MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CALEPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

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

COMMITTEE MEMBERS:

Ellen B. Gold, Ph.D., Chairperson

Diana Auyeung-Kim, Ph.D.

Laurence Baskin, M.D.

Suzan Carmichael, Ph.D.

Aydin Nazmi, Ph.D.

Charles Plopper, Ph.D.

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

STAFF:

Dr. Lauren Zeise, Acting Director

Ms. Carol Monahan Cummings, Chief Counsel

Dr. Marlissa Campbell, Reproductive and Cancer Hazard Assessment Branch

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

Dr. Farla Kaufman, Reproductive and Cancer Hazard Assessment Branch

Ms. Michelle Ramirez, Environmental Scientist, Proposition 65 Implementation Program

ALSO PRESENT:

Mr. Steve Risotto, American Chemistry Council

I N D E X

P R O C E E D I N G S

ACTING DIRECTOR ZEISE: All right. Good morning. I'd like to welcome everyone to this meeting of the Developmental and Reproductive Toxicant Identification Committee for Proposition 65. My name is Lauren Zeise. I'm Acting Director of the Office of Environmental Health Hazard Assessment. We are waiting for a couple of Committee members to arrive by train, so I just want to announce that they're not here, but will be here shortly, so we're going to rearrange the agenda a little bit to take some non-voting items.

Okay. So anyway. Welcome to the Committee meeting. The meeting is being transcribed and it's webcast, so please be sure to use your mics and speak clearly into your microphones. Just to make, before we get started, an announcement on a couple logistics. The restrooms and drinking fountains are out the door -- out the back door and to the left at the end of the hall. In the event of a fire alarm, you just go out the door down, the steps, outside, and we'll reconvene outside in the event of a fire alarm or other emergency. And the last housekeeping item is that we will be taking some breaks for the court reporter.

Okay. So today -- at today's meeting, we have one major agenda item, and that is chloroform. We will

be -- the Committee will be considering whether or not chloroform is to remain on the Proposition 65 list as known to cause reproductive toxicity. So that's our main agenda item.

Now, I'd like to introduce the members of the DART Identification Committee. To my right is Dr. Ellen Gold. She's Professor and Chief, Division of Epidemiology, Department of Health Services, University of California, Davis.

Then there is to her right Dr. Plopper -- Dr. Charles Plopper, Professor Emeritus, Department of Anatomy, Physiology, and Cell Biology, UC Davis School of Veterinary Medicine.

Then to my left is Dr. Diane Auyeung-Kim, Director, Toxicology and Non-Clinical and Translational Sciences Study Support Allergan, Incorporated.

And then to her left is Dr. Aydin Nazmi, Associate Professor, Department of Food Science and Nutrition, California Polytechnic Science -- sorry, Polytechnic State University, San Luis Obispo.

And then to his left is Dr. Suzan Carmichael, Professor, Neonatal and Developmental Medicine, Stanford University.

So welcome, Committee members.

Now, I'd like to introduce the OEHHA staff. So

Dr. Allan Hirsch is our Chief Deputy Director. Carol -- sorry, not Doctor, but Allan Hirsch, our -- gave you an honorary degree, Allan.

(Laughter.)

ACTING DIRECTOR ZEISE: Next to him is Carol Monahan Cummings our Chief Counsel. Next to her is Dr. Martha Sandy, Branch Chief for the Reproductive and Cancer Hazard Assessment Branch. And then next to her is Dr. James -- Jim Donald, Section Chief for Reproductive Toxicology and Epidemiology. And then Marlissa Campbell, Staff Toxicologist, RCHAB. And Farla over at the dais over here. Dr. Farla Kaufman, staff toxicologist, RCHAB.

And then our Proposition 65 implementation staff. Ester Barajas-Ochoa, Michelle Ramirez, and Julian Leichty and Sam Delson, our Deputy for External Affairs.

So, Carol, will you be giving some introductory remarks, before I turn the meeting over to Dr. Gold?

CHIEF COUNSEL MONAHAN CUMMINGS: I was thinking I might do that when the members get here, the other 2 members.

ACTING DIRECTOR ZEISE: Okay. Great.

Okay. Now, I'll turn the meeting over to Dr. Gold.

CHAIRPERSON GOLD: Thank you. Good morning, everyone.

Can you hear me?

Okay. So once we get to the discussion of chloroform, we will have a staff presentation, and then we'll also have just Committee questions, and then public comments. And for those of you in the public who wish to make comments, each person has 5 minutes. And we ask you to complete the blue cards, so they're in the back of the room and turn them over to Esther or Michelle before the public comment session, so we can know to call on you.

I think we decided to change the agenda just a little bit waiting for our colleagues to appear. And so I believe we were going to go to staff updates, is that correct? And so beginning with Michelle?

MS. RAMIREZ: I thought we were going to start with Carol. Sorry.

(Thereupon an overhead presentation was presented as follows.)

MS. RAMIREZ: All right. Good morning. My name is Michelle Ramirez, Environmental Scientist in the Prop 65 Implementation Program.

Since your last -- oh, it's not showing up yet.

All right. Since your last meeting, we've added a total of 8 chemicals administratively for causing reproductive toxicity, and 11 for causing cancer. This first slide shows that for reproductive toxicity,

Topiramate was added for the --

ACTING DIRECTOR ZEISE: Excuse me, Michelle. If you could speak into the microphone a little bit closer.

Thank you.

MS. RAMIREZ: Is that better?

Okay. The first -- did you want me to start over?

ACTING DIRECTOR ZEISE: That's okay.

MS. RAMIREZ: Okay. On this first slide, it shows that for reproductive toxicity, topiramate was added for the developmental endpoint, and abiraterone acetate was added for all 3 endpoints, developmental, female and male reproductive toxicity.

For cancer, the following chemicals were added, aloe vera, non-decolorized whole leaf extract, goldenseal root powder, styrene, tetrachlorvinphos, parathion, and malathion.

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MS. RAMIREZ: The next slide here shows that for reproductive toxicity, atrazine, propazine, simazine, and their metabolites DEA, DIA, and DACT were added for the developmental and female reproductive toxicity endpoints.

For cancer, the following chemicals were added:

Sedaxane, bromodichloroacetic acid, 1-bromopropane, furfuryl alcohol, and pentachlorophenol

and by-products of its synthesis (complex mixture).

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MS. RAMIREZ: On the next slide. We have a list of chemicals under consideration for administrative listing. The far right column indicates the date of the notice of intent to list. There are 4 chemicals under consideration for listing as causing reproductive toxicity: Perfluorooctanoic acid, also known as PFOA; perfluorooctane sulfonate, PFOS; pertuzumab, and vismodegib.

One chemical is under consideration for listing as causing cancer, and that's glyphosate.

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MS. RAMIREZ: Since your last meeting, one safe harbor level has been adopted in regulation effective October 1st, 2016. That safe harbor level is a Maximum Allowable Dose Level for bisphenol A, dermal exposure from solid materials.

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MS. RAMIREZ: And on this slide, as you can see, we've also proposed safe harbor levels for 8 chemicals. Maximum Allowable Dose Levels have been proposed for ethylene glycol, ingested; and for oral exposures to each of the 6 triazine compounds. A No Significant Risk Level has also been proposed for styrene.

And now I'll turn things over to Carol, if she's ready.

CHIEF COUNSEL MONAHAN CUMMINGS: Good morning. I'm just going to do a quick update on the litigation report for OEHHA. Currently, our office is defending 9 cases, 8 of those related to Proposition 65, 1 related to a public health goal for a chemical in drinking water.

Since our last meeting, 4 of our cases have gone up on appeal. We successfully defended all 4 of them. We -- currently on appeal is the decision to list the chemical BPA as a developmental toxicant. Also, a decision by your sister group to list DINP as a carcinogen is on appeal.

We did list the triazine chemicals as you saw on the earlier slide. And the case challenging that is on appeal, but the courts did not prevent the listing, pending the outcome of the appeal.

We also were successful in defending our current safe harbor level for lead. And that case is on appeal as well. We're hoping that those cases will be resolved within the next year or so, perhaps before your next meeting, but they're still -- most of them are -- have either been briefed, and we don't have a hearing date set yet, or we're in the briefing process for those.

The cases pending in the trial courts for the

most part are also Prop 65 cases, but 2 of them are derivative of ones that have already been decided. And they have to do with the Public Records Act and whether or not we produced enough records under those.

One, as I mentioned, is for challenging a level we set for our -- in our drinking water program. One challenges our current NSRL for the chemical chlorothalonil, which is known to cause cancer under Prop 65, and one that has been in the news a lot, I think, is the case filed by Monsanto against OEHHA to prevent the listing of glyphosate as a chemical known to cause cancer.

It's an interesting case in the sense that it's a Constitutional challenge to the listing process that we're using, which is called the Labor Code listing process. You've heard about that before. But it's a federal and State Constitutional challenge to that part of the law that's been in use for 30 years.

So it's -- that case is still pending in the Fresno court, and there's a hearing on a motion -- a potentially dispositive motion in December that may resolve that case or at least push it up to the Court of Appeal.

I don't know if you have any questions on any of those?

No. Okay. So I think we have a quorum now.

Well, we had a quorum before, but now we really have a quorum. So do you want me to just go ahead and do the comments I normally would?

CHAIRPERSON GOLD: (Nods head.)

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. Since I've got the microphone, I'll go ahead.

So good morning. I just want to remind the Committee of a few items before you get started today. First of all, I'd like to remind you that in your binder you have materials that we've provided you earlier, and that's in your binder today, which is the criteria that was developed for listing chemicals under Prop 65 by this Committee. And those are available to you to help you determine whether or not the evidence is sufficient for listing for chloroform.

So if you have questions about the data that you're looking at for the chloroform today, please refer to the criteria that are in your binder. These are scientific criteria that were developed by the Committee. And they are provided as guidance. There's certainly room for scientific judgment calls. And the application of the criteria, of course, has to move along with the science. So I hope that the criteria is useful to you in that regard.

The charge for this Committee is to do -- has to

do with listing a chemical under Prop 65. And sometimes, even though that's your charge, you'll hear comments from individuals or groups that give you information about whether or not the -- what the impact of a listing might be, whether or not a warning is required, for example, or what the level of current exposure for humans might be, or impacts on the economy.

While this information is helpful in a general sense, it's not part of your criteria. And so you should apply the criteria that you have available in your binder when you're making your scientific decisions based on your scientific judgment.

You'll also hear about the clearly shown standard, which was part of the statute. You're required to find whether or not a chemical has been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity. This is a scientific question and not a legal standard of proof.

This Committee is also allowed, and it often does, make decisions based entirely on animal evidence. The chemical that you're considering need not be shown to be a reproductive -- human reproductive toxicant. You don't need to have information about whether or not a human -- not human exposures to the chemical are

sufficiently high enough today to cause reproductive toxicity in order to limit -- to list the chemical.

The members of this Committee are very well qualified scientists. You were appointed to this Committee by the Governor because of your scientific expertise. And you don't need to feel compelled to go outside that charge to make other kinds of decisions.

In the event that you have or feel you have insufficient information or you need more time to think about it as you discuss the question before you today, there's no requirement that you make a decision today. You can always ask the staff to prepare additional information, and you can ask to defer the question to another meeting.

Anybody have questions on that?

Okay. Thank you.

CHAIRPERSON GOLD: Are you finished?

CHIEF COUNSEL MONAHAN CUMMINGS: (Nods head.)

CHAIRPERSON GOLD: Okay. So before we get started, I want to introduce the latest members that arrived, Dr. Laurence Baskin to my left here who is Professor and Chief of Urology in Pediatrics at UC San Francisco.

THE COURT REPORTER: Could you get a little closer to the mic?

CHAIRPERSON GOLD: Oh, it's on. I'm just not speaking into it.

Okay. Is that better?

Okay. Should I repeat that or are you good?

THE COURT REPORTER: No.

CHAIRPERSON GOLD: Okay. And then on my right is Dr. Tracy Woodruff, who's Professor and Director of the Program on Reproductive Health and the Environment at UC San Francisco.

So now, I think we'll go back to the original agenda. In which case, I'm going to turn it over to staff presentations. I believe Dr. Kaufman is going first.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN CUMMINGS: Actually, I'm just going to make one real brief introductory remark. This is Carol Monahan-Cummings again. I just want to mention that chloroform is the chemical that's in front of the Committee today for reconsideration.

This Chemical was added to the Prop 65 list in 2009. And the listing was based on certain provisions of Prop 65, and incorporate the federal Hazard Communication Standard, which is maintained by federal OSHA.

The reason that we're looking at this chemical again today is because the basis for the listing, which,

at that time, relied on the fact that there is a threshold limit value, or TLV, set for this chemical by the American Conference of Governmental Industrial Hygienists, also known as ACGIH, no longer meets the requirements for listing under the Labor Code listing mechanism of Prop 65, because of some changes that were made to the federal Hazard Communication Standard regulations in 2012.

We've referred a number of chemicals to you over the last couple of years for reconsideration of listing because of the changes to the federal HazCom Standard. Chloroform is the last one -- yay -- of these chemicals being referred to you for reconsideration.

So essentially what we're asking you to do is to conduct a de novo review of the scientific information for this chemical, and determine if it meets your criteria for listing. And if it does, it will remain on the list. If it doesn't, then we'll remove it from the list.

So I think Dr. Donald was going to give further information about background for this chemical.

Questions?

CHAIRPERSON GOLD: Yeah, my apologies. When we switched around the agenda, I neglected to call on Dr. Donald. So we'll postpone Dr. Kaufman for a moment.

DR. DONALD: Okay. Excuse me.

Good morning. In a moment, Dr. Farla Kaufman

will summarize the data on chloroform from human epidemiological studies, and then Dr. Marlissa Campbell will summarize the data from animal studies. Before they begin, I was asked to just remind the Committee that the only question before you today is whether chloroform has been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity.

