whether or not it meets the standard in the statute, the clearly-shown standard. So you're not tied to that little excerpt from the regulation as you make your deliberation.

DR. BURK: Okay. Does everyone understand that? I think so. Thank you. Are there any other -- are there any other cards? Okay. So we can not begin our discussion. For those that are new to the Committee, I won't call on you right away. That's why I agreed to be the Chair, so I could call on people.

Now, I think what I -- the only thing I wanted to say was that we generally are asked to vote at the end of our discussion on

whether we would vote to list the chemical as a developmental, male or female reproductive toxicant. So we need to discuss all three of those. So when you're discussing it, please mention which one you're referring to, if relevant.

Does anyone have any comments they want to make to start off?

Kenneth Jones?

DR. JONES: I'd just like to ask Steve, you made this comment about the significance in the skeletal examination. Could you expand that a little bit? Do you think that this is not --

DR. SAMUELS: I don't know. It may well be, but the p-value quoted is certainly not correct if the description of their test is as stated. It still looks as if there's a trend. But I can't -- we can't take their p-value, as it's going to be greater, but how much greater, I don't know.

DR. SHIONO: So the p-value is based on the number --

DR. BURK: Could you speak into the microphone?

DR. SHIONO: The p-value is based on the number of pups, not the number of litters. That's the question.

DR. JONES: Linda, could you comment on these hemangiomas? You asked about the hemangiomas just as well. I don't know how to interpret that at all.

DR. ROBERTS: The reason I asked is sometimes when a technician is removing a fetus or handling a pup, they're a little bit rough and those pups end up being (inaudible) pushing them off. And I was hoping that there would be some description that would indicate what type, generalized, related specifically to a certain part of the body that may be more indicative of a real effect.

I'm personally not real impressed with the hematoma finding as being clear evidence.

DR. JONES: Can the representative from the DuPont company tell?

DR. GHANTOUS: No. I don't know. It's not stated in the report. I mean, if this report was done these days, you know, it could be written better than that. Most of these reports were done in the early 80's. I'm

afraid that is the way those were done. They weren't that clear.

DR. ROBERTS: I've been asked to speak louder. Do I need to repeat for anyone?

Thank you.

DR. KEEN: Just to add, I agree with you. I'm not really impressed with that data. Particularly, take a look at the control value of the F-0, and notice that the controls have a very high frequency. It's not present after that, which, again, is suggestive of maybe a learning curve of technical staff as opposed to a real effect.

Also, perhaps just for a completeness of the record, Table 2, page 3, the change in bodyweight in the parental weight in the rats, if it can be corrected, I'm fairly confident that there is an error for the weights for the F-0 female gestation day, 2 day, zero 7. If that's really 4 grams, that's a rather significant effect. But I'm pretty sure it's probably 44.

DR. DONALD: Which table is that?

DR. KEEN: Table 2, the change in bodyweight grams in parental rats, the F-0

female, gestation 2 day, zero to 7.

DR. DONALD: Thank you. I think that probably is the case.

DR. JONES: How about -- how about the increase in animals with retained placenta? What's the significance of that in a rat study, if anything?

DR. ROBERTS: I'm not sure what retained placenta actually means. I'm assuming since I couldn't find -- I went up Thursday to look at some of these reports, and I'm assuming that it's an indication there was a very small early absorption. That's the best I can think of. And so I would term it as an early absorption.

Is that better?

DR. BURK: Jim?

DR. DONALD: That was our conclusion also, we looked but couldn't find any clarification in the report as to what it actually meant.

DR. ROBERTS: I want to make one other comment. We were talking about 14th ribs. And in the '83 study with quizalofop, prenatally, there seems to be a higher

incidence of 14th ribs, but they're cervical. I'm not sure -- if you turn to page 32 of what we got in September, these are the postnatal ones, and the number of skeletal variations is significantly lower with dose than the controls.

I don't know if it's -- I don't know what they're basing -- what unit they're basing the statistics on. It's just interesting finding that you see a lower incidence of that afterwards. I know that lumbar ribs, the 14th ribs, have been reported to resorb postnatally. I don't know if there's such a (inaudible) for cervical ribs or not.

DR. DONALD: Thank you, Dr. Samuels. With regard to your point, you're absolutely right. It should be 34.4.

DR. JONES: Wait a minute. 14 ribs unilateral and 14 --

DR. DONALD: No. I'm saying this with regard to bodyweight during gestation. It's Table 2 in the brief handout that you've received, page 3 of that report.

DR. BURK: Give people a chance to look; there's a lot to absorb here.

Perhaps we could discuss by male, female, and developmental, and try to come to some decision. These, again, are personal decisions, and we will take a vote. But I like to hear what people think. So maybe we'll start easier.

Does anyone want to say -- anyone want to say anything about effects on female reproductive outcomes?

DR. SAMUELS: I don't think we've had ovarian or uterine weights as an outcome. And I'm wondering what is the -- even though they are sometimes isolated, instead of a general effect on other organs, I'm not sure of their status as reproductive outcomes.

DR. BURK: Well, that's a good question. It's the question I have, because I actually went back to our criteria, you know, and looked at the various endpoints that were given in there. And there's no mention of weight specifically. That's why I'm trying to get a sense of what it really means.

DR. KEEN: I think, though, if we were talking about an endocrine disrupter, we would focus a lot on that. And certainly, the

weights of those organs are often times looked at as an indicator of some reproductive abnormality. With that said, I'm underwhelmed with the magnitude of the effects being reported in this particular study. But I -- I do think there's precedence for looking at those weights, and is routinely done with some of the endocrine disrupters.

DR. SAMUELS: I found interesting the comments of the scientist from DuPont, who mentioned that cysts were present --

DR. GHANTOUS: In the mouse study.

DR. BURK: All right. What about the male reproductive toxicity? I think that one was the basis for the original TRI identification. What do people make of --

Oh. Go ahead, Linda.

DR. ROBERTS: Just to follow up on the cysts, what we were mailed in September on pages 54 and 55, it doesn't look, at least in glancing over it for the dose response that it would be -- because there's some big cysts there -- that it would be response for (inaudible).

DR. GHANTOUS: In that report -- In the

mouse study, the authors actually do say that in the report, they had problems with the weight because of the cysts, also because of the trimming of these ovaries and weighing them. And I mean, you're all scientists, and you know how difficult that is to do in the lab. And I think that, that's one of the problems with the weight in the ovaries.

DR. BURK: Okay. Does anyone want to say anything about the testicular atrophy findings?

DR. MILLER: I'd like to address those.

DR. BURK: Thank you, Marion.

DR. MILLER: I was.

DR. BURK: If other people -- I'd like to hear other comments as well.

DR. MILLER: I was not particularly impressed by the data in that we seem to see often times a lack of dose response relationships. And when we don't see those relationships often, you do wonder whether or not those really are related to the chemical. So that was an overall impression I had from reviewing much of this data.

But to specifically address the fine

point, I think, Jim brought up, and ones that were relevant in evaluating whether or not there was male reproductive toxicity, the dog studies, where we had a 6-month exposure and 12-month exposure at the same dose level, and the 12-month exposure showed no evidence of testicular atrophy, with the 6-month exposure only showing two animals, to me, you know, with the likelihood of some random event associated with testicular changes, I did not view that evidence as great, strong evidence to support a male reproductive effect.

And to get through the next (inaudible), they're reasonably easy -- or, the increased incidence of testicular atrophy in mice exposed for 78 weeks, again, I was not hugely impressed by that.

When you have a unilateral atrophy, that really does not suggest a chemical relationship in that you've got one testes exposed. You've also got the other testes exposed. And there really seems to be a very high incidence of unilateral atrophy. And I think that those were also -- could be associated with some bilateral atrophies to

also be spontaneous in nature.

And I know that rodents are classically -- have been increasingly difficult to do the male repro studies. In fact, we were discussing a few years ago that they were saying 20-plus percent incidence of testicular histopathology in normal animals. So I really do have some considerations when you don't see dose response relationships, and you're basing things on one or two animals that have got a little bit more bilateral atrophy.

DR. SHIONO: What do you think about the -- even though there's maybe not a dose response relationship in the independent, individual studies, what do you think about the cross-species, so it's showing up in dogs and rats and mice? It looks relatively consistent to me, even though it may be sort of spotty.

DR. MILLER: This is where I would be going with the rat study. And the rat study is the one where I see real evidence to support testicular damage, where I don't have to raise questions about, "Oh. I'd like to see more animals to be sure that this is

clearly shown".

The rat study, which was done at the substantially higher level, the 1280 ppm, and that the difference in this one from the other studies in that those were carried out of 400 ppm's, where the difficulty of clearly showing a response may indeed be at a marginal level is probably more difficult.

So at 1280, the twelve hundred and eighty parts per million, there really was an increased incidence of testicular atrophy in the rats at close to 13 weeks, and no doubt that spermatogenesis was effected in these animals, even though there was relatively small numbers. It was five. And there was some indication that it was dose-related as well.

So to me, there's the strongest evidence for testicular atrophy at that dose level. It's a very high dose level. I'd like other people to perhaps comment on that. Liver weights were increased. And there's no indication of any histopathology, so the animals were not behaving clinically (inaudible). And so that would suggest that

that would have a specific effect on the male reproductive system.

I was kind of interested -- I should have thought this in my review study, but this is a peroxisomal proliferator. There are known peroxisomal proliferators. And if I remember rightly in the literature, that the peroxisomal proliferation -- I hate that word -- has been associated with -- peroxisomal proliferation exposure has been associated with (inaudible)-cell hyperplasia. And we have that one animal showing up.

It was in interstitial-cell hyperplasia?

DR. DONALD: Yes.

DR. MILLER: Any other comments?

DR. BURK: Thank you very much. It's nice to hear from someone that really knows the male very well.

Any other discussion about the male effects? Shall we talk about the possible developmental effects? We started already, but does anyone want to say anything else about developmental toxicity?

I know Linda, you've sort of, and Steve, dismissed a few of the things as perhaps --

DR. SAMUELS: Not dismissed.

DR. BURK: Not dismissed, but questioned, perhaps. Maybe that's fair. I shouldn't say dismissed. But are any of these endpoints very clear to you, say, or strong?

DR. KEEN: I would certainly argue they're not. You know, I'm underwhelmed with any data that argues strong reproductive effects. The modest changes which are seen, I suspect could be attributed in some cases to simple food intake reduction. The data, unfortunately, are not given in such a manner that it's easy to interpret what was really going on. That's a bit of a problem. But still, they're very modest effects, if any.

DR. SHIONO: And what about the malformations, things going on with the ribs? Do you still see that as --

DR. KEEN: Well, the skeletal abnormalities -- I would classify them as abnormalities as opposed to malformations -- are really quite minor, and ones which typically in our group we would not necessarily dismiss, but would be underwhelmed by what I see in this particular report.

DR. SHIONO: Minor because they're not life-threatening or minor --

DR. KEEN: Oh. Because if you look at enough control animals, you see often times the same set of variations. So the frequencies here are not particularly profound.

DR. SHIONO: They do have a control group, right? So if we were going to see this (inaudible), we'd see it in the control group.

DR. KEEN: Well, the frequencies which are being reported are not unusual to see in control groups. That's where -- again, it's difficult to kind of figure out exactly what they looked at.

And one thing that's a concern: In many of these analysis, they looked at a relatively small number of fetuses. They -- what the basis was for selecting the ones that were examined is not clear. It's not clear to me.

DR. ROBERTS: If I can make a couple of comments about the study. On page 18 and 19, we have the rabbit. And the rabbit, in my mind at least, is pretty clear -- clean, I should say, of effects. If you look down on

Table C.1.2.2, at the number of variations that are given there, in rabbits, basically, you have 12 or 13 ribs.

Both cases are normal. Both cases are both seen in normal rabbits. And it's more a matter of whether or not there's a shift between 12 and 13. That's considered to perhaps be an indication.

In this particular case, if you look at it, it would be 98.4 having 12 ribs, I believe, if I'm looking at it correctly down the table, and 98.5 having 12 ribs in the high-dose group. It's not an indication.

In the next page, page 19, if you look at malformation, there's no trend. And there's as much seen in the control and the low-dose group as there is in the higher doses.

Going on to page 23, where we have the retained placenta, it's -- I agree with Carl. These are not effects that jump out. These are effects that are a little difficult. We -- I usually look at them as the historical control range that a laboratory has. I would expect that if there's a real effect that there would be a more, a bigger difference

between the control group and the high-dose group.

DR. SAMUELS: And the retained placenta statistic has the same defect as the percent of the (inaudible) variation.

DR. ROBERTS: That would be my guess. Yeah.

DR. BURK: Is there any other discussion?

DR. ROBERTS: One last question, Dr. Ghantous. I notice that this was conducted as (inaudible) experimental medical research. Was this report a translation of the report, the original report in Japanese?

DR. GHANTOUS: I don't know. It was before my time.

DR. ROBERTS: I thought that might explain --

DR. GHANTOUS: It could have, yeah. It could have very well been.

DR. ROBERTS: I -- Okay. I did once come across a finding that there was a statistically significant increase fetuses with umbilical cords. And I knew it had to be something --

DR. SAMUELS: I just want -- I have one

more question, and Marion has already started to address it. Is it our impression, or is it the impression of the people who are more knowledgable than me that the, that with the -- that the highest dose in these studies was a dose of excessive toxicity or not, since that plays a role in our judgement, since that seems to be where the effects were generally found, even the sporadic atrophy effects?

DR. MILLER: I did go and look and see (inaudible). There is no indication of the animals under huge duress.

The bodyweights were less, so -- the bodyweights were obviously less, but there were not huge drops in bodyweight in either of the chemicals we're reviewing today. They are less over the time period of studies, but it's not a dramatic loss of bodyweight. And the lack of recovery after the 6 weeks, and the withdrawal of the compound is also of concern.

And the most dramatic effect systemically, I think, was the increase in liver weight, which would be associated -- which a peroxisomal proliferator could cause without necessarily really markedly altering

liver function. Just because there's enlargement, that doesn't mean to say it's not performing.

DR. BURK: Any other comments?

DR. KLONOFF-COHEN: I have a question about the male.

DR. BURK: Fine. Anything. Anything at all.

DR. KLONOFF-COHEN: I'm still trying to sort out the testicular atrophy. And you had mentioned, Dr. Miller, about the mouse study, and I'm finding that it looked like -- at the beginning in the summary, it says that it's actually bilateral testicular atrophy. Is it further on it says unilateral?

DR. MILLER: If you look in the table, there's a large "A", unilateral testicular atrophy as well as bilateral, which really (inaudible) my confidence in the bilateral (inaudible).

DR. KLONOFF-COHEN: I guess I'm having difficulty -- how do you extrapolate the findings in terms of -- it's difficult when you look through the studies.

One study says there is no effect. The

next study says that there is an effect. I mean, when you're looking at these dosages, and you're knowing they're forming with a herbicide, what dosages are relevant in terms of for humans and in terms of route? Like, because these -- these animals are being fed pesticides versus humans. How do we make heads or tails --

DR. MILLER: Maybe Joan or Dorothy could address this, but my impression is the toxic (inaudible) we really don't consider exposure.

DR. BURK: Yes. I know. And this is something we all went through, particularly at the beginning, that our job is basically the hazard identification stage. And we look for sufficient evidence. But there's further -- trusted -- further steps where the dose-response portion of the risk assessment would be considered.

And the -- of course, the statute automatically applies a thousand-fold safety factor to the NOEL. But what I'm saying is that there will be further interpretation of the risk beyond our step in the process. You know, is that a fair thing to say?

DR. KLONOFF-COHEN: A second question about controls. It sounds like for these particular studies, we're talking about a control group, and we'll say there's a statistically significant relationship going on here. And then somebody else will say that this is reasonable because looking at historical controls in a lab, you would expect this. So I guess in research you would usually -- if you're having two different control groups, you would have the results comparing the control group of the animals they have. And then if you were talking about historical controls, they would look at historical controls and they would compare it that way. I'm just wondering in terms of are we reading more into the data than is actually here or -- I'm just sorting that question out.

DR. ROBERTS: When I look at the full report, they usually have the historical control data right there with it. And I expect them to evaluate that, particularly if there's something that is not statistically significant but looks like a trend, looks like it might be biologically significant.