The hazard identification materials you received in advance of the meeting contain data on some other chemicals, particularly other trihalomethanes that commonly co-occur with chloroform. But those data were provided only to help inform your decision about chloroform. And those other chemicals are not under consideration for listing today. So Dr. Kaufman and Dr. Campbell will focus entirely on the data in chloroform in their presentations.

So unless there are any questions, I'll now turn it over to Dr. Kaufman.

CHAIRPERSON GOLD: Any questions?

Now, Dr. Kaufman, sorry.

DR. KAUFMAN: So as Dr. Donald mentioned, I'll review the evidence for reproductive and developmental toxicity of chloroform with regard to the human studies.

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DR. KAUFMAN: For the benefit of the audience, I'll review the materials provided to the DART Committee. These include the current document for reconsideration of chloroform and cited studies, as well as the hazard identification document from 2004.

In 2004, the Committee requested the authors of 2 studies for supplemental analyses. Those results were presented to the Committee at a meeting in 2005.

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DR. KAUFMAN: So chloroform is a tetrahedral, polar compound. It's used as a solvent and in the synthesis of various products. It's also a by-product of water disinfection using chlorine. Many of these -- of the many disinfection byproducts, chloroform is the predominant type in most water treatment systems, and it's formed when residual chlorine reacts with organic matter.

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DR. KAUFMAN: So the human studies reviewed in this document comprise a complex data set, including different study designs, different windows of exposure, different measures of exposure, as well as different routes of exposure. In total, 35 studies were reviewed. Twenty-four of these were published after the review by -- review of chloroform by the DART Committee in 2004, and after the reviews by the World Health Organization in 2004

and the new U.S. EPA in 2001.

Almost all of the studies in humans examined exposure to chloroform from treated drinking water. So of these 35 studies, they generally fall into categories for exposure as 21 looked at water concentration, 11 studies used estimated internal dose, and 4 studies used either blood, air samples, or questionnaire data.

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DR. KAUFMAN: Chloroform is formed in drinking water, as I mentioned, when it reacts with chlorine and when chlorine reacts with organic matter. When considering exposure to chloroform as a disinfection by-product, it's recognized that levels in water can vary, depending on a number of factors including: Water source, pH, temperature, residual chlorine levels, organic matter, and the residence time in transporting water from the treatment plants to the households.

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DR. KAUFMAN: So various sources or routes of exposure include ingestion of tap water, showering and bathing, swimming, and dish washing by hand.

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DR. KAUFMAN: In considering exposure assessment, we think of ingestion as perhaps the major route of exposure. However, chloroform is volatile and thus

showering and bathing, as well as swimming, can contribute to uptake that occurs via inhalation and dermal absorption. Exposure studies measuring blood levels after showering and bathing reported very significant chloroform uptake. Approximately only a third of the studies reviewed here collected information on showering and bathing.

Dishwashing is another infrequently considered source of exposure. It's also been shown that triclosan-containing soaps react with free chlorine to form chloroform. This may also be a significant route of exposure. Few studies asked about dishwashing habits, and none asked about triclosan or antibacterial soaps. So these factors can contribute to exposure misclassification.

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DR. KAUFMAN: Other potential misclassification of exposure in human studies can result from a number of factors. Chloroform concentrations are mostly measured at the water treatment plant. Most studies used monitoring data collected by the water utility, generally on a quarterly basis. There are differences in temporal and spatial formation of chloroform in systems. However, very few studies measured chloroform in tap water at the residence.

Individual variability in water use practices includes the amount of water ingested, use of filters, and time spent showering or bathing. These were captured to varying degrees. Although, none of the studies collected information on water temperature.

Maternal residence at birth is commonly used to estimate chloroform exposure throughout pregnancy. Although, it's possible that the women moved during pregnancy, so it's not a perfect measure.

Most studies did not include information on estimates of workplace exposure.

So most of this misclassification is likely to be non-differential, in that the probability of being misclassified should not differ according to groups of study participants. This would likely result in a bias towards a null, i.e. that of detecting -- not detecting an effect that is truly there.

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DR. KAUFMAN: Other factors that may be important to consider include possible gene environment interactions. Important genes include those from metabolizing enzymes such as CYP2E1, and the glutathione S-transferase theta 1 or GSTTI, and the glutathione S-transferase mu 1 or GSTM1 which catalyze the conjugation of glutathione to a wide range of potential toxicants as a

first step in detoxification. Thus, the absence or presence of a gene activity may lead to altered individual susceptibility to environmental exposures.

Other trihalomethanes co-occur with chloroform to varying degrees. Haloacetic acids are also disinfection byproducts. These factors could be potential confounders of the association between chloroform and reproductive outcomes. Due to the complexity of the chloroform data set, we provided more extensive material than for other Labor Code chemicals. So information on exposure levels to these other trihalomethanes and related risk factors or risk estimates were provided in the appendices to the 2016 hazard identification document.

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DR. KAUFMAN: Various reproductive outcomes were assessed in the human study. These include pre-term birth, small for gestational age, low birth weight defined as birth weight less than 2500 grams, very low birth date defined as birth weight less than 1500 grams, birth weight, spontaneous abortion, stillbirth, birth defects, postnatal weight gain -- oh -- yeah, postnatal weight gain -- sorry -- menstrual function, fertility, and sperm quality.

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DR. KAUFMAN: So 9 studies examined pre-term

birth.

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DR. KAUFMAN: I'll be showing a number of these forest plots. Some have very small print, as there were many studies for certain outcomes, but I'll describe each plot. So this is a forest plot of association between chloroform exposure, measured as concentration in water and pre-term birth. This -- in all the forest plots, the studies are presented in increasing order of exposure as one moves down the table, so that the study with the lowest exposure is at the top of the plot and the study with the highest exposure is at the bottom. Exposure was based on the lowest value of the highest exposure category.

In this plot, it ranges from 10 micrograms per liter, in the study by Kramer et al. at the top, to greater than 63 micrograms per liter in study by Wright at al. at the bottom. The odds ratios and the 95 percent confidence intervals are illustrated relative to the null value of 1 indicated by the vertical dotted line. When the confidence intervals, represented by these horizontal lines cross one or include one, it's considered not to be a statistically significant finding.

For this presentation when referring to statistically significant results, I'll simply use the

word "significant". On the scale -- the scale on the bottom for odds ratios ranges from 0.25 to 1.75. The scale changes for the various plots I'll be showing.

Unless otherwise noted, the results shown in these plots are for third trimester exposures. For some studies, different symbols appear after the authors, such as in this plot for Savitz et al. and in Lewis at al. These symbols indicate which -- studies which were related in some manner such as regarding the study populations.

So in this plot, 4 studies observed significantly decreased odds ratios, indicating that exposure to chloroform was protective against pre-term birth. Although for the study by Costet et al. highlighted at the top, only the middle exposure category was significant.

In the prospective cohort study by Savitz et al., the 2 highest categories were significant. And for the study by Lewis et al., the highest category for the entire pregnancy and for both categories, and for the categories for the second trimester were significant.

In the study by Wright et al. at the bottom, both categories were significant. The study by Rivera-Nunez and Wright observed an increased odds ratio representing an adverse association, but only in the second exposure quartile.

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DR. KAUFMAN: This plot shows exposure as estimated internal dose in pre-term birth. The well-conducted study by Savitz et al. again observed a significantly decreased risk of pre-term birth, although it only reached significance in the second exposure quartile.

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DR. KAUFMAN: Fifteen studies examined small for gestational age. This plot shows the association between water conservation and that outcome. The odds ratio scale on the bottom ranges from 0 on the left to 5 -- sorry, it didn't go --

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DR. KAUFMAN: -- 5 on the right.

Okay. Most of the 11 studies observed odds ratios very close to 1. Four studies observed significantly increased odds ratios. The odds ratios for Kramer et al. and Hoffman et al. on the top half of the plot are 1.8 and 4.9 respectively. While for Summerhayes at al. and Wright et al. shown on the bottom, the odds ratios are very close to 1 with narrow confidence intervals.

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DR. KAUFMAN: This plot shows estimated internal dose and small for gestational age. The nested

case-control study at the top by Danileviciute et al. characterized exposure as above versus below the median. This study also examined the genotype for individuals with respect to genes GSTT1 and GSTM1. The absence of the genotype or the null variant is denoted by the 0 at the end.

The findings were not significant for the presence of GSTT1 genotype or for its absence. The odds ratios for GSTM1 suggest a divergence where the -- where the odds ratio was 0.88 when the genotype is present, and 1.74 when it's absent. The study also looked at these genotypes for low birth weight, which I'll show shortly.

So although 5 of the 6 studies observed odds ratios above 1, the confidence intervals were wide and none were significant.

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DR. KAUFMAN: Nine studies examined low birth weight and very low birth weight.

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DR. KAUFMAN: This plot is for water concentration for these outcomes. All of the odds ratios are above 1. Two of the studies have significant findings for low birth weight. In the study by Toledano et al., both exposure categories were associated with small but significantly increased odds ratios. In the study by

Lewis et al., the highest exposure category showed a significantly increased odds ratio of 1.5 with the suggested dose-dependent association.

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DR. KAUFMAN: The study by Iszatt at al. in this plot also assessed exposure using water concentration, however, they examined the change in water concentration. In this retrospective study, a process of enhanced coagulation was introduced in a portion of the water treatment zones. This process improves the removal of disinfection by-product precursors, thus reducing the disinfection by-product formation potential.

So 2 time periods were sampled. A 3-year period before and a 3-year period after the enhanced coagulation intervention. So the measure on the right-hand side is the change in rates as a percent, before and after intervention, and the vertical dotted line represents 0.

Values to the left line are negative, so they represent better outcomes, in that they show a decrease in the rate of low birth weight or very low birth weight. For low birth weight, there was a significant decrease in the rates for all exposure categories.

The high category represents a decrease of 30 to 65 micrograms per liter in chloroform levels, which was associated with a decrease in the rate of 9 percent. For

very low birth weight, only the high category with decreased water chloroform concentration was associated with a significant rate decrease of 16 percent. The time frame of exposure was the entire pregnancy.

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DR. KAUFMAN: So here we see chloroform exposure as a estimated in internal dose and low birth weight. Note that the scale on the bottom is a bit different with the highest odds ratio value being 7.5. At the top is the nested case control by Danileviciute et al., which contained extensive exposure assessment. The study dichotomized exposure at above versus below the median.

And as with small for gestational age, it examined the influence of specific genotypes, while the point estimate remains similar when considering the presence of GSTT1. In its absence, the odds ratio is larger, although the confidence interval is wide. Obviously, neither of these were significant.

Looking at the estimates for GSTM1, the presence of the genotype results in an odds ratio below 1, though not significant. However, the association for the null variant shows significantly increased risk of low birth weight with a large odds ratio of 5.06, and a wide confidence interval.

The interaction between chloroform exposure and

low birth weight and the genotype, not shown on this plot, was also significant with a much larger odds ratio of 15.8, and a wide confidence interval.

At the bottom of the plot, the findings for Grazuleviciene et al., a study from the same cohort as Danileviciute, observed significantly increased odds ratios for all exposure categories, with the category at the bottom representing chloroform analyzed as a continuous variable using increases of 0.1 micrograms per day.

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DR. KAUFMAN: Ten studies examined birth weight.

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DR. KAUFMAN: This plot shows water concentration as the change in birth weight, so the vertical line is -- on the plot is at 0. Point estimates to the right of the line represent an increase in birth weight, and those to the left a decrease.

In the study at the top by Summerhayes et al., significant decreases in birth weight were seen for the entire pregnancy, and the first and second trimester. Also -- although these -- although the decreases were small, the largest was 5 grams.

In the study by Rivera-Nunez and Wright, significant decreases in birth weight were seen in the

highest 3 categories, suggestive of dose-response. At the bottom, the study by Wright at al. saw significant decreases in birth weight in both exposure categories, which were 14 and 18 grams.

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DR. KAUFMAN: Continuing with water concentration and birth weight, this retrospective study by Zhou et al. reported odds ratios with birth weight classified as above or below the median. The study observed increasing odds ratios with increasing exposure across the 3rd trimester and the entire pregnancy. However, the only significant finding was for exposure in the fourth quartile during the third trimester.

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DR. KAUFMAN: In the plot of estimated internal dose and birth weight, the estimate is for change in birth weight. So the vertical dotted line is at 0. Therefore, the point estimates to the right of the line are increases in birth weight, while those to the left are decreases, i.e. adverse outcomes.

The prospective cohort study by Grazuleviciene et al. at the top shows a significantly lower birth weight of 57.8 grams for exposure as a continuous variable, again using 0.1 micrograms per day.

The study by Smith et al., also a prospective

cohort study, did not observe a significant change in birth weight for the total population. However, when the analysis was examined by ethnicity, a significant decrement in birth weight of 42.8 grams was seen in the higher exposure category for infants of Pakistani origin. This differed from the estimate for the infants of white British ethnicity, as shown below, where the highest exposure category for that category there was no significant change in birth weight.

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DR. KAUFMAN: A total of 10 studies looked at spontaneous abortion, stillbirth, or birth defects -- and birth defects.

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DR. KAUFMAN: Three studies looked at spontaneous abortion. None of the findings were reported as significant. However, when the DART Committee reviewed the study by Wennborg et al. in 2004, they requested the author to reanalyze the data excluding previous spontaneous abortions. In the reanalysis, the odds ratio of 2.1 was not very different from the original odds ratio of 2.3, but the confidence intervals -- interval was narrower, now at 1.1 to 4. And so the findings were then significantly associated with exposure to chloroform while working in a lab.

Four studies examined stillbirth. Three studies observed an increased risk of chloroform exposure. Although, for 2 of the studies, the estimates were not consistently significant across exposure categories. The study by Toledano et al. showed a small but significant increased risk which is consistent in both exposure categories.

The study by Iszatt et al., which examined before and after changes in water treatment method, reported no significant change in the rates of stillbirth.

Many different birth defects were assessed across 3 studies. No significant associations were reported for Iszatt et al. for hypospadias. Nor by Grazuleviciene et al. for heart, musculoskeletal, or urogenital abnormalities. The study by Dodds and King reported increased odds ratios in association with chromosomal abnormalities. However, only exposure in the third quartile reached significance. The authors reported no significant associations for neural tube detects, cardiovascular anomalies, or cleft defects. This study is notable in that it was the -- one of the only studies that actually measured participants' tap water.

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DR. KAUFMAN: One study examined the outcome of postnatal weight gain.

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DR. KAUFMAN: This prospective study examined this outcome in infants born in 3 study sites. The study used estimated internal dose during pregnancy. A significant decrease of 151 grams in postnatal weight gain over 6 months was associated with an interquartile range increase in chloroform uptake through ingestion. In the community -- this was in the community with the highest chloroform water concentration.

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DR. KAUFMAN: One study examined menstrual function and another fertility.

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DR. KAUFMAN: A prospective study of menstrual cycle function observed no significant association with cycle length. One occupational retrospective cohort study examined fertility. No association was observed for time to pregnancy in female dental surgeons using questionnaire data to assess exposure.

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DR. KAUFMAN: And at last, 4 studies examined sperm quality.

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DR. KAUFMAN: So chloroform exposure was assessed in different ways among these studies.

The prospective study by Zeng at al. in 2014 reported significantly decreased sperm concentration associated with higher -- with the higher exposure from ingestion, and suggested decreases in sperm count.

No -- hold on -- I'm just trying to get my mouse. There we go.

These values are regression coefficients where they analysis used natural log transformations. For -- I'm getting there. Okay.

For sperm motion, seen on the right here -- no, it's not showing up, is it? Oh there it is. Okay -- seen on the right, trends were observed surprisingly for increase in straight line and curvilinear velocity. In the case control study by Iszatt et al., examining water concentration, no significant findings were seen for sperm concentration or sperm -- motile sperm concentration. For Zeng at al., in 2013, using blood concentration, again an inverse association with a significant trend test was seen between chloroform concentration in blood and straight line velocity. There, it's in there.

So the study by Chang et al. reports on a case where a laboratory worker was exposed to chloroform for 8 months due to a shut down in the ventilation system. Chloroform exposure levels were estimated from sampling during a re-creation of the shut down. And significantly

reduced sperm motility was reported following chloroform exposure -- following chloroform exposure as compared to normal baseline measures taken before exposure.

And after exposure -- so this is time since end of exposure. So after exposure stopped, the levels for sperm count, for sperm motility, and for path velocity improved as shown by the 3-, 6 -- 3-, 4-, and 6-month post-exposure values.

And that concludes my portion of the presentation.

CHAIRPERSON GOLD: Thank you very much. I think before we go to Dr. Campbell, I want to just see if the Panel has any questions of Dr. Kaufman regarding the human studies?

Hearing and seeing none, Dr. Campbell.

(Thereupon an overhead presentation was presented as follows.)

DR. CAMPBELL: Okay. How's that? Can you hear me?

Okay. All right. Animal studies are useful for isolating the potential of agents such as chloroform to disrupt normal development and cause adverse DART effects, while at the same time controlling for other environmental factors as well as genetic background.

In general, evidence supports developmental

effects observed in animal studies as predictive of the potential to cause adverse effects on human development. However, the specific types of developmental outcomes observed in animal studies are not necessarily the same as those that would be produced in humans by the same agent.

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DR. CAMPBELL: For chloroform, there are quite a few animal studies providing data relevant to developmental, female and male reproductive toxicity. Both oral and inhalation routes have been tested, and in the most common test species. And on this slide, the numbers in parentheses just refer to the number of studies of each type.

That 4th major heading refers to a single multi-generation study that was performed in mice by the drinking water route. And the data in that study combines subgroups from a complicated protocol in looking at DART effects. So for clarity's sake I pulled it out to present as a stand-alone. Because there are so many animal studies of chloroform, this presentation won't present every detail that's summarized in the hazard identification materials that you have, but instead will focus on the most informative studies, and where possible on the observations at the lowest effective dose or concentration reported. And similarly, emphasis will be

on those effects considered to be adverse as well as likely to be treatment related.

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DR. CAMPBELL: The first data slide is a summary of the 3 most informative inhalation developmental toxicity studies of chloroform conducted in rats. The top row is the Schwetz 1974 study. 30 ppm was the lowest concentration associated with statistically significant developmental effects. The frequency of skeletal anomalies was increased and crown rump Length was decreased.

The dams of this 30 ppm group weighed approximately 90 percent of the average body weight for ad lib controls, and that was specifically on gestation day 13. And in the interpretation of co-occurring developmental and maternal toxicity is something I'm going to talk about in a little more detail in the next few slides.

But just to finish with the data presented here, the middle row, Baeder & Hoffman, '88, another standard teratology study. And again, 30 ppm was the lowest effective concentration for developmental effects resulting in an increase in totally resorbed litters and a decreased crown rump length.

In 1991, they did another study looking at a

lower range of chloroform concentrations. This time 30 ppm served as the highest concentration. They observed increases in the frequency of ossification variations at all test concentrations, including 3 ppm, the lowest tested in this case, and a concentration at which no maternal toxicity was reported.

And at the higher concentration of 30 ppm, there was significant decreases in fetal weight and length.

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DR. CAMPBELL: Now, just to look in a little more detail. In evaluating whether potential DART effects have been clearly shown through scientifically valid testing, according to generally accepted principles, it can be helpful to consider the principles documented in U.S. EPA's risk assessment guidance for developmental toxicity, a document which incorporated widespread public comment as well as recommendation of that agency's scientific advisory panel.

And that guidance specifically states that when adverse developmental effects are produced only at doses that cause minimal maternal toxicity, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity.

Factors to take into consideration include noting

that standard teratology studies are designed to produce minimal maternal toxicity at the highest dose tested, such as reduced body weight or body weight gain, but no more than maternal -- than 10 percent maternal mortality.

Also, we need to remember that many agents may be minimally or reversibly toxic to adults, but can cause permanent damage to developing offspring. And the finding of maternal and developmental effects at the same dose may simply indicate that both mother and offspring are sensitive to that dose.

And even in cases where developmental toxicity may result indirectly from toxic effects on the maternal animal, such as altered nutritional status, it doesn't somehow negate the occurrence of developmental effects. And fortunately, as I'll be showing in the next slide, there are empirical data to help us understand the relationship between effects on the maternal system and the developing organism.

In, general what we've learned is that there are species differences in sensitivity to maternal feed restriction, which appear to have a relationship to size. That is mice are more sensitive than rats, which are in turn more sensitive than rabbits.

Also, duration and timing of feed restriction during gestation as well as the severity of that

restriction impact the magnitude of any effects on offspring.

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DR. CAMPBELL: And here just to illustrate this graphically, this slide shows 4 studies conducted in Sprague-Dawley rats with maternal feed restriction during gestation days 6 through 15, the normal days of treatment in a teratology study. The blue bars on this slide represent the feed intake of restricted animals as a percentage of consumption by ad lib fed controls. And as emphasized by that black diagonal trend line, the studies have been arranged in order of severity of feed restriction from 84 percent of controls down to 17 percent of controls.

And the study on the far right, the Schwetz et al. 1974, might look familiar because the data there are taken from a severely feed-restricted control group that was included in the rat inhalation chloroform study that we just looked at.

The only consistent effect of feed restriction was reduced fetal body weight, as represented by the purple bars. And that affect was not proportionate to the degree of maternal feed restriction, but sits at about 10 percent reduction in fetal weights relative to controls, a magnitude of change that would be statistically detectable

in a standard teratology study.

Note also the green bar showing that litter -- live litter size, a measure of fetal viability, was not affected by maternal feed restriction in these studies.

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DR. CAMPBELL: Now just to go back to take another look at the Schwetz study in particular, this slide shows feed consumption over time for the treated and starved dams, again expressed as a percentage of ad lib fed controls. The dashed green line represents the -- what they called their starved control group. And all of the treatments, whether chloroform exposure or the very low feed restriction, were applied only during gestation day 6 through 15.

All 3 of the chloroform exposed groups showed significant decreases in feed consumption at the beginning of treatment on gestation day 6. At the highest chloroform concentration of 300 ppm, which is represented by the black line, the feed consumption remains significantly below control levels throughout the study. And just in contrast, the blue line is the 30 ppm group. It only showed significantly reduced feed consumption on the first day of treatment.

And then you can see it comes back up and is actually somewhat in excess of the control values in a

catch-up phenomenon.

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DR. CAMPBELL: Now this slide tries to illustrate the effects on fetal endpoints of maternal feed restriction. And that's the front row of blue bars is the feed-restricted groups, as compared to increasing concentration of chloroform. And again, all are expressed as a percentage of control values.

And what you can see is the entire graph is skewed out of shape by the big green bar right in the middle. And that represents the frequency of gross anomalies that were seen at a chloroform concentration of 100 ppm. And what they found were 13 fetuses and 3 litters had a defect called imperforate anus, a gross malformation that is externally visible without dissection.

There were no gross malformations at all in the starved group or in the other 2 treated groups. The lack of gross anomalies observed at the highest concentration of 300 ppm may be reflective of the very low fetal viability at this level. And you can see that's visualized by the purple column in the back left-hand corner.

Although the paper does not report maternal mortality at this concentration, only 3 out of the 20 bred

females in that group were still pregnant at term. And of those 3 remaining litters, they averaged only 4 fetuses per litter.

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DR. CAMPBELL: Now, just to focus in on a couple of endpoints, fetal viability and body weight data, you know, taking the skewing defects out, what now stands out is the profound effect of 300 ppm chloroform, the purple bar, on fetal viability in the absence of an effect of severe feed restriction alone on this endpoint.

And with that we'll go back to the regular data.

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DR. CAMPBELL: This slide shows developmental toxicity data in the mouse by the inhalation route. So we're still on inhalation. This study was by Murray et al., '79. And what they did was expose pregnant mice to only one test concentration and that was 100 ppm. And what they varied was the days of exposure. The gestation days 1 through 7 covers the pre-implantation period and embryogenesis. Gestation days 6 through 15 covers the major period of organogenesis or formation of the organ systems, and that's what's classically covered in teratology studies. Gestation days 8 through 15 covers the latter part of that organogenesis period.

And in each of the time points tested, exposure

to 100 ppm chloroform was associated with manifestations of developmental toxicity, as well as evidence of minimal maternal toxicity.

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DR. CAMPBELL: Moving on to the oral route, we're back looking at rats. Here we have 3 of the most informative studies on the developmental toxicity of oral chloroform in rats. The Thompson '74 presents data from 2 experiments, a dose-range finding study, as well as a subsequent full scale teratology study. The range finding studies are done with large number of doses with only a very few animals per dose in order to try to establish appropriate dose range to use in the larger scale study.

In this case, the range finding study found increased resorptions and decreased live litter size and fetal weights at 316 milligrams per kilogram per day; a dose at which decreased maternal weight gain, as well as mortality of 1 out of 6 dams were also seen.

In the full scale teratology study, that would be the middle row there, fetal effects were observed at 126 milligrams per kilogram per day, the highest dose tested.

And then the bottom row is another study Ruddick et al., '83. Their top dose was 400 milligrams per kilogram per day. And at that dose, they saw decreases in the mean fetal weights and increases of runting and

findings of aberrant sternebrae.

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DR. CAMPBELL: Now, we've got mice by the oral route. One dose level of 31.1 milligrams per kilogram per day by gavage was given to mice from prior to mating, then throughout gestation, and then treatment was continued postnatally. They were mostly interested in postnatal effects. The mean live -- mean live litter size at birth was not affected, which is the only endpoint for which an influence of postnatal exposure can be ruled out.

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DR. CAMPBELL: There are also rabbit data by the oral route. And again, this is the Thompson paper, which reported on rabbits as well as rats. Again, a range finding study found increased frequency of aborted litters and fewer live fetuses in surviving litters at 63 milligrams per kilogram per day. And then in the full scale study at the lowest dose tested of 20 milligrams per kilogram per day, fetal weights were decreased, and the fetal incidents of incompletely ossified skull bones was increased.

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DR. CAMPBELL: And here we have the newest study. This one was actually published in 2015 using zebrafish embryos. And they started at 4 hours post-fertilization,

abbreviated as HPF, with 30 embryos per chloroform concentration, and then cultured them for 72 hours in a buffered embryo medium.

And just to explain a little bit about the endpoints they observed, the EC20 or 50, that's an effective concentration that produced either 20 or 50 percent abnormal embryos. The LC50 concentration that was lethal to 50 percent of the embryos. The TI, or teratogenic index, for chloroform, the 50 percent lethal concentration was 2½ times greater than the 50 percent effective concentration.

The MCIG is the minimum concentration causing growth inhibition. And the fingerprint endpoints are whatever specific types of malformations were seen in at least 50 percent of the embryos. And you can see what they've listed here are defects of eyes, heart, and tail, and then the percentages following.

And then just in the interests of time, I'm not going to go through the remaining endpoints in detail.

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DR. CAMPBELL: Now, we're turning to female reproductive toxicity. This is in rats by the inhalation route. The 3 studies shown here are all teratology studies, which included data on outcomes that could represent female reproductive toxicity as well as

developmental toxicity. So we've already seen a bit about these studies. Here, we're focusing on specific outcomes of fetal viability that could indicate effects on the female reproductive system.

An overlap could similarly be argued for measures of fetal growth, but, you know, that wasn't incorporated into the HIM table, so I didn't add them in here.

The top row, the Schwetz study, 300 ppm, pregnancy rate, live litter size were reduced and resorption frequency was increased. The middle row -- the Baeder & Hoffman, '88, found significant increases in totally absorbed litters at all concentrations tested with the lowest effective concentration of 30 ppm. And then in their 1991 study, where 30 ppm was the highest concentration, was associated with no significant evidence for female reproductive toxicity.