I went up on Thursday to look at some of these reports. And the OEHHA staff did a wonderful job trying to make these things intelligible to us. Most -- not all, but a good number of the reports for both of these materials were not containing all of the information that we would look for. And I don't recall some of these having historical control information.

DR. GHANTOUS: Can I add something?

DR. BURK: You have to come up. Sorry.

DR. GHANTOUS: Most of these studies that the DART Committee or Dr. Jim looked at, they are chronic and subchronic studies. But if you look at the historical control, usually the data that is available is tumors. And you're not going to find testes or weight of testes or anything, you know, available.

We really have to go back to the lab and dig that information out to be able to compare it, because I tried also to take the historical control and look at it. If it was a multi-generation study, you will find that historical control, not with these studies.

And another thing, if I can answer your

first question, this compound is an herbicide. It is used in very, very small quantities. The highest concentration used is around 8 ounces per acre. And the reference dose that EPA agreed to when this was registered is 0.009 milligrams per kilogram per day. And that came from the 2-year rat study.

DR. KEEN: Just a comment again. It's frustrating when you have sometimes data which is not presented in the best of ways. I look at that 1280 parts per million dose range, which proves there is an effect on testes weight.

It's also clear that there is a huge effect on food intake over that 13-week period. And there's a 25 percent difference of bodyweight gain. And it would be -- I would not be surprised if the majority of that food intake reduction was not spread out equally over the 13 weeks, but probably occurred over the first several weeks of treatment.

At least in our own lab, we do work similar to this at the control, where we use para-fed animals. And we'll see marked

effects on testes. It would not be unusual in severely food-restricted animals to see this much of a reduction in testes weights.

I'm still left with the sense that much of what we're seeing is an indirect effect due to probably pronounced reductions of food intake, if I'm interpreting Table C.3.2.6 correctly.

DR. MILLER: The Table C.3.2.6, they lost about one-third of their bodyweight over the 13-week time period.

DR. KEEN: Right. And my suspicion is that that was not equally spaced. Typically, if you have a really noxious compound in the diet, that food intake will drop to almost zero for a period of a few weeks. And that's when you'll really have the most profound effects.

So again, the data are unfortunately are not being given to us in a way to interpret that. If I saw that, I would say that these are really much more indicative of just severe toxicity that may be a general effect as opposed to a specific effect of the compound.

DR. MILLER: I think this is an important

point of discussion. And I don't know whether we can really have a clear conclusion, unfortunately, if you don't see those precipitous drops in weight gain. Because as you know, with the Chapin study, he can deprive food for 75 percent, which isn't far away from 67 percent, and just see relative changes in testes size compared to bodyweight.

So unless you know something about the overall health for the duration of the 13-week experiment --

DR. KEEN: Absolutely. In any situation the data, though, which are shown, C.3.2.5, which are just total weights, should be corrected, certainly the bodyweight is, because you just immediately get rid of 25 percent of your difference. I mean it's just not well-presented information.

DR. JONES: I must say the issue, however, that is intriguing to me is the thing that Marion brought up about biological plausibility as it relates to this.

DR. KEEN: I think the liver weight data makes a lot of sense. It looks like the peroxisome proliferator, my guess, is

(inaudible). That that necessarily will translate into direct effect on the testes, I don't know. I would tend to think it would be confined in the liver.

DR. MILLER: And OEHHA -- the report that I'm aware of reported testicular effects of peroxisomal proliferators (inaudible). So that's not general atrophy.

DR. JONES: So it's different than what we've got?

DR. MILLER: It's potentially the same as that one animal.

DR. JONES: Okay. Okay.

DR. BURK: Any other comments? Questions?

Before we take a vote, I do want to formally thank Jim and the staff for preparing the report. So even though, you know, we know how difficult it is to do this, I have to say you did a beautiful job of summarizing the available studies for us.

All right. What I'm going to do then -- and this is for the record -- I will ask by a show of hands your opinion on quizolofop ethyl for each of the three endpoints, developmental

toxicity, female, and male. And I'll go in that order. Okay?

Please indicate by a show of hands if in your opinion quizolofop ethyl has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity.

How many say yes? Zero. So I'm assuming everyone is saying no. Okay. So the record should reflect zero votes were cast to add quizolofop ethyl to the Prop 65 list as causing developmental toxicity.

All right. Please indicate by a show of hands if in your opinion quizolofop ethyl has been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity.

A show of hands? Okay. The record should reflect zero votes were cast to add quizolofop ethyl to the Proposition 65 list as causing female reproductive toxicity.

Okay. Finally. Please indicate by a show of hands if in your opinion quizolofop ethyl has been clearly shown through

scientifically valid testing according to generally accepted principles to cause male reproductive toxicity.

1, 2, 3. Okay. 7. The record should reflect 7 votes were cast to add quizolofop ethyl to the Proposition 65 list as causing male reproductive toxicity.

Okay. A majority of the nine-appointed members is required to add a chemical to the list. Accordingly, quizolofop ethyl is added to the Proposition 65 list.

Okay. Shall we go on? All right. Let me ask you. We have a choice now. We can proceed on to the next chemical or -- which we predict will take a little longer than, than -- Joan predicts it will take a little longer -- or we can take a break now and start again after lunch. Any strong feelings one way or the other?

DR. JONES: Keep going.

DR. BURK: We'll keep going. All right.

UNIDENTIFIED AUDIENCE MEMBER: Can we get a five-minute break?

DR. BURK: All right. How about -- that's a very good compromise. Let's have a

five-minute break.

(Whereupon a five-minute break was taken.)

DR. BURK: Okay. If everyone would be seated, we'll get started again.

The next chemical up for consideration is fenbutatin oxide. I wasn't sure which syllable to stress, but I'm stressing the "tin" part. And first, we'll have a staff presentation by Dr. Jim Morgan.

DR. MORGAN: Good morning. I'm Jim Morgan, a toxicologist with RCHAS, and I will be presenting a brief overview of the evidence on fenbutatin oxide.

As you know, fenbutatin oxide is coming before the Committee today because it dropped out of the administrative listing process. It should be noted that a much larger body of data is being presented to the DART Committee than was reviewed by the U.S. EPA.

Next slide.

Fenbutatin oxide is a relatively large, organotin pesticide. It's insoluble in water, but somewhat soluble in aromatic solvents. It is used as a miticide on some food crops and

flowers. It is poorly absorbed orally, and is low oral acute toxicity. The typical endpoint observed in chronic studies is reduced bodyweight.

Next slide.

Turning to studies with possible evidence of developmental effects, we were unable to find any human data. There are several industry-sponsored studies, some dating from the early 1970's. There's -- are one rat developmental study, three rabbit developmental studies, and two rat reproductive studies.

Next slide.

In the rat developmental study, there were reductions of pregnancies at mid and high doses. And this effect was statistically significant at mid dose, and marginally significant at the high dose. Pre-Implantation losses were elevated at the low dose and the high dose, but not the mid dose. And the effect was statistically significant only at the high dose. There was no effect on litter size.

Additional considerations about this

study are that implantation in rats occurs on gestation days 5 to 6, and treatment started on day 6. Also, there was no dose response of pregnancies or the mean pre-implantation losses.

And finally, there were a number of animals with "negative" pre-implant losses, which is to say, more implants than corpora lutea counted.

Next slide, please.

There were two studies performed in Dutch rabbits. Both of these studies used only two dose levels, and had a considerable number of maternal deaths, which apparently were randomly distributed. In some cases, up to 15 percent of individual groups had maternal deaths.

In the first study, Study A, there were increases in resorptions plus early fetal deaths at the low dose and increases in major abnormalities also at the low dose, but neither of those endpoints was elevated at the high dose.

Considerations for this study are that there is a lack of dose response for those two

endpoints. Also, there was a lack of statistical analysis by the authors for those endpoints.

Next slide, please.

The second study was performed because of the difficulty in interpreting the results of the first study, Study A. In the second study, there was an increase in resorptions plus early fetal deaths, which was small, but dose related. There were no increases in major abnormalities.

Again, additional consideration is that no statistical analysis was performed of the endpoint.

Next slide.