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DR. CAMPBELL: Again turning to mice, inhalation route. Again, we're looking at previously discussed teratology studies. As a reminder in this study, there was a single concentration of 100 ppm. And then what was varied was the days of exposure. Exposure on gestation days 1 through 7 was associated with increased resorptions and decreased pregnancy rate. And a decreased pregnancy rate was also reported with exposure on gestation day 6

through 15.

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DR. CAMPBELL: Okay. Here, we have -- now, we're turning to oral exposure. This is rats, female reproductive toxicity. And again, the data come from teratology studies. The range finding study that -- of the portion of the Thompson study found increased resorptions and decreased live litter size at 316 milligrams per kilogram per day.

And then in the full scale teratology study, they found no clear evidence of female reproductive toxicity at their top dose of 126 milligrams per kilogram per day.

And Reddick -- Ruddick also found no effects on live litter size or resorption frequency with their doses up to 400 milligrams per kilogram per day, which was the highest they tested.

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DR. CAMPBELL: Now, just a brief digression to go through the protocol, before we look at the next data slide. This is the NTP continuous breeding protocol. And what they do is it's an 18-week reproductive study. The parental animals represented by the P0 at the top of the slide are treated daily for one week prior to cohabitation, then daily through a 14-week cohabitation period, and for 3 weeks following the end of cohabitation.

The mated pairs are left together to produce as many litters as they can during the cohabitation period. That's not necessarily four litters like you have here. Although, that would probably be a maximum. Only the final F1 litters are left with their dams through lactation and retained for post-weaning treatment and evaluation. And of that final F1 group, only the high dose and control animals are carried through for breeding the second generation or F2. And as you can see from the slide, the data are collected for only a few outcomes.

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DR. CAMPBELL: So looking at what they found, that's the Chapin et al., '97, the top row here. For chloroform -- oh, I think -- I think I explained -- they -- oh, the highest dose tested under this protocol is set at the adult maximum tolerated dose, or MTD. And that's defined specifically as a dose that does not depress weight gain by more than 10 percent or cause more than 10 percent mortality.

So for chloroform, the MTD was 41.2 milligrams per kilogram per day as given by gavage, which did not produce clear adverse effects on the reproductive outcomes that were evaluated.

The other study on this slide, the EPA 1980, was a 90-day subacute drinking water study in which pathology

of the reproductive organs was part of their evaluation. And they didn't identify any effects.

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DR. CAMPBELL: Okay. Now, we're in the oral route in rabbits. And again, this is from a teratology study that we've already seen. At 63 milligrams per kilogram per day 1 out of 5 does died. And 2 out of the remaining 4 does were not pregnant. And the 2 pregnant does had litters with reduced viability.

In the full scale teratology study, where 50 milligrams per kilogram per day was the high dose, there were aborted litters sporadically through all doses and controls with no apparent dose response.

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DR. CAMPBELL: We also have data on -- from a 7½ year chronic toxicity study performed in beagles. These dogs were given chloroform mixed with toothpaste and provided in pill capsule form to a high dose of 30 milligrams per kilogram per day, given 6 days per week. And again, there was pathology including the reproductive organs. And they found no pathological changes in the ovaries or uteri.

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DR. CAMPBELL: Moving on to male reproductive toxicity of chloroform by the inhalation route. This Land

at al. study exposed 10 groups of male mice to air concentrations of 0.04 or 0.08 percent chloroform for 4 hours on each of 5 consecutive days. And the sperm parameters were evaluated at 28 days following the first day of exposure. Compared to controls, statistically significant increases were found in the percentage of abnormal sperm for both exposed groups.

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DR. CAMPBELL: Now, on to male reproductive toxicity in the rat by the oral route. This is the U.S. EPA 90-day subacute drinking water study. It's not a reproductive study, so there were no endpoints of fertility or sperm quality. But again, there was some pathology on male reproductive organs, and all they reported was one case each of testicular hyperplasia and interstitial cell hyperplasia in the 160 milligram per kilogram per day group. And it isn't even clear if this represents 2 separate animals or only a single individual with both effects.

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DR. CAMPBELL: Now, we've got male reproductive toxicity of -- in mice by the oral route, and this is the -- from the continuous breeding study. The increases in fertility indices and epidiymal effects seen at 41.2 milligrams per kilogram per day really didn't provide

clear evidence of adverse effects on the male reproductive system.

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DR. CAMPBELL: And then again, we have the males from the beagle study, the 7½ year chronic oral study. They also looked at organ weights and pathology for productive organs. No significant changes in testes or prostate weights were identified. The pathological examination indicated some cases of what they called ectopic testes with inhibition of spermatogenesis, which couldn't be clearly related to treatment.

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DR. CAMPBELL: Now, onto the last study. Again, I'm going to digress just to go through the protocol. This is the Borzelleca and Carchman, 1982, a multi-generation reproductive toxicity study with dominant lethal and teratology studies incorporated as satellites to the larger study. And it reports data relevant to all 3 endpoints, developmental, female/male reproductive toxicity.

The document itself is an unpublished study that was provided to U.S. EPA by the Medical College of Virginia. And some of the tables in that document cite a preference -- cite a reference as being in press, but we could find no evidence that that cited paper was ever

actually published.

And just to go through the protocol, the parental or, what they call here, the F/0 generation were randomly mated to produce 3 sequential litters, the F/1A, the F/1B, and the F/1C. The F/1B generation were randomized and mated to produce the F/2A generation, then re-randomized and mated again to produce the F/2B generation. So there were 3 litters in the first filial generation, and 2 in the second filial generation.

Except for the animals used for breeding, all pups were sacrificed at weaning on postnatal day 21. Both the parental generation the, F/0, and the F/1B were started with 10 males and 30 females per group. The breeding animals were sacrificed once the last litter of the generation was weaned. And then teratology and dominant lethal satellite studies were spun off from the F/1C and F/2B litters.

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DR. CAMPBELL: Now, this slide just shows an overview of the combined data for all the generations and litters. These animals were exposed by drinking water, so the dosing is expressed as milligrams per milliliter. The maternal and systemic effects column on the left includes observations on the 2 generations used for breeding. So it's not all of them. It's the F/0 and the F/1B.

The developmental or reproductive findings and -- are like all the litters as shown on the slide. And there are significant -- were significant findings on a number of reproductive indices. The first one, the mating index, is the number of pairs that mated out of the number -- divided by the number of pairs that cohabited.

The gestation index is the number of females that actually delivered live young divided by the number of females that were originally determined to be pregnant.

The viability index is the number of live pups on postnatal day 4 divided by the number of live pups at birth, so it's the 4-day survival. The lactation index is the number of live pups per litter at weaning on postnatal day 21, divided by the number of live pups at birth, and then adjusted for culling, if necessary.

Also, at the bottom of that slide, you can see litter size at birth in the 5 milligrams per milliliter group was decreased for all offspring generations. And then I have a second slide just showing the results from the satellite experiments for the dominant lethal protocol treated males from the parental, the F/0 and F/1B generations, were mated with unexposed females in order to produce a portion of F/1C and F/2B litters, and they did not identify any dominant lethal effects.

And they really found nothing in the teratology

satellites. But if you remember from the previous slide, litter sizes were considered to be significantly reduced for all litters, including the F/1C and F/2B animals included in the teratology study.

So in trying to figure out why, what happens is that in the report there's a table of the overall data where they compared exposed animals to vehicle controls, and found a significant difference. Now, for the specific teratology satellites, they compared litter sizes to untreated controls, and did not find a difference.

So that's why the inconsistency.

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DR. CAMPBELL: And then just a couple of quick summary slides. And expressed here is a matrix of species and route of exposure. The numbers on the slide represent the lowest effective concentration or dose as just as reported in the study. The ones marked NE, that is no observed reported effect. And then the number in parentheses, in that case, represents the highest dose that was tested.

So for developmental toxicity, effects were observed in rats and mice by the inhalation route at concentrations as low as 30 ppm. Oral studies also provided evidence for developmental effects of chloroform in rats and rabbits, and adverse developmental effects

were noted in an in vitro study of zebrafish embryos.

For female reproductive toxicity with inhalation exposure in rats adverse effects were reported at concentrations as low as 30 ppm. An inhalation study in mice also reported adverse effects on resorption frequency and pregnancy rate.

The available studies conducted by the oral route of exposure did not show clear evidence of adverse effects on the female reproductive system in rats, mice, rabbits, or beagles.

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DR. CAMPBELL: And the final slide. For male reproductive toxicity, an inhalation study in mice found significant increases in the frequency of abnormal sperm with increasing concentration of chloroform. Oral studies in rats, mice, and beagles failed to demonstrate clear adverse effects on the outcome -- outcomes of male reproductive toxicity.

And then that multi-generation toxicity study is an oral drinking water study in mice reported significant changes in indices of mating pregnancy and offspring viability. The mating index may reflect male as well as female reproductive toxicity. Alterations in the gestation index and viable litter size may reflect changes in the female reproductive system and/or developing

organism. And that concludes my presentation.

CHAIRPERSON GOLD: Thank you, Dr. Campbell.

Are there any questions from the Panel for Dr. Campbell?

Okay. Seeing and hearing none, we could, at this point, take a break. Would that be desirable?

Yes, 10 minutes maybe.

Okay. So let's come back at 11:35 roughly, try and reconvene, and we'll proceed with public comments at that time.

CHIEF COUNSEL MONAHAN CUMMINGS: And if the members could make sure that they don't discuss the issues among themselves during the break, that would be great. Thanks.

(Off record: 11:26 a.m.)

(Thereupon a recess was taken.)

(On record: 11:36 a.m.)

CHAIRPERSON GOLD: Can we please try and reconvene. Okay. If we can take our seats.

Maybe I'll ask the Panel one more time if they have any questions for either Dr. Campbell or Dr. Kaufman?

COMMITTEE MEMBER WOODRUFF: Okay. I have one.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Okay. Thanks. Hi. That was a nice presentation. I really appreciated the

graphical representations from the studies. It was very useful to see the numerical estimates put out on the graphs. I was wondering if you had considering doing a meta-analysis of the studies that were amenable to that?

DR. KAUFMAN: Well, it crossed my mind, but the studies are so different and their exposure measures are so different, I -- it would be difficult. There have been people who have done meta-analyses for trihalomethanes, because it's just an easier way when they group them. Exposure is kind of easier, but I -- I -- it would be difficult, so we didn't do it.

CHAIRPERSON GOLD: Dr. Plopper.

COMMITTEE MEMBER PLOPPER: Yeah. This is -- I wanted to compliment Dr. Campbell on the very nice summary of all the data there. And I wondered if you could expand a little bit on your initial comment about how the impact of a toxicant on the system of the -- say like the mother, which, in this case, this is a hepatotoxicant, how we should or should not be considered that when we're evaluating the impact on reproduction and development. You made a comment at the beginning. I guess if you could expand that out a bit.

DR. CAMPBELL: I think the point is more is it's -- it's an area to look at the biology closely and interpret, rather than just assuming, oh, there's a little

change in the dam, so this isn't really developmental toxicity. It's just not that simple. But certainly, if there's enough toxicity in the dam, it's going to affect the offspring, so -- but it's just -- it's something that you really have to look at.

CHAIRPERSON GOLD: Dr. Kim.

COMMITTEE MEMBER AUYEUNG-KIM: And I think we're -- Dr. Campbell was citing EPA standards as far as assessing maternal toxicity and the effect on the developing fetus. So it's not necessarily that that's how it should be interpreted, but that's EPA's strategy.

CHAIRPERSON GOLD: Any further questions or comments from the Panel, from the staff?

Okay. Okay. I think we can turn -- we have one public comment, unless somebody else. I only have one card. And so it's Steve Risotto who is with the American Chemistry Council.

You'll have 5 minutes.

MR. RISOTTO: Hello. Does that sound good?

Okay. Sorry. Good morning. I'm going to try and go paperless here, so hopefully it will go smoothly. My name is Steve Risotto. I'm a senior director at the American Chemistry Council, and I appreciate this opportunity to provide comments to the DART concerning your review of chloroform under Prop 65.

I'm here on behalf of the American Chemistry Council's Chlorine Chemistry Division, which represents major producers of users of chlorine in North America, and works to promote the sustainability of chlorine chemistry processes, products, and applications. And I'd like to suggest just a couple of seconds of silence for those poor beagles who were exposed to chloroform for 7½ years. Just staggering how we used to run our tests, I guess.

The chlorine division submitted written comments on the hazard identification materials that OEHHA staff developed in support of reconsideration of chloroform back in September. I'd like to briefly summarize those comments.

As evidenced by the presentations, a significant amount of human and animal data exists for chloroform. These data show a lack of consistent evidence to support a conclusion that chloroform has been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicants.

Numerous reviews of chloroform have been conducted. In 2001 -- excuse me -- the U.S. Environmental Protection Agency conducted a review of chloroform, including reproductive and developmental toxicity. EPA's assessment found that chloroform had been evaluated in a number of chronic and reproductive and developmental

studies. And although some effects had been reserved -- observed, those effects were generally secondary to maternal toxicity.

In a 2004 review, the World Health Organization noted no impacts on fertility and reproduction -- excuse me, just a second -- in rodents. While some impacts on development were observed, the WHO review concluded that the results were inconsistent and generally resulted from maternally toxics doses when toxic doses were given.

The DART Committee itself has conducted 2 previous reviews of chloroform in 2004 and 2005, and on both occasions decided against listing of the chemical as a reproductive toxicant. And more recently, a 2011 review by the Committee on Risk Assessment of the European Chemical Agency confirmed an earlier 2007 decision that the data for fertility do not justify a classification for male or reproductive -- male or female reproductive toxicity. And the data on developmental effects support classification in the lowest category, Category 3, under the European Union's Dangerous Substances Directive.

This classification has been subsequently converted to an equivalent classification under EU's regulation on the classification labeling and packaging of substances and mixtures, or the CLP, which has replaced the dangerous substance directive to better align with the

global harmonization system for classification and labeling.