This is a later study by the same laboratory performed in New Zealand white rabbits and using three doses of fenbutatin oxide. In the high dose, there were increased maternal deaths, with 5 out of 23 animal dying, statistically significant reductions in maternal weight, increased abortions with 60 percent of the animals aborting, also significant, and increased pre-implantation loss, which was not statistically significant;

and as a consequence of all of those, a reduced number of litters with live fetuses, statistically significant.

At the mid dose, there were some maternal deaths, with 2 out of 18 animals dying, and an increase in post-implantation losses, which was not statistically significant. Maternal deaths also occurred in the control group, with 2 out of 18 animals dying, but not in the low dose of fenbutatin oxide, nor in the thalidomide-positive control group.

Next slide.

The earlier rat reproduction study used three generations with two litters per generation. There is a small but consistent reduction in litter size at the high dose. This effect was statistically significant only for one litter out of 6, the F1B litter.

There's also a significantly reduced postnatal survival at the high dose in both litters of the third generation. And there was reduced postnatal weight at day 21 at the high dose, which was statistically significant for 5 out of 6 litters. Finally, there was reduced parental weight at the high dose for

all generations.

Additional considerations here are that a later rat reproduction study, which used a higher concentration of fenbutatin oxide did not find a reduction in the litter size. Also, since exposure began before the developmental period, results could potentially be described as developmental, female reproductive, or to a limited extent, male reproductive effects. And finally, the pups may have been exposed postnatally via the milk or via the food.

Next slide, please.

The later rat reproduction study, two generations, with one litter per generation were used. Again, the dose or the concentration of this study was somewhat higher than in the earlier study. The main effect seen was reduced, postnatal weight gain, which was statistically significant at the high dose in both generations. Also, reduced parental weight again statistically significant; again, in both generations.

Additional considerations, as with the previous study: Exposure began prior to the

developmental period, and the pups may have been exposed postnatally.

Next slide.

Turning now to possible evidence for female reproductive effects, no human data were located. There were the two-rat reproductive toxicity studies, three rat acute inhalation studies, and rat, mouse, and dog chronic oral studies. I've already covered the rat reproduction studies and will not repeat the data, as the endpoints could potentially be attributed to female reproductive endpoints.

Next slide, please.

No effects on fertility were seen in either of these rat reproduction studies. Examination of tissues from the rat from the acute and chronic studies found no gross or histopathological effects on ovaries or other female reproductive organs.

Next slide, please.

Turning now to possible evidence for male reproductive toxicity; again, no human data were found, and the two rat reproductive studies, a mouse-dominant lethal study, and

acute and subchronic studies from rats and chronic studies in rats and mice and dogs.

I already covered the rat reproduction studies. The slight reduction in litter size in the first rat reproduction study could possibly be attributed to a male dominant lethal-type effects. However, again, there was no reduction in litter size in the second rat study.

Next slide, please.

The mouse-dominant lethal study used two doses. Treated males were mated with untreated females for 1 week. And then matings were performed again each week for 8 weeks. Females were sacrificed on gestation day 13. There were no dominant lethal effects found; i.e., that there were no effects on number of pregnancies or pre or post-implantation losses.

An additional consideration with this study, however, is that it's not clear if a systemically toxic dose was used.

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There were no effects on fertility in either of the rat reproduction studies or the

mouse-dominant lethal study. An examination of tissues found no gross or histopathological effects on testes or other male reproductive organs in any of these studies.

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There were, however, some indications of testicular weight effects in the rat studies. Now, I've tried to summarize this in a way to, to weed through all these studies. There's so many of them, if we just went through them, it would be difficult to follow.

Among animals exposed when mature, there are inconsistent observations of increased testes weight. In the 1-month study and in the chronic study with terminal sacrifice at 24 months, there were both increases in testes weight. However, there were not, were not increases in testes weight at the interim sacrifices of the chronic study at 3, 6, or 12 months. And there was no increase in testes weight in the P-1 generation of the two-generation rat reproductive study.

Additional considerations for these studies are that reduced bodyweight was found in all studies. A 15-week food restriction

study performed by Chapin et al, 1993, where animals were reduced to 90 percent, 80 percent, or 70 percent of their control bodyweight, found that in general, there was no effect on absolute testes weight, but that relative testes weights were increased due to reduced bodyweight.

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In studies where there was perinatal exposure of the animals, there was indications of reduction in testes weights. Specifically, in the three-generation study, there were the absolute and relative testes weights of F3b weanlings, reduced at the mid and high concentrations. And also, in the two-generation study, the absolute testes weights of the F1 males were reduced. However, the relative testes weights were increased.

Additional considerations: Again, we had reduced bodyweight at the high concentration in both of these studies.

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So to briefly summarize the developmental data, in the rat developmental study, there

were reduced pregnancies and increased pre-implantation losses. In three rabbit developmental studies, there were increased post-implantation losses, together with considerable numbers of maternal deaths, both random and dose related.

In the rat, three-generation study, there was reduced litter size, reduced postnatal growth and reduced postnatal survival, together with reduced parental weight. And in the rat two-generation study, there was reduced postnatal growth, together with reduced parental weight.

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To briefly summarize the female repro data, in the rat three-generation study, we had reduced litter size, reduced postnatal growth, and reduced postnatal survival, together with reduced parental weight. In the rat two-generation study, there was reduced postnatal growth, together with reduced parental weight. Several studies in the rat, mouse, and dog found no ovarian gross or histopathology.

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The male reproductive data: In the rat three-generation study, there was no effect on fertility, but there was reduced litter size, together with reduced parental weight. In the two-generation study, there was no effect on fertility or litter size, but there was reduced parental weight.

The mouse-dominant lethal study found no dominant lethal effects; that is to say, no effect on fertility or pre or post-implantation losses. Several studies in rat and mouse and dog found no testicular gross or histopathology.

The rat testes weight effects in mature animals: There were inconsistent increases in absolute testes weight. And in perinatally treated animals, there were some indications of reduced testes weight.

That concludes my presentation. And I'd be glad to respond to questions at this time.

DR. BURK: Thank you, Jim.

Does anyone on the Committee have a question for Jim? Are there any cards?

Oh. Where are they? Well, we're pretty sure -- Did you put in a card, Gina? Well,

I'll find it. It's here somewhere. But come on up.

All right. Gina Solomon. Here it is. I found it. Thank you.

DR. MILLER: Before Gina starts, can I ask a question of the Chair?

I think we need to consider the postnatal effects of this compound or not consider them. We need to clarify whether or not those are part of our items of consideration today.

DR. BURK: Okay. I think Colleen can speak to that. This is really a legal matter to some extent.

MS. HECK: Thank you, Dr. Burk. The position of OEHHA, through previous house council and concurrence of the Office of the Attorney General is that effects that result from postnatal exposures are not properly within the ambit of Proposition 65 or the Committee.

Certainly, postnatal effects that result from prenatal exposures are well within your purview. The difficulty comes when there are exposures that are both pre and postnatal, sorting that out.

If it is the determination of the Committee that it can conclude that the effect would have been the same solely from a prenatal exposure, it could proceed to list. That's a scientific determination. But it is our legal opinion that it is not the intent of the drafters to cover postnatal exposures.

So I don't know if that clarifies or answers your question, Dr. Miller.

DR. BURK: Does that answer your question, Marion?

Does everyone understand? This is basically a legal interpretation --

MS. HECK: That's correct.

DR. BURK: -- not our scientific interpretation.

DR. BURK: Okay. Gina Solomon.

DR. SOLOMON: Yes. Thank you. My name is Gina Solomon. I'm a physician and senior scientist with the Natural Resources Defense Council in San Francisco. And I'm actually -- that was a very apropos question, because I am here to speak on this postnatal issue.

Fenbutatin oxide is -- has implications and significance that touch on how the

Committee and OEHHA will be dealing with postnatal exposures or situations in which it is not completely clear whether the exposures that caused an effect were in the prenatal or immediate postnatal period. And that's the exact point at issue here.

And my -- what I'd like to just do today is briefly go over some of the history of this issue for the new members of the Committee -- I'll make it very brief -- and then briefly mention why NRDC and the Environmental Defense Fund have disagreed with OEHHA's current interpretation, and what we are hoping that you might do about that, and then also point out how OEHHA's determination in the case of fenbutatin oxide may not even comply with OEHHA's own current interpretation of the postnatal issue.