Under the CLP, chloroform is classified in Category 2 as a suspected human reproductive toxicant. The CLP guidance notes that if deficiencies in the study make the quality of evidence less convincing, Category should be -- Category 2 should be the more appropriate classification, such as the case for chloroform.

A review of the literature by OEHHA staff through 2015 confirms that the available evidence for chloroform remains inconsistent. Human and animal data are mixed when evaluating impacts on sperm quality. Some studies have reported a decrease in sperm quality associated with chloroform exposure while others found no association.

Data are lacking and inconsistent for impacts to fertility among females exposed to chloroform. The available human studies observed -- human study observed no impacts, while fertility in female mouse -- in mice was reported to decrease in one study and increase in another.

Three epidemiology studies demonstrate a lack of consistency for increased risk of spontaneous abortions, as a result of exposure to chloroform and/or trihalomethanes. A 2000 study by Wennborg et al. reported a weak association with increased risk from chloroform exposure. While the study by Savitz and colleagues found

the pregnancy loss was not associated with high trihalomethane exposures. Similar inconsistencies were seen in the results from studies in laboratory animals.

And epidemiologic data are not consistent for increased risk of stillbirths with chloroform concentrations in water. A 2014 study found no increased risk, while 2 other studies reported the observed increase in risk was not statistically significant and the 4th observed a small but significant increase.

Related to developmental toxicity, no effects of chloroform on gestation length were reported in experimental studies in animals. Of the 8 epidemiology studies that examined the risk of pre-term birth associated with chloroform exposure, 5 found no significant association, and 3 studies observed a significant, fairly consistent, inverse risk of pre-term birth associated with chloroform, i.e., a protective effect.

A large number of epidemiologic studies examined the risk of small for gestational age -- I'll be wrapping up very soon -- associated with exposure to chloroform. Ten studies observed no increased risk or no statistically significant increased risks with chloroform exposure, while 3 others reported an increase.

Of the 3 epidemiology studies that examined the

risk of birth defects while exposure -- with exposure to chloroform, only 1 reported an association. While birth defects have been seen in animal studies, they appear to be more indicative of general developmental delay, rather than frank malformations.

Finally, interpreting the results of epidemiology studies reporting an association with low birth weight is complicated by the fact that several studies reported an association with trihalomethane levels, rather than with levels of chloroform, and few, if any, actually measured concentrations at the individual tap.

Based on these inconsistent results, we encourage the Committee to recommend that chloroform be removed from the Prop 65 list of chemicals known to the State to cause reproductive toxicity.

Thank you for considering our comments.

CHAIRPERSON GOLD: Thank you.

Does the Committee have any comments or questions?

Thank you.

Okay. We'll now turn to the Committee discussion of the various papers, and we have established an order. And we're going to ask Dr. Nazmi to lead off with discussions of the -- so we divided the papers up into human and animal, and then into pregnancy outcomes, female

reproductive toxicity, male reproductive toxicity, developmental toxicity. And so Dr. Nazmi is going to start with studies that discuss human pre-term, small for gestational age, low birth weight, and birth weight, correct?

COMMITTEE MEMBER NAZMI: That's right.

CHAIRPERSON GOLD: And he'll be followed as a discussant by Dr. Carmichael.

COMMITTEE MEMBER NAZMI: Thank you, everybody.

I want to start off by saying thanks to Dr. Kaufman. You did all the hard work for us and the rest of the OEHHA staff, and we are just up here as a Committee discussing that you make our jobs really easy. So, much appreciated.

Because you gave such a thorough review of the evidence, I'm just going to point out a couple of -- a couple of items. It seems to me that given the evidence from the human studies for what I was charged to review, which was pre-term birth, small for gestational age, low birth weight, and birth weight, the data to me indicating a significant effect of chloroform exposure is most convincing with low birth weight and birth weight outcomes, which show that risk for low birth weight as increased and mean low birth weight has decreased, as shown by the 18 studies that included these outcomes.

I just want to point out 2 studies that I thought were notable that, in my opinion, were methodologically really strong. And, in some ways, these studies break down to -- I'm an epidemiologist by training, so I'm always thinking about the methods, and the sampling, and the sample size. So these 2 stuck to me as notable, mostly because each of these studies were so different, and we had so much different study designs, and we have so many different approaches to studying chloroform and the outcomes.

So I made -- I made a longer list, but after Dr. Kaufman's review, I trimmed that down to 2, because these 2 studies -- one of them, Toledano et al., the UK study, with 3 study sites in 2005, which was a retrospective cohort. One thing that I thought was notable from that study is I believe it had the largest sample size at about almost 1 million.

So they looked at low birth weight and birth weight. I'm sorry low birth weight and very low birth weight, sampling water from 3 different -- 3 different companies, and showed a pretty clear dose response effect in terms of risk for low birth weight. Compared to the referent group, it was about a 5 and a 10 percent increase in low birth weight outcomes. That is Toledano et al., 2005.

It was a retrospective birth cohort, so they were looking at -- retrospective cohorts, so they were looking at birth and stillbirth records. The models seem to me that they will -- seem to me pretty extensively designed. The low birth weight and very low birth weight models adjusted for slightly different things, but they both included maternal age, socioeconomic status, and the low birth weight studies, the year of the study, and sex of the infant as well.

Besides having such a large study sample, the hierarchical links that were built into the model that Dr. Kaufman pointed out were -- I think took this -- took this study into a higher -- a higher level of design. Even though there were no data on gestational age, the dose response association together with the multi-site design and the large sample size were notable to me. So I wanted to point out that study, and wanted to point out the -- I'm afraid I'm going to butcher the name -- Grazuleviciene study from Lithuania, which had a significantly smaller sample size. It was only about 5,400, but it was a prospective -- prospective birth cohort.

Water sampling happened at 4 different treatment plants. And so what we had was a range for internal dose of chloroform that was from 0.0013 to 2.1328. So the terciles, I thought, were pretty broad, although a

relatively low exposure, given some of the other studies. But again, here, we saw really convincing dose response effect for low birth weight at about 12 and 13 percent increase.

The participation rate of that study was really high at about 79 percent. And given the fact that it was a prospective cohort design, the participation rate was really important and kind of keeping kind of a standard -- a standard follow up.

Besides that, there were a couple of -- there were a couple of items that I wrote down, and Dr. Kaufman mentioned them, so I don't want to be too redundant here. But I think there are still a few unknowns in terms of chloroform exposure. And one of those is genetic predisposition, for example, this GSTM10 versus 11 genotype. I think potentially some additional studies down the pike in the next 5 or 10 years, I think, might help us out a little bit with determining some sort of genetic predisposition with low birth weight or with birth weight outcomes.

But the way I read it, the low birth weight and the birth weight outcomes were suggestive of good evidence indicating an impact with chloroform exposure. Not so much so, I thought, with pre-term birth and small for gestational age, but there's also another question of this

protective effect that we saw or evident -- protective effects that were evident with the pre-term studies that I think also raise a few more questions that they -- than they answer.

So I think with that, I'm just going to wrap it up. I want to open it up to any of the colleagues or otherwise that have any anything to add.

CHAIRPERSON GOLD: Thank you, Dr. Nazmi. Dr. Carmichael, would you like to comment?

COMMITTEE MEMBER CARMICHAEL: Okay. Am I on?

Great. Well, thanks, everybody again. Extended thanks to the OEHHA staff for all that you've done. This was a huge amount of work.

So I'm just trying to focus and not be redundant. It did seem with pre-term and small for gestational age, there was minimal evidence of increased risk. With birth weight, there was a little bit -- seemed to be a bit more of a mixture. I agree that Grazuleviciene -- however you say that -- was definitely one of the stronger studies and was one of the ones that showed a positive association. But then again, there were many that did not.

And just one thing to point out with Toledano, I agree that they were -- I believe relatively -- had some strengths in their exposure assessment, because that's definitely a theme of concern among all of these. I just

wanted to point out though that it was a -- it was a large study. So when their so very, very small effects become significant -- so looking back at one of your tables, the odds ratio for -- let me see, is this the -- either -- oh, here it is. Sorry. Trying to just -- odds ratios for low birth weight are what was significant, and the odds ratios for -- were 1.05 and 1.10. So it was very, very, very small risk, which just was very precise because of the sample size. I just wanted to point that out, given that it was just 1 of the 2 that had been highlighted.

And then I think that's the end of my comments.

CHAIRPERSON GOLD: Okay thank you. Maybe I'll pause and see if the Panel has any questions or discussion for these two presenters and this topic -- this set of topics?

COMMITTEE MEMBER NAZMI: Can I just point out one more thing real quick?

CHAIRPERSON GOLD: Yeah, sure.

COMMITTEE MEMBER NAZMI: You're absolutely right. I have here in my notes that -- and I didn't cover this, but the Iszatt et al. 2014 study, which, as Dr. Kaufman mentioned, showed a pretty strong dose response effect with low birth weight, and some effect with very low birth weight as well. That one stuck out to me methodologically because of the -- it was that enhanced coagulation study,

which basically halved the amount of chloroform in drinking water over time. And the outcome measures were -- percent change for rates before and after this EC, this enhance coagulation.

So as -- even though it was a retrospective cohort, it seemed -- it seemed that it provided a lot of good evidence that removing half of the chloroform in the water supply had a dose response effect on the low birth weight outcomes.

So I just wanted to throw that one out there as well, because it was a -- the design was very unique.

CHAIRPERSON GOLD: Thank you.

Dr. Woodruff, did you have a comment?

COMMITTEE MEMBER WOODRUFF: Yes.

CHAIRPERSON GOLD: Question.

COMMITTEE MEMBER WOODRUFF: Thank you. I really appreciated the comments that were given, and I wanted to agree with what I thought was that the effects on pre-term birth were not very consistent, but that there was consistent effects seen with -- whether it was measured as low birth weight as -- or birth weight changes. And I would just note, I agree about the comment in terms of the number being these are relatively large.

So even though I said that thing about the meta-analysis, which I still think is something important

to do, I'm not sure it would have been substantially added information, because the sample sizes were so large in these studies. But I would also note that because of the potential for the exposure misclassification, because it's very difficult to model it, that these effect estimates have a higher likelihood of being underestimated because of that, because of the exposure misclassification.

And I want to also comment that the birth weight -- effects on birth weight are supported by the findings in the animal studies.

CHAIRPERSON GOLD: Okay. Thank you.

Any other comments by the Panel, questions?

Okay. All right. I think what we'll do is go to the next topic, and then we'll see where we are in terms of taking a lunch break.

So the next topic, Dr. Carmichael will take the lead on talking about human birth defect studies, studies of spontaneous abortions and stillbirths. These, as I understand it -- I welcome being corrected by the Panel -- can either be considered developmental toxicities or female reproductive. They fall sort of in both categories. And so -- but we'll discuss them separately. Is that -- am I incorrect about that?

DR. DONALD: Yes, that's correct.

CHAIRPERSON GOLD: Okay. Good. All right.

First, Dr. Carmichael, then Dr. Nazmi. And I've also asked Dr. Plopper if he would comment on the 3 studies on birth defects. So, first, Dr. Carmichael.

COMMITTEE MEMBER CARMICHAEL: Okay. A lot fewer studies here. So start with birth defects. There were 3 studies and they varied to a great extent in design. Two of the 3 looked at multiple different types of birth defects in my -- so all 3 were basically not significant, but I just wanted to make the point that 2 of the 3 looked at multiple different types of phenotypes. And they really -- they grouped them together like grouping all heart defects together, grouping all musculoskeletal together, and so forth.

And just in -- in each -- that involves a lot of different specific types of phenotypes with what we see is they typically have very different etiologies. So while the -- so I consider that a strong negative that they -- that they grouped them in that way. So I just wanted to say that although all 3 were negative, definitely too few studies with the substantial methodologic weakness for us to really -- it doesn't provide evidence for an association, but it also doesn't really tell us whether there really and truly isn't one.

As far as spontaneous abortion, again 3 studies. I think Savitz and Waller had some definite strengths as

far as how they were measuring the exposure. And then the 3rd one by Wennborg was just -- was occupation -- associated with just an occupation where chloroform was present, which is really not specific at all. So the other 2 Savitz and Waller both were not significant and were, I thought, relatively well done. So no real evidence for an association there.

And then stillbirth, there were 4 studies, again, quite heterogeneous. And with regard to design and potential strengths and weaknesses, none of them showed a strong evidence for an association. But again, I want to note that stillbirth again is a very heterogeneous outcome with respect to cause, and with respect to timing and so forth.

So there's no evidence for an effect, but I don't feel like we've studied it well enough to really know whether there really is one. So that is the extent of my comments.

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Nazmi, would you like to follow up.

COMMITTEE MEMBER NAZMI: I'd like to defer to Dr. Plopper.

CHAIRPERSON GOLD: I'm sorry, I didn't hear you.

COMMITTEE MEMBER NAZMI: I'd like to defer to Dr. Plopper, first.

CHAIRPERSON GOLD: Okay. Dr. Plopper, any comments specifically on birth defects, but anything you would like to -- any of the foregoing.

COMMITTEE MEMBER PLOPPER: I thought the -- in terms of looking at a range of birth defects, I think they -- all 3 of the studies -- 2 of the studies did a very good job of looking around, but they did lump things, which was of concern, but -- and it appears that for -- there were changes related to concentrations of other trihalomethanes, but not for chloroform, with the exception of the chromosomal aberrations in one study. And one of the studies did not base their assessments on maternal intake, another did, and they essentially found no effects for either one.

And the one that focused only on male urogenital damage found that chloroform concentration was not major. I thought they were fairly consistent that this is not a major problem. It doesn't seem to show up anywhere. I mean, they did about as thorough a job as you can do on these types of studies.

CHAIRPERSON GOLD: Thank you.

So, Dr. Nazmi, did you want to comment now?

COMMITTEE MEMBER NAZMI: Yeah. I have no further comments.

CHAIRPERSON GOLD: Okay. No further comments.

Okay. Anyone else on the Panel have questions or comments based on the discussion about birth defects, spontaneous abortions, or stillbirths.

Okay. Hearing none, we can go on to female reproductive toxicity before we do a lunch break. Does that sound -- yeah, so I'm -- it might go relatively quickly, and so do that before lunch break. Okay.

So I will start and then Dr. Woodruff will comment as the second discussant.

So basically, we had 2 studies, 1 dealing with the outcome of time to pregnancy, and the other one dealing with measures of a menstrual cycle disruption. They were rather different types of studies, in terms of their exposures assessment, their outcome assessment, and the quality of the study.

The one study that looked at time to pregnancy was looking at whether the -- that whether dental surgeons had exposure to chloroform based route canal sealers, and compared their time to pregnancy to teachers -- high school teachers. And basically, I had a number of concerns with the study design, but they found no effect on time to pregnancy.

And then the second study by Windham and colleagues was a well-constructed prospective study that followed up women and looked at their -- the exposure and

consumption and use of water, in terms of chloroform exposures.

And the outcomes of interest were changes in menstrual cycle length and in different phase lengths, follicular luteal phase length. And while this was a better constructed study, and they did find some effects with trihalomethanes, these were -- these changes were not observed in association with chloroform exposure. Although, it was associated with a shortened luteal phase.

And I will say in all of the -- many of these studies, I have concerns sort of about multiple comparisons, as well as -- we only have this 1 study. And so I would say that in terms of human female reproductive toxicity on the 2 measures that we have, which are time to pregnancy and disturbed menstrual cycles, which by the menstrual -- disturbed menstrual cycles can affect the ability to conceive and so forth. So it can have impacts on fertility. But I would say that the evidence before us is not sufficient to indicate suggestive perhaps from the Windham study.

I'd also note that, as I said earlier, we could consider spontaneous abortions and stillbirths under this category of female reproductive toxicity, but I don't have anything to add to what my colleagues have already said on that regard.

So, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Thank you. That was an excellent summary. I would agree that the Windham study was very well done, and they did find some potential effects on menstrual cycle. But the reality is we only have these 2 studies. And I do think that the Dahl study had a lot of challenges, including probably a very high risk of bias for their exposure assessment, which was based on recall and estimating the number of root fillings per week, so it's very far from having actual exposures for chloroform.

CHAIRPERSON GOLD: Okay. Thank you.

Anyone on the Committee have any comments or questions regarding the human female reproductive toxicity studies?

Okay. Well, given our speed, I wonder if we ought to take up the human and animal male reproductive? Do we think we could do that before lunch?

Yes. Okay. Dr. Baskin, you're nodding, so I'm going to turn it over to you.

COMMITTEE MEMBER BASKIN: Thanks again to Dr. Kaufman for an outstanding summary. There were 4 papers in this category. One paper was a case report. And since no journal will publish a case report anymore, I don't think we really need to discuss it, because it's a case

report with very low level of evidence, but something that should be researched in other papers.

And so we have 3 other papers that looked at humans. And 2 of them, as summarized by Dr. Kaufman, really showed no significant changes. And the Zeng paper in 2014 was the one that there was a potential suggestion that there was a decrease in the parameter of spermatogenesis.

Measuring outcomes of male reproductive fertility that's based on spermatogenesis in itself may have some problems, since the World Health Organization and a number of other well-documented reference papers have shown that over time there's been a decrease in the number of sperm to begin with. Although, that doesn't necessarily relate to fertility. But saying that, it's a reasonable surrogate, although not perfect.

I have some kind of global critiques of the 2014 Zeng paper, which also relates to the 2013 paper, in that the patients were recruited from a fertility clinic. So there is already some question of subfertility, which makes it reasonably biased in respect to looking at the data. And I think a stronger epidemiologic study would have just picked people who weren't in a fertility clinic, as what I would say would be better controls.

We talked about the sperm as a surrogate for male

reproductivity. And it's a reasonable thing to study, but none of the papers really look at pregnancy or actual fertility.

The 2014 paper also looked at the estimation of the oral ingestion of chloroform. In other words, there was no actual measurement in this cohort, even though it was a prospective cohort, in contrast to the 2013 paper, which actually had a blood test measurement, which I think is -- would be a little more reliable. So in designing the paper, I think that would be something that would have made the evidence a little bit stronger.

Certainly, and as was talked about in the papers, there's multiple co-founders, because there's multiple exposure. It's not just chloroform. And that obviously could just come up with -- the conclusion could be this was all true, true, and unrelated, which makes the findings, although suggestive, not as strong.

So summarizing. One of the papers was a case report. And that doesn't have much credence. And then the -- there was an English study, which also recruited patients from a subfertility clinic, and found no changes. There was a 2013 Zeng paper, which actually measured the level in blood, which showed no changes in respect to analyzing.

The outcome was sperm morphology in all these

papers, which didn't show any significant changes. And a 2014 paper is the only one that showed a decrease in sperm concentration, but not in many other parameters. And that's suggestive that chloroform could be an issue, but in my mind, not definitive.

CHAIRPERSON GOLD: Okay. Thank you. Dr. Plopper, do you have any comments on this?

COMMITTEE MEMBER PLOPPER: I think I share his comments. I was a little concerned, because the recruitment of all these patients had to do with fertility clinics, and so they already made selection. And I noticed in the case of the study from Britain, that actually the -- the ones that were used as referents actually had higher -- an average higher concentration exposure than the ones that were supposed to be the subjects for this.

So it's sort of -- I would agree with you, I don't think the evidence is very strong that there is a male reproductive impact. I thought they did a -- I think we -- it -- they did a careful job of trying to assess sperm function, but you don't know how that affects fertility. Okay. That's all.

CHAIRPERSON GOLD: Thank you.

Dr. Woodruff, any comments?

COMMITTEE MEMBER WOODRUFF: No, I agree with all

the previous comments. I had essentially the same evaluation though. I would note there's more people in that first Zeng study with the -- where they model the exposures. And I thought that they actually did a pretty good job of trying to estimate -- evaluate the exposures from that study.

COMMITTEE MEMBER PLOPPER: I would agree. I think that's probably the best of 3 in terms of that.

CHAIRPERSON GOLD: Okay. Thank you. Any comments on male reproductive studies, animal or human, from the Committee, questions, comments?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: We just --

CHAIRPERSON GOLD: Okay. You only commented on humans, but the category included males, so do you want to comment on the male?

COMMITTEE MEMBER BASKIN: No. Just for confusion, I just studied the -

CHAIRPERSON GOLD: The animals.

COMMITTEE MEMBER BASKIN: We just discussed the humans

CHAIRPERSON GOLD: Commented on -- right. Do you want to comment on the animal studies?

COMMITTEE MEMBER BASKIN: Well, aren't we going to discuss the animal studies in more detail?

CHAIRPERSON GOLD: Well, they were put into this category because -- because there were relatively few studies.

COMMITTEE MEMBER BASKIN: Yeah.

CHAIRPERSON GOLD: But if you'd prefer to do it later, we can do it later.

COMMITTEE MEMBER BASKIN: Let's do it later.

CHAIRPERSON GOLD: So we'll do it after lunch.

Okay. Any other comments or questions about male reproductive studies -- human male reproductive studies?

Yes. We'll do -- we'll start with -- if it's all right with you, we'll start with the animal male reproductive studies right after lunch, okay?

Okay. So do we need a half hour, 45 minutes? What would people prefer for lunch?

Half hour? Going, going, going. You prefer 45. More feasible. Well, let's aim for 30-ish, and, you know, it will probably be more like 40-ish. So let's aim for being back at 12:45, but it will probably be a few minutes after that, okay?

Thank you.

(Off record: 12:15 p.m.)

(Thereupon a lunch break was taken.)

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

(On record: 12:58 p.m.)

CHAIRPERSON GOLD: Okay. We can now reconvene, as all Committee members have returned. And as promised, what we'll do is turn now to the animal male reproductive studies. And, Dr. Baskin, you're going to lead us first.

COMMITTEE MEMBER BASKIN: Thank you to Dr. Campbell for summarizing these quite elegantly.

So there were 4 studies. And the one that is the most concerning was from 1981, where mice were given quite a bit of chloroform by inhalation, and didn't die from arrythmia, so I was kind of surprised about that.

(Laughter.)

COMMITTEE MEMBER BASKIN: But they showed -- I mean, the study -- there were -- there were controls, as well as -- I'm forgetting the number of actually experimental, but they're relatively equal. And the outcome was epidiymal sperm of morphology. So they analyzed the sperm in the epididymis, and they essentially showed a dose response of increasing abnormalities. And again that's from 1981.

There is then 4 other studies, which 2 in mice, 1 in rats, and 1 in dogs, which essentially showed no other -- which essentially showed no, what I would call, abnormalities in relationship to either analyzing the

sperm or, in some cases, specifically the dog study, which is quite a long-term study of long-term exposure. No histologic abnormalities in the testes.

I might note that in the Land study, they would have had a nice chance to actually analyze morphology of the testes, which would have been a little more interesting and a little more suggestive. But again, this is quite old.

So as to not really to belabor the point, there's one study that's slightly concerning, but it's 35 odd years old. And the other studies, which were I think of actually slightly higher scientific quality, which include rats, dogs as well as mice, did not show really any significant abnormalities in male reproductive toxicity.

CHAIRPERSON GOLD: Thank you. So now, Dr. Plopper, I believe you were going to comment on these.

COMMITTEE MEMBER PLOPPER: Okay. The one that I agree with his comments, the inhalation study in the mice was a very high concentration. And it was quite awhile ago, but they did show sperm changes. The other 2 studies, 1 on rats and 1 on mice that were long term did not -- one of them did not do a very comprehensive evaluation, but they did find a change in 1 testis in 1 study and some change in epidemiology -- epidiymal weight was in another study, but no change in any of the sperm

parameters.

And then the study that fed the toothpaste to the dogs had one change in, and that was it. So essentially there really were no definitive changes except that very high inhalation study.

CHAIRPERSON GOLD: Okay. Thank you. Dr. Woodruff, anything additional?

COMMITTEE MEMBER WOODRUFF: I don't have anything additional to say, other than I did want to point out that we've had this situation in the past where we often have not very good studies, and not necessarily a very sensitive endpoint. So a lot of the ones that you mentioned were of the weights of the epidiymal and the testes. And those are not really going to be very sensitive markers necessarily for effects on sperm function or motility or volume.

So I just would note that, as we have said in the past, that just because we don't find this, doesn't mean that more studies couldn't be done to evaluate this in more methodologically superior approaches.

CHAIRPERSON GOLD: All right. And any comments or questions from the rest of the Panel?

Dr. Baskin

COMMITTEE MEMBER BASKIN: I mean, on the other hand, the dog study was an incredibly long study 7 years.

And dogs are probably closer to the humans than mice and rats. And they did look histologically at the animals and didn't see anything. And that's pretty solid evidence in my mind that at least chloroform doesn't affect dogs. It doesn't say anything about humans.

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Campbell.

DR. CAMPBELL: I just wanted to remind the Committee there's also that multi-generation study, which did show effects on various indices of mating infertility that could be related female or male reproduction as one more endpoint that didn't come up.

CHAIRPERSON GOLD: Dr. Baskin.

COMMITTEE MEMBER BASKIN: Thank you for pointing that out, because since it wasn't published --

DR. CAMPBELL: Yeah, I know.

COMMITTEE MEMBER BASKIN: -- we kind of missed it, or at least I did.

DR. CAMPBELL: Yeah, I know.

COMMITTEE MEMBER BASKIN: But it's conclusion with all the data again is as you stated.

CHAIRPERSON GOLD: Any other Committee members have comments, questions?

Anything further on either the human or the animal male reproductive studies?

Okay. Hearing none, let's move ahead. We have two more categories, one is animal developmental studies, and Dr. Auyeung-Kim is going to be the primary discussant followed by Dr. Woodruff and maybe Dr. Plopper might have something to say.

COMMITTEE MEMBER AUYEUNG-KIM: Thank you. I want to echo whatever everyone else has said about the OEHHA staff presenting that was especially Dr. Campbell for providing the comprehensive review of the animal data. And so the studies that were conducted in the rat, mouse, and rabbit, the rat and mouse had inhalation as well as oral administration, and the rabbit only had the oral administration as well as there was a zebrafish study.

And so most of the studies were of high quality and well designed with the typical endpoints that are appropriate to evaluate the developmental toxicity. And as we briefly touched upon earlier, when we had the questions after the staff presentation, most of the fetal effects were -- the decreased body weight was seen at doses that maternal toxicity was also observed, which included the decrease -- the maternal toxicity being decreased weight and death and hepatotoxicity.

And so I understand that EPA, their strategy for evaluation is that they couple both the maternal tox as well as the fetal toxicity and would label it as possibly

being a fetal -- a developmental -- or resulting in developmental effects.

However, I personally feel that you can't really -- because of -- you can't really say that the decrease fetal waits is a direct developmental insult, because of the maternal toxicity that was seen in the studies.

And so I would look at it as -- I would uncouple them and feel that there is no development -- that the fetal weight -- or the decrease in fetal weight is a result of the maternal toxicity, and not due to a primary developmental effect.

In looking at the designs of the studies, they were robust. Most of them had a sufficient number of animals. And there was a couple of studies that did not, which I think the rat and mouse oral studies that lack whether there was maternal -- lacked whether there was maternal toxicity observed in those studies. Additionally, the studies were conducted mostly in the 70s and 80s, so, you know, 30-plus years ago. A couple in 19 -- there was a couple in the 1990s, 2004.

The inhalation studies also were high exposures, high concentrations for up to 7 hours per day. And, you know, the one study that the exposure was only 1 hour per day, the dose administered was up to 4,100 parts per

million per day -- or parts per million.

So I think that for these studies that extremely highly doses were administered.

And I think that's...

CHAIRPERSON GOLD: Thank you.

So, Dr. Woodruff, do you have anything?