Briefly, the main reason cited by OEHHA for not listing this chemical under the Authoritative Bodies mechanism was that, "treatment of the dams continued postnatally"-- I'm quoting here -- "the relevant exposures may have occurred via nursing or even from direct consumption of the

dams feed by the pups.

As currently interpreted, the Proposition 65 statute precludes listing on the basis of developmental effects resulting solely from postnatal exposures".

What has happened in the past on this issue, back in May 1994, a question arose at a DART Identification Committee meeting about whether effects that stem from postnatal exposures such as in infancy or lactation should be included under the purview of Prop 65 or are included in the purview.

That was discussed at the DART Committee meeting in more detail. And in April 1995, that was when environmental tobacco smoke came up for consideration. At that meeting, the OEHHA Chief Counsel at the time, Bill Soo Hoo, sought the advise of the DART Identification Committee about whether the terms "reproductive toxicity" or "birth defects or other reproductive harm" are broad enough to include postnatal effects.

At that time, it was considered an issue that might be appropriately resolved by the scientists. And that issue, of course, was

Sudden Infant Death Syndrome from environmental tobacco smoke. In that context, the OEHHA scientific staff prepared a memo which outlined the fact that reproductive toxicity is widely recognized to include developmental toxicity and that numerous authoritative bodies and other well-recognized sources agreed that developmental toxicity encompasses the postnatal period.

The records of that DART Committee meeting indicate that there was a fair -- it appeared that there was fair agreement that the postnatal period should be considered to be -- come up in the rubric of developmental toxicity. But no votes were taken at that time.

The agreement was to have a workshop on the issue. The workshop did not occur. And instead, in December '96, Mr. Soo Hoo presented a legal opinion to the Committee saying that a workshop was not needed. He presented the opinion that postnatal exposures are not encompassed by Proposition 65.

His main citations were to informal discussions with a prior OEHHA director and a

prior OEHHA chief counsel. He does, however -- and you should know this -- state that the statute -- this is a quote -- "the statute grants the DART Committee broad authority and it is free to consider all scientifically valid data, including postnatal effects".

In June 1997, Mr. Soo Hoo wrote a letter clarifying his December statement in response to questions from some members of the public. And in that letter, he emphasizes that "we believe there to be no restrictions on the ability of the DART Committee to consider any and all evidence it considers to be relevant and consistent with sound science in determining whether a chemical has been clearly shown to cause reproductive toxicity".

He also says that the -- that he's -- Oh. He also re-emphasize that the DART Committee is free to consider any and all information that it determines relevant. And then the last part of the sentence is very important. It said, "including revising these criteria, if it so chooses".

It is the opinion of the attorneys and the scientists at NRDC and the Environmental

Defense Fund that the Soo Hoo interpretation, which is also theoretically the current OEHHA interpretation, is flawed, both legally and scientifically.

In particular, the statute uses the key term "reproductive toxicity". And in the statutory language, it's quite clear that in issues relating to how this term should be defined or what should be considered to be a reproductive toxicant, there are two, two points of deference, two places that the statute refers. It refers to "generally accepted scientific principles" and it refers to the "State's qualified experts".

You are the State's qualified experts, and therefore, should be one of the key points of ultimate authority for whether postnatal exposure should be considered under the rubric of reproductive toxicity.

And with regard to "generally accepted scientific principles", I just wanted to point out that the Environmental Protection Agency, Food and Drug Administration, the National Institutes of Occupational Safety and Health, the National Toxicology Program, European

Union, and International Life Sciences Institute have all developed fairly similar scientific policies on this matter.

And all of these bodies consider developmental toxicity to be a component of reproductive toxicity. And all of these bodies define developmental toxicity in ways that are very similar and that include exposures during the postnatal period up until the time of sexual maturity.

The U.S. EPA definition defines developmental toxicity as "adverse effects on the developing organism that may result from exposure prior to conception, either parent" -- in parentheses -- "during prenatal development or postnatally to the time of sexual maturation".

So as a result, this is something where we are respectfully requesting that OEHHA submit its troubled interpretation of the postnatal issue to you, the State's qualified experts, to review the generally accepted scientific principles. And that this is not a -- something that has been resolved legally, despite what, what some others might tell you.

The current relevance to fenbutatin oxide is basically this: There's six chemicals that were listed by U.S. EPA under the Toxics Release Inventory, all of which are caught up in this inconsistency. These six chemicals are fenbutatin oxide, fenoxycarb, dimethoate, tebuthiuron, naled, and sodium nitrite.

Not all of these will be coming before your committee, because some of them were stopped before they even got to the Notice of Intent To List phase, just after the data call-in. So you will unfortunately not get a chance to grapple with all of this issue with regard to all the chemicals.

But the problem here is that OEHHA is explicitly instructed to give broad authority to an authoritative body, in this case, U.S. EPA. U.S. EPA was designated by this Committee as an Authoritative Body with no restrictions. In other words, the Committee did not say, "Yes, EPA is authoritative except in the cases where they looked at postnatal issues".

And in multi-generational studies, as we all know, if a health effect is subtle, if a

health effect is delayed or is not immediately apparent at birth, it may often be unclear whether that actually stemmed from a prenatal or postnatal exposure. And in that situation, where do we put the benefit of the doubt? And that's the issue here.

What OEHHA has currently done under its, under what I think is going beyond its current interpretation, is it said, "If there's a shadow of a doubt about whether the exposure was prenatal or postnatal, the result of this health effect, we won't even look at it. We'll close our eyes and turn away, because it might have been a postnatal exposure".

And that is putting the complete burden of proof on showing that the effect appeared immediately at birth and was clearly due to prenatal exposures. And that is actually even going beyond the Soo Hoo interpretation and Soo Hoo memo.

And so -- and of course, you know, Soo Hoo spoke to this directly when he emphatically allowed the DART Identification Committee to consider postnatal exposures. Presumably, EPA is allowed to consider

postnatal exposures when they appear to be relevant to the decision at hand.

So what I am urging you to do is consider fenbutatin oxide on its own merits, including the results of the Hines Laboratory -- Hine Laboratory study, the DuPont study, in both cases, where there was some question about whether the exposures of concern were postnatal; consider in its totality may it rise or fall on the totality of the evidence.

But in addition, I'm asking the Committee to go a step further and discuss this issue, bring it up and say if you believe that the current OEHHA interpretation is not consistent with sound science or with generally accepted scientific principles, ask again to have a workshop.

Ask again to reconsider this interpretation, because I can guarantee you, it will come up again, and it will be a stumbling block over and over again as we deal with questions about listing chemicals, particularly that have undergone multi-generation studies where they have subtle and delayed health effects that appear

not immediately after birth.

Thanks very much.

DR. BURK: Thank you. Are there any questions for Gina before she sits down? I guess not. Okay. Thank you very much. Joan?

DR. DENTON: For the benefit of the new members of the Committee, this is a -- this issue has a long history to it. And in prior discussions before this Committee, at least in my reading of the transcript, there was quite a bit of discussion of scientifically what is the definition of "developmental".

The problem is that, that this item is where you have the clash of legal interpretation and science. And I don't know that there's any easy -- there isn't. There's no easy resolution to something where there's a legal interpretation, but as scientists, we may feel one way. But there's a legal interpretation which can supersede that.

But regardless of that, since those discussions were held in the mid '90's, nothing has, nothing different has happened, I guess, that would alter OEHHA's legal interpretation of what the intent of the

proposition is regarding developmental and birth defects. So there's, there's nothing new there.

If the Committee obviously wants to reopen the issue and discuss it, then we will certainly provide the technical support that's needed. And so the request is to you as a Committee. But again, it's a, it's a clash of science and legal interpretation.

And I think that the cards are pretty clear that OEHHA would respond from the legal perspective that we have, as Colleen elucidated, regarding what we see, and the AG's Office see as the legal definition of developmental toxicity.

DR. BURK: Are there any comments or questions from the Committee?

DR. JONES: Yeah.

DR. BURK: Ken?

DR. JONES: I forget exactly what the issue was about the environmental cigarette smoke, but it's my recollection that it was environmental cigarette smoke that the mother was exposed to prior to delivery as opposed to post -- environmental cigarette smoke that the

baby was exposed to after birth. Am I correct or -- am I incorrect as far as this Committee?