COMMITTEE MEMBER WOODRUFF: Yes, I do. So I -- yes, there were a number of studies that evaluated developmental effects from maternal exposures during the developmental period to chloroform as was noted, both inhalation and oral.

I would say that the studies were reasonably well conducted. And they were experimental, so that gives them -- we have a higher confidence in their findings because they're experimental. But a lot of the studies did have some issues in terms of not every study mentioned whether they randomized. And it wasn't always clear whether the outcomes were blinded.

I did note the -- I agree that there was maternal toxicity in some of the higher exposures in the studies, so what I did was I looked at the studies because some of the studies looked -- particularly in the inhalation, looked above 100 -- or in the oral dosing looked above 100 milligrams per kilogram day, but there were a number of studies that looked at lower exposures.

And the higher exposure studies it's true had decrements in birth weight, but the lower exposure studies actually whether -- if there were -- there either were not decrements of maternal birth weight and/or the decrements were pretty modest, as was said by OEHHA, that minor decrements in maternal birth weight should not necessarily influence our evaluation of the outcomes among the fetal -- the fetal outcomes for birth weight.

And this was actually something I think that it would be good for OEHHA to consider in the future was it actually used -- the National Toxicology Program has available software that they have for graph -- both extracting data and studies into -- their program was called HAWC project.

And so I used that to look at the differences in birth weight for the fetal measurements that were done in 1, 2, 3, 4, 5 of the studies. And it's true that if you look at just the tables that the decrements and birth weight don't look -- they look modest, but once you graph them, they're modest, but consistent decrements in birth weight, especially in the Thompson study with the female Dutch-Belted rabbit, you see a nice dose response in the outcomes below the maternal -- the doses where they had maternal -- more frank maternal toxicity.

And the Garcia -- I would note that also the

Garcia-Estrada study which -- I don't remember if you talked about that, was -- saw consistent decrements in birth weight, though I have to say that study was a little bit difficult to interpret, because it's in Spanish. So I did ask for the English translation of the tables from the OEHHA staff, which I used to look at -- and then in terms of the -- kind of the birth defects piece, there were both findings in a number of studies in terms of impaired fertility.

So, for example, in the Murray study in the mice, they saw decrement in percentage of the mice that were pregnant. There was a decline in implants in the U.S. EPA study. Then there was an increase in birth defects in a number of the studies, including the Thompson and the Murray study. And I didn't count the Ruddick study because of the maternal toxicity effects that were observed at the higher exposures.

And then I also noted there were a number of studies that looked at embryo toxicity, and it didn't mention, but that zebrafish study was actually a very nice study that looked at effects on the -- this is the -- oh, and also the Lim study, which I didn't mention, which is not a study of directly looking at birth defects, but was evaluating maternal exposures to chloroform really to look at glucose tolerance tests in the out -- in the offspring.

But what's interesting about that study was there was consistent postnatal decrements in growth among the offspring. So while they didn't see necessarily decreases fertile -- fetal weights, they saw that the pups, as they were growing, were consistently -- those exposed to chloroform had consistently lower weights compared to the controls.

And finally, that Teixidó study -- I don't know if I'm pronouncing that correct -- in the zebrafish looked at a number of different developmental outcomes. And because that was an experimental study, and performed more recently in 2015, was quite a nice study that found a number of different effects on the offspring in the zebrafish.

That's it.

CHAIRPERSON GOLD: Thank you.

Dr. Plopper, do you have anything to add?

COMMITTEE MEMBER PLOPPER: Yeah. For not much I think they've covered just about everything. I just wanted to point out that the one study that -- by gavage at 1 dose did find problems with neuromotor control of the forelimb, which would indicate that there was some sort of a disruption there for development.

And I agree with the last comments that the changes in the zebrafish in vitro were quite startling,

quite interesting, but then there were clear developmental changes there. And it was inhibiting how that attached for the rest of it. It's all in vitro, but at least that means there's a control dose.

CHAIRPERSON GOLD: Thank you.

Anymore comments or questions by the Panel pertaining to the animal developmental studies?

Okay. So we'll go to our final category, which is the animal female reproductive studies. And, Dr. Plopper, you're going to lead us off and then Dr. Auyeung-Kim, you will be our secondary discussant.

COMMITTEE MEMBER PLOPPER: Okay. There were 10 studies in this category. There's 11, but we addressed the -- most of these are -- have already been discussed in other aspects. There were 4 of these that were inhalation studies, and maybe we can talk about those first in -- either in rats or in mice.

And the Schwetz study actually was -- had variable -- exposure over 6 to 15 days of gestation in pregnant rats, and did, in fact, find changes at the highest concentration, which included changes in ratios of male to female, and fetal body weights. I don't know if you consider those reproductive or not.

And there were changes in body weights of the mothers down to, but not including, the lowest of the 3

doses.

There was also changes in the other inhalation exposures with the Wistar rats. The mothers had considerable problem with body weight and food consumption, but the drop in fetal body weight was significant, but that was pretty much some skeletal abnormalities.

The same was true for both of the studies by Baeder and Hoffman. There were some changes there. And they were reasonably well-controlled studies. The mouse inhalation study showed really marked changes with exposure, as Dr. Campbell has already said, at the lowest -- in the low -- the 1 to 5 day gestational ages, and increases in absorption, decreases in fetal body weight, and crown rump length.

And then Ruddick study, which was -- also was by gavage or it was a drinking -- I'm sorry, that was a drinking study, also found some changes in fetal -- mostly in aberrations in the growth of the fetus. And so did the Thompson study really didn't find much except skeletal changes. Again, these were both studies where it was oral during gestational time. And the Chapin study, which was a gavage study, must have been a tremendous amount of work, did not really show much that was significantly different, except some changes in fertility index.

And then finally, the Thompson study, again oral in rats -- rabbits, had some problems with skeletal were the significant things, and some changes with fetal viability down.

And I think that -- maybe that's pretty much it for the start of those. So maybe we could discuss that first and then talk about this multi-generational study at the end, because there's a lot -- that's another whole story completely. So that was...

CHAIRPERSON GOLD: Okay. That sounds fine.

Dr. Auyeung-Kim, do you want to add anything to this part?

COMMITTEE MEMBER AUYEUNG-KIM: No, I think Dr. Plopper as well as Dr. Campbell have covered everything that I was going to say.

CHAIRPERSON GOLD: Okay. So well done. So now we could -- I think, if you want to address the multi-generational studies Dr. Plopper.

COMMITTEE MEMBER PLOPPER: Yes, this is an interesting study that Dr. Campbell has outlined very well already. But it's 3 -- 2 different, an F/0, an F/1, and an F/2. And some of the study they abandoned, but the issue was -- the thing that -- one of the concerns I had with this study, besides the fact that it was never actually published, which probably would have helped

interpretation tremendously, is that they only did a toxic evaluation of the mothers -- and the males and the females from 2 groups, the F/0 group and the F/1B. So we don't really know what the full range of toxicity to the males and females is in all the other groups.

And that can sort of impact how the rest of it is evaluated. But for those 2 groups, they had the 3 doses is a 0, which was a vehicle, and then a naive, and then a 0.1, 1.0, and 5.0. And these were exposed continuously as they mixed up. The strength of this study is they did a really excellent job of trying to randomize everything within these various groups, so that as not to generate any extra bias. And they did find significant drops in the mating index, particularly in the F/1 and F/2 groups, not in all of them, just in part of them.

They found a change in gestational index again in F/1 and F/2, but not in all of those. There are 5 different -- 3 F/1s and 2 F/2s that were being considered here. Unfortunately, one of them they didn't have controls for, so I don't know how it fits into this. Pups per litter were down, and as was viability index for the pups was also down, and lactation for the mothers index in 2 groups was down, and then postnatal body weight was down.

Now, these were all in the high concentration

group, except for a few, and that includes the viability index in one of those groups. But remember, we have 5 groups, it only showed up in 1.

And the same is true for the mating index was also down in one of these -- at one of the very low doses. So it did appear that there -- that there was some sort of a negative impact on, I don't know if you'd call it, reproduction fertility, all of the functional things that one would expect when you have actively breeding males and females put together in a relatively random fashion and record it as it goes along.

My main concern was there wasn't enough pathology at the end of this study. And, of course, it wasn't published, but there -- if we're not going to consider the fact that we don't know what the toxicity for all but one of these F/1 and F/2 groups is for this compound with this type of exposure, there -- at the highest concentration, there was, in fact, a change. It's some kind of indication of reproductive problems that seem to go on from generation to generation almost, but it's not a complete -- none of them are complete. There are groups in each F/1 and F/2 that didn't really have a significant change.

So I don't know if that's -- that's a start anyway.

CHAIRPERSON GOLD: Okay. Thank you,

Dr. Auyeung-Kim, do you want to add to this?

COMMITTEE MEMBER AUYEUNG-KIM: I think that in looking at the study that they evaluated only at the high dose is that I think wasn't -- wasn't the -- if I recall correctly, the animals were -- fell sleep, where they were --

COMMITTEE MEMBER BASKIN: It's hard to mate if you're sleeping.

(Laughter.)

COMMITTEE MEMBER AUYEUNG-KIM: Yeah. So I think that that contributes to some of the findings.

COMMITTEE MEMBER PLOPPER: Right.

COMMITTEE MEMBER AUYEUNG-KIM: Human or animals.

COMMITTEE MEMBER PLOPPER: Yeah, it definitely did depress brain function. And these animals were not awake and not functioning, yes, I agree.

COMMITTEE MEMBER BASKIN: I mean, on the other hand, it did seem to pass through the generations, which could not be explained by that.

CHAIRPERSON GOLD: Okay. Sorry. Anyone have anything to add regarding the female reproductive studies in the animals?

Any other questions, comments?

Okay. Well, I think then we can open the Panel

up to just discussing developmental and reproductive toxicity of chloroform in general before we vote, whether there are any issues remaining that we haven't yet discussed or questions that remain unanswered?

Everybody is very quiet. Does that mean we're ready to vote, yes?

COMMITTEE MEMBER WOODRUFF: Yes.

CHAIRPERSON GOLD: Okay. I don't want to rush anybody.

Okay.

COMMITTEE MEMBER WOODRUFF: I'm ready. I don't know about anybody else.

CHAIRPERSON GOLD: Anybody not ready, let's put it that way?

Everybody is ready. Okay.

All right. So we'll start with male reproductive toxicity. We have formal language. So Has chloroform been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? All those voting yes, raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see 0.

All those voting no?

(Hands raised.)

CHAIRPERSON GOLD: Five, six, seven.

Any abstentions?

I count none, but just checking.

Okay. You have a question.

COMMITTEE MEMBER WOODRUFF: Yeah, because we're going to go on to the female, is that right?

CHAIRPERSON GOLD: Yes.

COMMITTEE MEMBER WOODRUFF: So if we see some of these effects or we're concerned about some of these effects about reabsorption, or not -- less successful pregnancies, is that -- we just had this. We can consider that a developmental, right?

CHAIRPERSON GOLD: So as I understand it, it can be considered either developmental or female reproductive. And if there's any guidance as to which category we should decide it in, that would be appreciated.

COMMITTEE MEMBER WOODRUFF: I know. I've known this for a while.

DR. DONALD: Yes, there are many endpoints. Well, as we all know, male, female -- male and female reproduction and development are not independent categories. They're all biologically interrelated. So it's really the Committee's prerogative to decide whether you think the evidence for any particular endpoint reaches your standard of clearly shown. And then also your

prerogative to decide whether you believe it's indicative of developmental or male or female reproductive toxicity, or some combination of those.

COMMITTEE MEMBER WOODRUFF: Can we vote on the developmental first then?

CHAIRPERSON GOLD: Okay. There's no problem with that, I don't believe, but -- I mean, I think the issue is particularly -- and correct me if I'm wrong -- with spontaneous abortions and stillbirths in humans and resorptions in animals, or lower litter size that it could be a female -- you know, an issue with a female exposure, it can be an issue with -- some issue with the fetus itself. And so it's not a clear distinction. You can --

DR. DONALD: That's exactly right.

CHAIRPERSON GOLD: -- pretty decide which basket you want to put it in.

DR. DONALD: That's exactly right, so it may be a direct effect on the conceptus. It may be entirely mediated through some effect on the female reproductive system that makes it incapable of supporting the pregnancy, or it may be both. So the empirical outcome is usually clear and is clearly an effect on development.

Usually, it comes down to a question of how well you understand the mechanism by which that empirical outcome is being induced as to whether you can also

determine whether it's an effect on the female reproductive system.

CHAIRPERSON GOLD: Yeah, and I just mentioned 2 outcomes, but really I guess you could consider like pre-term birth, and small for gestational age, and low birth weight as also not -- either -- it could be either one, either the fetus or --

DR. DONALD: Yes, there are many developmental outcomes that can be directly impacted by effects on the female reproductive system. There are others where it's less likely that that's happening. But again, it's usually a question of how well do we understand the mechanism or multiple mechanisms by which those effects are being induced, whether we can attribute it to effects on female or male reproductive function or a direct effect on development.

CHAIRPERSON GOLD: I don't mean to leave the male out. I guess that's a possibility as well.

All right. So the request is that we take up developmental toxicity next. Okay. So we'll be voting on that.

So according to general accepted principles -- sorry. Has chloroform been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? All

those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see 3, 4, 5. Going, going 1, 2, 3, 4, 5. Yes.

All those voting no?

(Hands raised.)

CHAIRPERSON GOLD: One, two.

Okay.

And no abstentions, correct?

Right.

So now we'll go back to female reproductive toxicity. Has chloroform been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? All those voting yes, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see 0.

All those voting no?

(Hands raised.)

CHAIRPERSON GOLD: 1, 2, 3, 4, 5, 6, 7.

Everybody raise your hand if you're voting no?

(Hands raised.)

CHAIRPERSON GOLD: I see 7.

Those abstaining should be easier?

(No hands raised.)

CHAIRPERSON GOLD: No one.