DR. SAMUELS: I remember the discussion, since I certainly voted in favor of it. And the epidemiology of it, as Ken was -- the postnatal exposure to the infant. But there was and may still in the future be animal evidence of prenatal exposure affecting lung function.

And certainly, we could not separate out postnatal exposure of the infant from prenatal exposure of the mother. And I didn't consider them different. But it was not exposure of the mother postnatally, it was exposure of the infant.

DR. JONES: Okay.

DR. BURK: Any other comments? Well, we have another speaker from the audience.

DR. LI: I'm Ling-Hong Li. I'm a new member of OEHHA, but today I'm here as a member of the audience. I'm just sitting in to listen and get myself formalized with the process.

Talking about development and repro, I just want to remind the audience and the

experts that, remember, the postnatal or prenatal, if you are talking about the development of the male repro, which I have worked with for more than 10 years.

Almost the whole male reproductive system, except for the testes, barely start to develop after birth. Talking about the epididymis, from the scientific point of review, the epididymis, all those cell types, organs, prostate, really start to develop after birth. That's just my personal view, just science, just the truth.

I'm just reminding you of the difference in organs in their developmental period. When we think about the male reproductive system, we have to include the first two weeks after birth in rats. In humans, it's up to 20 years old. That's my comment on the issue.

DR. BURK: Thank you. Carl?

DR. KEEN: I certainly understand the position of the last two speakers. I also felt -- feel that our hands are a bit tied. I mean, we have a legal interpretation which has been issued to us. And it seems to me that with some regards, we should operate under

those guidelines. If we're not going to, then we should first off convene a workshop so we have well-defined criteria.

I for one, as much as I look at postnatal development, I agree, there's developmental effects. But we cannot be so open-ended. For example, to suddenly say, "Well, exposure is up to the age of 20", is exactly the problem, I think, we're faced. We have to say, "No. Where are we going to draw the lines for the purposes of this particular committee?"

And that's what the initial workshop was supposed to do that we -- I recall we all asked to be convened, and for various reasons, it was not held, and I think it was because there was an interpretation. If we're back at that crossroads, I would urge us to again have a workshop, come to a conclusion, and put this to rest, because otherwise, I feel very strongly that we should operate under the guidelines that we're given and not just kind of make them up on the fly. I think that's inappropriate.

DR. DONALD: Can I just add one brief augmentation of what Dr. Li said. Effects on

the reproductive system that result from postnatal developmental exposures are included under this Committee's purview.

DR. BURK: Yeah. I think we understand that. I mean, male/female reproductive toxicity, anytime in their lives, as I recall the issue there was perhaps lung effects that might result in SIDS, and how we couldn't separate pre and postnatal exposure.

DR. DONALD: I just wanted to clarify that for the record.

DR. BURK: Yeah. No. I think that's very important.

Does anyone else have any --

DR. SAMUELS: I do.

DR. BURK: -- comments?

DR. SAMUELS: I would just like to point out that the virtue of the multi-generational study is that one gets lifetime exposure in the parental rats, which therefore can show itself as an effect on fertility or in their offspring, so that we in fact do cover --

These multi-generational studies are very valuable for the very kind of long-term exposure beyond the prenatal period -- or

postnatal period that the previous speaker mentioned. And it's just that the difficulty is when we see an effect early in the postnatal period but not at birth. That's our problem.

DR. BURK: Well, I think perhaps we should go on and just discuss this chemical at the moment. And if there's any strong feelings later, someone can bring it up.

So back to fenbutatin oxide. And again, I would like to perhaps try to discuss it by the male/female developmental, perhaps just to focus us. So why don't we start again with female, mainly because I think that's the, perhaps the easiest.

Does anybody have any comments about female reproductive toxicity?

DR. ROBERTS: I'd just say I'm not impressed that it meets the clear evidence of female reproductive toxicity.

DR. BURK: Well, I agree. And that's why I did that one first.

All right. Let's -- well, let's talk about the male, then. That one is a little more -- we'll put Marion on the spot again.

Why don't you go ahead, Marion. Tell us what you think about these -- particularly about these changing weight things.

DR. MILLER: Well, I think I start on the first simple endpoints that we looked at in terms of the histopathology in testes. There was no effect in multiple studies, in multiple species. And to me, that's very clear.

The question arises about the impact of the bodyweight of the animal on the relative testes size. And I think the Chapin study in 1993 really showed -- did a nice job showing that with reduced bodyweight, they maintained testicular size, so that the relative testes size is now increased, because you get a lower total bodyweight and maintain absolute weight in testes. You're going to see an increase in the relative testes weight. And that is seen in some studies, but not in all studies and at all times. So there's some studies I really wouldn't consider the bodyweight effects as clear and causing changes in testes weight.

Some -- but now the question that has to be raised, because it's not always, the results are not always consistent, is one

study which was a long-term study, the last, the terminal measurement of the testes weights -- and I had it open a minute ago -- and showed that in the highest dose level of the animals, relative testes weight was further increased.

I thought this was interesting in that at this point in the study, it was two years into the study. The testes weight in the control group was actually decreasing, which would be associated with aging and diminution of spermatogenesis in the aging animals.

In the animals that were treated with the compound, they had less bodyweight and generally, it's shown that lighter animals are healthier. So you could propose that that one timepoint where you saw a relative increase compared to control in testes size was because the onset of diminution of spermatogenesis associated with aging was marginally delayed or delayed slightly because of the lower animal bodyweight. And that's, I think, the major discrepancy in terms of testes weight that I saw in the studies.

In that-- the other timepoints in that

same 2-year study, 3, 6, and 12 months, had no effects that couldn't be attributed to bodyweight changes.

DR. BURK: Okay.

DR. KEEN: I just want to echo what Marion said. If we were given these data blind and they were listed A, B, C, D, and E, and A was -- turns out to be the controls, we'd all be pointing at it and saying, "There's our reproductive toxic agent".

If you look at this, frankly, from an unbiased perspective, you're left with the impression that it's a protective agent, not a -- it's not a negative agent, particularly the absence of any histopathology on any of the reports.

DR. SHIONO: Can you point to the table that shows that?

DR. KEEN: It's -- you see it on page 53. There's a rather consistent expression of them. And you're right, 61 for the 2-year study.

DR. BURK: Okay. Any other comments about the male reproductive toxicity? Questions?

Marion, is there anything else that can explain weight change, you know, that you don't see pathologically? That's the problem I have. You'd expect to, If you looked at it, you'd expect to see something. It's hard to understand otherwise.

DR. MILLER: In the absence of any pathology, I have a hard time making an interpretation.

DR. BURK: Okay. All right. Question?

DR. SAMUELS: Where is Hine Laboratory?

DR. MORGAN: It used to be in San Francisco.

DR. BURK: All right. Let's talk about the developmental toxicity, then. Would anyone like to make a comment on that?

Linda?

DR. ROBERTS: This is something of a bridging comment, perhaps. I was looking at the three-gen repro study, which I guess -- I looked at the original. It's not a terribly good study, but it had a slight decrease in relative organ weight for testes in the F3B weanlings; no data for the F1B's or F2B's. I also noticed that there's a slight decrease in

bodyweight. And I've interpreted that to mean that they're postnatally growth-delayed, and that the testes weight is delayed appropriately. Does that seem --

DR. MILLER: Um-hum.

DR. ROBERTS: Yeah. I didn't make much of that. I just wanted to see if you did.

DR. SAMUELS: I mean, the issue which struck me in the developmental study was the weanling bodyweight study. And of course, we get into the issue of postnatal questions. And what provided an additional difficulty for me, of course, was that the parental weight was also decreased.

However, I mean, my belief is that if the effects of a chemical is going to make the parents so sick as to lose weight and reduce the birthweight of the offspring thereby, I would still count that as a reproductive effect, however indirect. But that's an issue that we discussed. So I just, just wanted to throw that out.

DR. MORGAN: If I could clarify, I don't believe we saw an actual reduction in birthweights.

DR. SAMUELS: It was wean -- it was weanling bodyweights.

DR. MORGAN: Yeah, weanling bodyweights.

DR. SAMUELS: Right. I didn't -- I didn't mean to say birthweight, if I did.

DR. MILLER: Steve, I noticed that there were a couple of quotes from EPA in their definition of maternal toxicity and subsequent developmental toxicity. I actually like their definition in that it gives us a lot of flexibility in how we want to interpret the data.

And it -- I can't remember the exact quote, but in essence, it said that if there was some minimal toxicity in the dams, we shouldn't discount -- this as not a reproductive toxicant.

And then they defined what minimal toxicity was. And I think we should consider things on a case-by-case basis as we've done in the past, in terms of maternal toxicity with respect to effects on the offspring.

DR. MORGAN: That quote is on page 30, if anybody is interested in looking at it.

DR. BURK: I think that you're correct

that we have considered maternal toxicity in the past. And it's just always a difficult issue.

Is there anything here that one can see in the absence of any maternal toxicity? That would be nice.

DR. KEEN: Well, I think you just put your finger on it; in the absence of maternal toxicity. And I don't see any. And the trouble with that EPA quote is it gives us a fence for minimal toxicity. It gives us a fence for severe toxicity. It doesn't define the mid-ground. And that really is the problem.

And that's why I go back to I think we have to agree -- case by case is fine, but it can also cause a lot of complications, because it almost depends on what mood that a committee is in in a given day or a given audience or a set of data. And I think that's just not the best way to approach it.

I don't see any evidence of repro-toxicity here in the absence of apparent maternal toxicity. And I don't know how to define that as minimal or severe because it's

too vague as it's currently constructed.

DR. ROBERTS: I wanted to make a comment about pre-implantation loss. It was noted in the rat developmental study on Table -- excuse me, on page 13 of the document. It's not dose related here, by the way. It's been my interpretation that the implantation actually starts about day 6 rather than day 5. So we should be seeing something.

Normally, I don't know if a study done in 1980 would have done this, but there's the Salusky staining method for looking to see if there's very, very early implantation loss in the uterine horn. If so, there should be a very small stain in there, almost like a little pin point type of dot on the uterine horn.

I do know from personal experience that cyclophosphamide can be given starting on day 7 when implantation should be complete, and we don't get any staining. So it's not an absolute method. So when I look at pre-implantation loss, I don't assume that it is something that cannot be attributed to a test material. But the only mechanism that I

know of for it is something that is clastogenic. And I spoke to Jim Morgan about it last week. And he checked. And this material doesn't have any -- it's clean on the genetic toxicity.

So in looking at that endpoint and in looking at the pre-implantation loss, I think it's simply a matter of natural variability. It goes from lowest to highest dose, .6, 1.4.6, 1.1. If that was a real effect, I would expect it to be much higher. I would expect it to be something more along the lines of a third or fifty percent reduction in litter size or complete absence of litters at that level.

In the rabbit developmental studies, one of the things that I asked them about were the gastric lesions. And the reports do indicate a number of cases where the animals are not eating, and at necropsy, they have gastric lesions.

The reason I asked for that is that I know although it's not considered a severe skin irritant, it is considered a severe eye irritant. And if it's severely irritating to

the eye, a lot of times, those materials are very irritating to any sort of membrane. And apparently that may be why those gastric lesions are in there, which would be a fairly significant discomfort to the animals as well as fairly strong adverse toxicity.

The rabbit studies have the most positive findings, but they also have the strongest level of maternal toxicity. And I'm surprised that the control group has 11 percent mortality. I don't have a lot of confidence in a study when you've got your normal, healthy rat and rabbit dying. But when I see the increase at the high dose, that makes -- that further suggests to me that there's a complication or confounder in interpretation at that level.

And I guess -- I went back and looked -- it indicates in the dairy -- this is a cow study, that's what they looked at for pesticide distribution. They didn't find it in the milk, so I would guess that -- this is an assumption.

I don't even know if it's a totally valid assumption, but if you can't find it in cow

milk, you may not be finding it in rat milk either. So I'm guessing it's not lactationally transferred or not transferred substantially at that point.

But since the mom still seemed to be affected, it would be at least my guess that there's a definite -- the odds are stronger that it's postnatally mom's toxicity affecting the pups versus the pups actually being affected directly or prenatally.

DR. SAMUELS: Or such as a reduction in the amount of lactation, simply.

DR. ROBERTS: That could be something as well.

DR. KEEN: Since you brought up pre-implantation loss, maybe someone could just help me. I couldn't understand Table C.2.1.2. I see a whole bunch of zeros which, if I read the footnote correctly, indicates that there was, there were some problems in the sense that it exceeded total implantations, exceeded the corpora lutea. So they gave it a zero. I guess I'm confused as to where the minus numbers come from, the positive numbers. I was left --

DR. MORGAN: More questions? Hopefully, I can clarify that a little bit. The numbers in Table C.2.1.2 are the actual numbers by individual animals of the corpora lutea minus the implants. Okay. So if there were more implants than counted corpora lutea, it comes up as a negative number. If there were less implants, it comes up as a positive number.

DR. KEEN: Right.

DR. MORGAN: And those were calculations that -- I actually went through the raw animal data and did those.

DR. KEEN: Well, I understand that, but how do you get the negative numbers which are in the table?

DR. MORGAN: Those are the ones where the number of implants exceed the number of corpora lutea.

DR. KEEN: But then that should have been a zero. That's what it says in the table.

DR. MORGAN: Oh. No. When the authors calculated the averages, okay, they made all the negative numbers into zeros.

DR. KEEN: But --

DR. BURK: But he's showing you he did it

himself.

Right? You figured this out, each one?

DR. MORGAN: Right.

DR. KEEN: Okay. So this table does not, is not what the authors report. There's something wrong. You can't -- it says their zeros are their positive numbers. I'm just trying to clarify the table.

DR. MORGAN: Sure. When the -- the table C.2.1.2 is the actual calculations we did based on individual animal data of what the number of corpora lutea minus the number of implants was, which is to say the "pre-implantation losses" by individual animals.

When the authors calculated the averages, which you see in the previous table, C.2.1.1. Okay? They took all the negative numbers and changed them to zeros. And then they calculated the averages based on that.

DR. KEEN: Okay. So the table that you have in here, the zeros really are true zeros.

DR. MORGAN: That's correct.

DR. KEEN: Okay. You might want to add a footnote to make that clear, because as it

currently reads, it looks like this is a table directly from the authors' data. That's what was confusing me.

DR. MORGAN: Okay. We'll do that.

DR. BURK: I thought what you were trying to show was how it spread over more animals to help understand the statistics.

DR. MORGAN: That's correct.

DR. BURK: Okay.

DR. SHIONO: In my reading of the study, I see some consistent effects of resorption across different species. It would be helpful for me to have some discussion about this. Is this an important reduction? Is this a measure of reduction in fertility in animals? You know, they seem to be real. They're statistically significant across species, and there's a dose response effect in a couple of them.

DR. ROBERTS: I'm sorry. Can you point out which pages have the dose response and statistical significance for resorptions?

DR. SHIONO: I have in my notes that in the Trial B of the rabbit study, there was a statistically significant increase in

resorptions, and that also had a dose response effect.

DR. MORGAN: Actually, if I could clarify, the authors did not do statistical tests on the resorptions in the Trial B rabbit study. So we don't actually know whether it was statistically significant or not. There wasn't enough information for us to run statistical tests on it.

DR. KEEN: Yeah. I think it's also worth noting I wasn't struck the same way you were in part because in Study A, again, it's the reverse. I mean, I think we're kind of -- if we're going to seize on the numbers, we have to -- you know, it's the lowest resorption. And early fetal deaths are reported in the high-dose group in Study A.

So if you kind of combine the two studies, you come to the conclusion that not much is happening in terms of the rabbits, at least that was my interpretation.

DR. BURK: Did you have anything else, Pat, that you wanted to --

DR. SHIONO: (Shaking head.)

DR. SAMUELS: Well, I do think -- I mean,

if we look -- again, I'm looking at 2.2.2.1, and it does look like there is an increase in loss, at least in the highest group, but it's not necessarily a dose-response relationship. But the number of resorptions or abortions or females with live fetuses at gestational day 29 is certainly reduced in that group.

DR. BURK: I agree with you there, but that was the case of what I would consider significant maternal toxicity.

DR. SAMUELS: I --

DR. BURK: Again, I know, it's one of those things where we have to keep that into perspective there.