Okay. So I'm supposed to announce the results. So for male reproductive toxicity, we had 0 voting yes, 7 voting no, and no abstentions. For female reproductive toxicity, we had 0 voting yes, 7 voting no, and 0 abstentions. And for developmental toxicity, we had 5 voting yes, 2 voting no, and 0 abstentions.

Okay.

ACTING DIRECTOR ZEISE: So I just want -- hi, this is Lauren Zeise. And I'd just like to interpret this result in terms of Proposition 65 listing. So there are, I believe, 8 members -- no, 9 members currently of DART Committee members. And what is required for listing is that the majority of the appointed members vote positively. So we have 5 votes. So this will be -- chloroform will be added to the Proposition -- or remain on the Proposition 65 list, and the parenthetical will be developmental toxicity.

CHAIRPERSON GOLD: Okay. So having completed that -- by the way, thank you to the staff for really excellent detailed, evaluations, reviews, and presentations.

Do you have something you want to say?

COMMITTEE MEMBER WOODRUFF: Yes, I do. Thank you. Yes, I wanted to echo that. And I think that the

presentation that -- I said this already, but I'm going to say it again, is that the presentation of the epidemiology studies graphically was very helpful. And I think this can also be done with the animal studies. And NTP has a program to do this now that's well vetted. And I just think -- I'm not going to think. I've asked about this before, so I want to see it at the next meeting. That's what I'm -- so...

CHAIRPERSON GOLD: Okay. Thank you.

So our next agenda item has to do with an update on the Section 27000 list of chemicals which have not been adequately tested as required. And I believe Carol Monahan-Cummings is going to update us.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN CUMMINGS: Right. So this is the other Prop 65 list. As you may recall, we've looked at this issue in the past. The law requires 2 different lists. The one that you were just talking about is the one that most people are aware of. And that's the list of chemicals that are known to cause cancer or reproductive toxicity.

However, there's another list that we call the Section 2700[sic] list, which is a list of chemicals that require testing that -- where the testing has not been

completed.

And so each year, we contact the U.S. EPA, a couple of different offices within U.S. EPA, and the California Department of Pesticide Regulation and ask them for updates on this list of chemicals that needs -- need testing.

And so earlier, I think in the last couple weeks, you got a letter from me that had attachments showing the responses we got from U.S. EPA and CDPR in regard to these chemicals. And so we're going to show you, I think, 3 slides. The first one being a change to an existing chemical on the list sodium fluoride. We're suggesting that you agree with U.S. EPA, or DPR in this case, and agree that some of the testing has been satisfied, but that there still needs to be these 2 tests completed.

So I don't know -- Dr. Gold, would you like me to go through all of these first and then you guys can vote once? Does that sound all right?

CHAIRPERSON GOLD: Yeah, that sounds good.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. All right. So next slide.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: All right. So here's some chemical -- or endpoints that need to be added to the list for these chemicals that are on the slide

here. And they're either adding the chemical or a particular endpoint that needs testing. And this is base on information from DPR again.

And the last slide.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: According to U.S. EPA, these 3 chemicals, they've received all of the testing that they've requested. And so they're suggesting we take these 3 off of our list.

All right. So maybe if you don't mind, Dr. Gold, if you can ask the question whether or not the Committee wants to agree with U.S. EPA and DPR about these changes to the list?

CHAIRPERSON GOLD: So I guess the question is whether we want to agree with U.S. EPA or if we want to go through these one by one. Any sense of the Committee on that?

CHIEF COUNSEL MONAHAN CUMMINGS: Well, we've got a protocol, so I suppose we could just go ahead and follow. We can go back to the first slide.

CHAIRPERSON GOLD: Okay. So the first one has to do with sodium fluoride.

CHIEF COUNSEL MONAHAN CUMMINGS: You want to go back to that.

CHAIRPERSON GOLD: Is that correct?

CHIEF COUNSEL MONAHAN CUMMINGS: Right.

CHAIRPERSON GOLD: And whether this is partially satisfied, and so should it be removed from the list is the question you're asking us?

CHIEF COUNSEL MONAHAN CUMMINGS: No. This is to add these 2. Woops, I'm sorry.

Okay. So there's 2 endpoints that we want to remove from the list for sodium fluoride, because they've already been satisfied.

CHAIRPERSON GOLD: So I have a question. It seems like this would be more --

CHIEF COUNSEL MONAHAN CUMMINGS: Of course, this -- it looks like it's a cancer endpoint.

CHAIRPERSON GOLD: This is would be a cancer endpoint, so shouldn't it go to the carcinogenesis --

CHIEF COUNSEL MONAHAN CUMMINGS: And it will. It will. And so --

COMMITTEE MEMBER WOODRUFF: But if it's not been tested for development and reproduction, does it stay on the list?

CHIEF COUNSEL MONAHAN CUMMINGS: Correct. If you'd look in your materials. I don't know if -- do they have the full list? I don't have it.

MS. RAMIREZ: They're in the meeting materials.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay.

Sorry. What we normally do is just give you the full list of the chemicals that the 2 departments have given us, and we don't separate them out for whether they're reproductive or carcinogenic testing.

You might decide to do that in the future. It would be probably make more sense, though the statute actually just says the State's qualified experts have to make the decision. And so that's both this Committee, as well as the CIC Committee.

CHAIRPERSON GOLD: So can I just clarify, is the EPA saying it should be tested for oncogenicity, or is it saying it needs testing for both oncogenicity and reproductive toxicity?

CHIEF COUNSEL MONAHAN CUMMINGS: Could you give me that?

She's giving it to the wrong person.

CHAIRPERSON GOLD: Oh, we have this long list, is that what you're referring to?

CHIEF COUNSEL MONAHAN CUMMINGS: Correct. Michelle, maybe I could see that, since I don't have a copy and they do.

CHAIRPERSON GOLD: Yeah. So this was in something that was recently sent to the Committee --

CHIEF COUNSEL MONAHAN CUMMINGS: Correct.

CHAIRPERSON GOLD: -- like about 10 days ago.

And so according to my list it says teratology in the rat, teratology in the rabbit.

CHIEF COUNSEL MONAHAN CUMMINGS: Could I see that, Michelle?

So what you should have is a markup of what we're trying to change for each of these chemicals. And, for example, for sodium fluoride, there's still -- what we're saying is that we want to take these 2 oncology tests off, because they've been satisfied, but there are still testing -- there's still testing requirements for repro and teratogenicity in the rat and the rabbit. And so this group -- I mean, it's still going to be tested for that. Does that make sense?

CHAIRPERSON GOLD: Okay. So you're asking for the concurrence of the Committee to remove it for oncogenicity, but to retain it for teratogenicity.

CHIEF COUNSEL MONAHAN CUMMINGS: Correct, right.

CHAIRPERSON GOLD: Okay. And we have to take a formal vote, is that --

CHAIRPERSON GOLD: Well, yes. Unfortunately, there's not a way around that. We have to have your concurrence on that in order to change the list.

CHAIRPERSON GOLD: Except the voting thing I have I don't think goes --

CHIEF COUNSEL MONAHAN CUMMINGS: Well, the first

one says that...

CHAIRPERSON GOLD: This one says should the 5 chemicals, so it's asking us to vote on 5 of them at once.

CHIEF COUNSEL MONAHAN CUMMINGS: So that's the next slide, I think.

CHAIRPERSON GOLD: Okay. Oh, I see, so you think maybe I've gone one for one endpoint.

CHIEF COUNSEL MONAHAN CUMMINGS: They're not necessarily in the order of the slides unfortunately.

COMMITTEE MEMBER AUYEUNG-KIM: So basically there's a list of studies that were request to be conducted and we're asking to approve that they remove those 2, because they've been satisfied?

CHIEF COUNSEL MONAHAN CUMMINGS: Correct.

COMMITTEE MEMBER AUYEUNG-KIM: Okay.

CHIEF COUNSEL MONAHAN CUMMINGS: And on this particular slide, we're talking about adding these testing -- these requirements for testing that haven't been completed yet. So I --

CHAIRPERSON GOLD: So the vote -- ballot that I have doesn't specify the chemicals, but it specifies the number of endpoint or the number of chemicals. And so this one --

CHIEF COUNSEL MONAHAN CUMMINGS: Right. So the first one on here, I believe, is for this slide.

CHAIRPERSON GOLD: Is for these 5. So the question is whether these 5 chemicals --

CHIEF COUNSEL MONAHAN CUMMINGS: If we're adding the end --

CHAIRPERSON GOLD: -- the 5 chemicals, as identified, have endpoints added is the question?

CHIEF COUNSEL MONAHAN CUMMINGS: Right.

CHAIRPERSON GOLD: Have added the list of chemicals.

CHIEF COUNSEL MONAHAN CUMMINGS: Right, so these 5 chemicals we're adding these studies, not really endpoints, but these studies that we're -- that are still required to be done, based on what CDPR has advised us. So you're -- the question is whether you agree that we should add these studies as still needing to be done based on the advice of CDPR?

CHAIRPERSON GOLD: Okay. And we have to vote on each of your 3 slides basically. So the first one we're voting on is the slide that's currently up, which has 5 chemicals on it with various outcomes listed.

Are we ready to vote?

COMMITTEE MEMBER WOODRUFF: So these are going to be added?

CHIEF COUNSEL MONAHAN CUMMINGS: Correct. These are added studies that are needed.

CHAIRPERSON GOLD: So maybe I should read what the vote says, so you'll understand what you're voting on?

Based upon the information you've been provided from the California Department of Pesticide Regulation, should the 5 chemicals as identified on the Section 27000 slides have endpoints added the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required?

That's what you're voting on for this particular slide, this particular set of chemicals.

Are we ready to vote?

Okay. Among all those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see 7.

All those voting no, please raise your hand.

(No hands raised.)

CHAIRPERSON GOLD: I see 0.

And all those abstaining --

(No hands raised.)

CHAIRPERSON GOLD: -- should be also be 0.

Okay. So the result is that we have 7 votes of yes, and 0 voting no or abstaining.

Okay. And then the next one.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. This is

the one that we were mentioning before. So the idea is that these 2 would be eliminated but there's still a number of other tests that are still needed, including reproductive tests.

CHAIRPERSON GOLD: Okay. So the next vote is pertaining to the slide that's currently up about sodium fluoride. Okay. And the vote reads based upon the information you've been provided from the California Department of Pesticide Regulation, should the 1 chemical as identified in the Section 27000 slides have endpoints removed from the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required?

Ready to vote?

Okay. All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see 1, 2, 3, 4, 5, 6, 7.

Voting no should be zero.

(No hands raised.)

CHAIRPERSON GOLD: Abstentions?

(No hands raised.)

CHAIRPERSON GOLD: Zero.

Okay. So we have 7 votes yes, 0 votes no, and 0 abstentions.

Okay. And then the final 3 chemicals that are listed on the slide that's currently up.

Based on the information you've been provided from the U.S. EPA, should the 3 chemicals as identified on the Section 2700[sic] slides be removed from the list of chemicals required by the State or -- required by State or federal law to be tested, but which have not been adequately tested as required?

COMMITTEE MEMBER WOODRUFF: Can I ask a question?

CHAIRPERSON GOLD: Yes.

COMMITTEE MEMBER WOODRUFF: Did we -- so they have all their tests -- the teratogen -- I don't see what the testing is that's been done on them. Is that --

CHAIRPERSON GOLD: That was the long list.

COMMITTEE MEMBER WOODRUFF: Oh, it was in the long list I can't find in my email. Okay. Fine.

CHIEF COUNSEL MONAHAN CUMMINGS: So according to the markup list that we gave you, this would be removing the entire chemical off the list, because all of the testing has been satisfied.

CHAIRPERSON GOLD: Okay. Are we ready to vote? Do we need to read it again or -- No. Okay.

All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Five, six, seven.

Any no votes?
(No hands raise.)
CHAIRPERSON GOLD: Zero.
Abstentions?
(No hands raised.)
CHAIRPERSON GOLD: Zero
So we have 7 voting yes, 0 voting no, and no abstentions.
Okay. Do we need a break?
CHIEF COUNSEL MONAHAN CUMMINGS: I think we're done.
CHAIRPERSON GOLD: Well we have any further staff updates, I guess.
ACTING DIRECTOR ZEISE: Yeah, we already did that
CHAIRPERSON GOLD: We did all of them.
CHIEF COUNSEL MONAHAN CUMMINGS: That was at the beginning.
CHAIRPERSON GOLD: And So now, Dr. Zeise, is going to summarize what we did today.
ACTING DIRECTOR ZEISE: Okay.
CHAIRPERSON GOLD: Okay.
ACTING DIRECTOR ZEISE: So the -- so to first to summarize the actions. The Committee deliberated on chloroform and -- which was on -- is on the Proposition 65 list. And their action was to vote 5 in favor, 2 against

for chloroform to be known to cause reproductive toxicity for the developmental endpoints. So chloroform will remain on the Proposition 65 list for the developmental endpoint.

The Committee also unanimously voted on chemicals in the Section 27000 to add 5 chemicals -- 5 chemicals for studies that are required by DPR, then to remove for sodium chloride -- fluoride oncogenicity studies, that are -- have been conducted, and then to take 3 chemicals off that list, because they have been adequately tested according to U.S. EPA.

So I guess to conclude, I'd like to conclude with some thank yous. Thank you to the Committee members for the enormous amount of time that you take reviewing the materials, and taking time out of your busy schedules to be here. We really appreciate it. You've donated a lot of time to the State and expertise to us. So again, really much appreciated.

Also, I'd like to thank the staff for all the hard work that they did. And we heard from many Committee members appreciation for all that work to tee up the discussions for them.

And also for the implementation staff for all of the work you take to organize these meetings, much, much appreciated. And to the members of the public for

participating by webcast and in person and for your comments.

So thank you so much. And with that, I guess we'll adjourn the meeting and safe travels home.

CHAIRPERSON GOLD: I think we are now adjourned.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 1:48 p.m.)

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

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 7th day of November, 2016.

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