DR. SAMUELS: So it's your judgement that that dosage group is a high toxicity group, I mean, so high as to -- because of the high mortality, primarily?

DR. BURK: Well, I thought it was high based on the, all of the gastric lesions and all the things they reported.

Was that not your thought too, that the New Zealand white rabbit study at 10 milligrams per kilogram per day --

DR. ROBERTS: Yeah, that was my

impression, although Jim Morgan has spent a lot more time on the report than I did. But yeah, that was my thought.

DR. KEEN: I mean it just -- and again, it's where I do think we have to at least develop some guidelines we follow, because if we use the EPA as to what's severe toxicity or minimal toxicity, if I recall, is less than 10 percent mortality. If 5 out of 20 died, we're 25 percent. So that's -- I mean, I -- I'm not necessarily comfortable with, with what I'm saying, but I think we have to go with the guidelines until we set them in place. And clearly, 25 percent would be considered severe.

DR. MILLER: I think a study with deaths in a goodly proportion of the animals is clearly not minimal toxicity. These animals looked like they are showing some major signs of toxic effects.

DR. ROBERTS: And there were notations that the animals were not eating for days before they were necropsied or found dead.

DR. BURK: Does anyone else have anything they want to discuss? Any comments before we

take our votes? No? So we're ready to vote? I'm not trying to rush anybody here.

All right. Well, again, I'll do it in the same way that I did last time. And we'll -- I'll read it exactly as it says.

Okay. Please indicate by a show of hands if in your opinion fenbutatin oxide has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity.

I see no hands, so the record should reflect zero votes were cast for -- sorry -- for developmental toxicity.

All right, next one. Please indicate by a show of hands if in your opinion fenbutatin oxide has been shown -- has been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity.

All right. I also see zero hands. Okay. So in that case, again, the record should reflect zero votes were cast.

And finally the third one. Please indicate by a show of hands if in your opinion fenbutatin oxide has been clearly shown

through scientifically valid testing according to generally accepted principles to cause male reproductive toxicity.

Okay. Again, zero votes. The record should reflect zero votes were cast to add fenbutatin oxide to the Proposition 65 list as causing either -- any of the three; developmental, female, or male reproductive toxicity.

A majority of the nine-appointed members is required to add a chemical to the list. Accordingly, fenbutatin oxide is not added to the Proposition 65 list.

Okay. The next agenda items are Staff updates. I'm not sure who's scheduled to make the updates. It looks like -- Oh.

So, Cynthia, are you going to make an update?

MS. OSHITA: (Nodding head.)

DR. BURK: Cynthia Oshita will update us on chemicals added via the Administrative Listing mechanism.

MS. OSHITA: Good afternoon. My name is Cynthia Oshita with OEHHA, and I would just like to bring the Committee members up to date

on the status of the administrative listings under Proposition 65.

Since the DART Committee met last December of 1998, OEHHA has administratively added 60 chemicals to the Prop 65 list. Of the 60, 55 were added as developmental and reproductive toxicants, and 5 were added as carcinogens.

A complete, current list of chemicals is available in your binders following the Staff update. We have underlined and highlighted in blue each of the chemicals which were newly added for your ease of reference.

Also included in that list are the four chemicals for which the Carcinogen Identification Committee recently delisted. Those four chemicals are allyl chloride, chlorodibromomethane, para-toluidine, and zineb. All four of these chemicals had been administratively listed by the Authoritative Bodies mechanism, and the authoritative body was the U.S. EPA.

The more recent information on these chemicals indicated that the U.S. EPA had changed its determinations And according to

the regulations, there is a mandatory referral to the appropriate committee for its determination on whether the chemicals should remain on the list. And the Carcinogen Identification Committee found that these should be removed.

DR. BURK: Thank you, Cindy. We also have a update by Colleen Heck on Proposition 65 litigation and rulings.

MS. HECK: Thank you. There's two matters to report on in that regard. The first is the Toxics Release Inventory litigation. I think it's important enough that I will trouble you with a very slight recount of the history here. And it may serve well for the new members.

In 1994, U.S. EPA came out with some additions to its Toxics Release Inventory, or TRI list. What finally shook out of that was approximately 65 chemicals that were formally identified as causing reproductive toxicity.

In 1997, a lawsuit was initiated by the Natural Resources Defense Council, seeking to compel OEHHA to, it's fair to characterize, promptly add all of those to the Proposition

65 list. There was a related but opposite conclusion sought by the Western Crop Protection Association seeking to prohibit OEHHA from adding any of those TRI chemicals to the Proposition 65 list. The cases were consolidated for a hearing before a local judge here in Sacramento back in April of '98.

Judge Ford, the judge assigned, ruled that OEHHA was proceeding correctly in its chemical-by-chemical review of those 65 chemicals in conformance with the regulations to determine whether or not they met the listing criteria for an Authoritative Bodies listing. And he did urge OEHHA to move promptly in its review.

In October of 1998 -- it was our second hearing on the same matter -- and Judge Ford, on this occasion, issued a writ setting timelines, primarily, telling OEHHA to continue with its chemical review, but to make final determinations to list or not to list.

He did not order us to list all the chemicals. He ordered us to make final listing determinations for at least 50 of the chemicals by June 30 of '99, and the

remainder, whichever number of the 65, but more than 50, were not gotten to in a timely fashion.

That was the backdrop for a lot of the recent listing activity that Cindy Oshita just reported on.

As of June 30, '99, when we were returning to the Court to let the judge know how we had done, we had made final listing decisions on 52 of the chemicals. 35 were added to the list, 17 were not.

As of today, there have been final decisions for 55 of the TRI chemicals, with 10 chemicals in various stages of the listing process, all different parts of the pipeline not yet completed. That's the status of the TRI litigation.

A related -- an unrelated matter, actually, but a Prop 65 case, nonetheless, is the matter of Baxter versus Denton. The backdrop of this case is we received a petition from Baxter Company to make significant changes to our regulations as concerns diethylhexylphthalate, DEHP, including changing the "no significant risk

level", conceding that the law of informed consent regarding physicians and how they give warnings to patients in effect superseded the Proposition 65 warning and other related avenues of relief.

OEHHA responded, denying the petition on all grounds. The petitioner, Baxter, has since filed for a writ again seeking to compel OEHHA what it sought in the earlier petition that was filed with us. And that matter is also pending here in Sacramento County Superior Court, but has not yet been heard. It will probably be heard in the spring of the coming year.

That's all I have. I don't know if there are any questions.

DR. BURK: Are there any questions? I guess not.

MS. HECK: Thank you.

DR. BURK: Are there any further public comments? It's very quiet.

Okay. Then I'll turn to Joan Denton for a summary of the Committee actions.

DR. DENTON: For the two chemicals which the Committee discussed today, the Committee

chose or added to the Proposition 65 quizolofop ethyl, based on male reproductive toxicity. The Committee decided not to list; therefore, it will not be listed, fenbutatin oxide to the Proposition 65 list.

Regarding closing comments, which I see I'm also listed on here to say, we're going to break the tradition of this Committee of meeting once a year in December by having another meeting in approximately, what, four, four months, four or five months in spring, in the spring of the year 2000. And the Committee will be discussing additional TRI chemicals, or additional Authoritative Body chemicals, which we will be bringing forward to the Committee.

Has that meeting date been set?

DR. ALEXEEFF: No, Joan.

DR. DENTON: No? Okay. So it will be -- it will be in the spring.

Also, I guess, I would like to again welcome the new members. We're glad that you're here, and we hope that you find the Committee discussion very scientifically challenging.

I think that's all I had to say.

DR. BURK: Is there any further business that the Committee members would like to bring up? Okay. If not, then I believe we're adjourned.

Thank you all for coming.

(Whereupon the meeting concluded at 1:02 p.m.)

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STATE OF CALIFORNIA)
) ss
COUNTY OF SACRAMENTO)

I, SAHAR DEMOS, do hereby certify: That on the 13th day of December, 1999, at the hour of 9:00 a.m; that I took down in shorthand notes the said proceedings had; that I thereafter transcribed my shorthand notes of such proceedings by computer-aided transcription, the above and foregoing being a full, true and correct transcript thereof, and a full, true and correct transcript of all the proceedings had.

Sahar Demos

Shorthand Reporter in and for the County of Sacramento, State of California