MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

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SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

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Ms. Cynthia Oshita, Proposition 65 Implementation

Dr. Lauren Zeise, Chief, Reproductive and Cancer Hazard Assessment Branch

ALSO PRESENT

Dr. Carol Burns, Dow Chemical Company

Dr. Daland R. Juberg, Dow AgroSciences

Dr. Jay Murray, Chlorine Chemistry Division, American Chemistry Council

Dr. Gina Solomon, Natural Resources Defense Council

Dr. Rebecca Sutton, Environmental Working Group

Dr. Robert Tardiff, Chlorine Chemistry Division, American Chemistry Council

Mr. Christian Volz, McKenna Long & Aldridge

INDEX

INDEX CONTINUED

PROCEEDINGS

DIRECTOR DENTON: Good morning. I'd like to ask everyone to take their seats and we'll get started. This is going to be a very interesting and maybe long meeting today. So it's a probably good idea to start very close to the starting time. My name is Joan Denton and I'm the Director of the Office of Environmental Health Hazard Assessment. And this is a meeting -- this is our pre-holiday annual meeting of the Dart ID Committee for Proposition 65. And I want to just take a minute to introduce the Committee Members whose name plates are in front.

But to my left is Dr. Dorothy Burk and she is our Chair. I'll be turning the meeting over to her momentarily. Next to her Dr. Hillary Klonoff-Cohen. Dr. Calvin Hobel is next to Dr. Klonoff-Cohen. And then finally Dr. Linda Roberts on the far left.

On my right Dr. Carl Keen, then Dr. Kenneth Jones followed by Dr. LaDonna White and then Dr. Ellen Gold at my very far right.

So I just want to -- I just have a couple of opening remarks and then the staff tables, I think that people will be introducing individuals as they begin to speak, so I'll leave that for George to do.

I just wanted to remind everyone that at our last

DART meeting, which was last December, December 10th, the Committee recommended that OEHHA evaluate or prepare hazard identification materials on eight, what we call, candidate chemicals. This was the result of looking at the epidemiology screen. And those chemicals were or are hexavalent chromium, chlorpyrifos, DDE, methylisocyanate, bromodichloromethane, sulfur dioxide, caffeine, and bisphenol A.

Now, all eight of these chemicals have undergone a data call-in in preparation for the hazard identification materials. So 2 of the 8 chemicals will be discussed today, those being hexavalent chromium, which is the first item on the agenda, and then chlorpyrifos which is the second item on the agenda. And the remaining six chemicals will be brought to the Committee at a future date or dates.

So with that, I think everyone has a copy of the agenda, and so I don't really need to go through that. I will turn it over to Dr. Burk.

CHAIRPERSON BURK: Good morning, everyone. Thank you all for coming today. Particularly, thank the Committee Members. It's great to see everyone here, again, at this, almost, holiday time of year. It won't start for me till after we get past this.

I also want to, before I even start, thank the

OEHHA staff so much for the huge amount of effort that went into preparing the documents that we're looking at today and for, I think, the presentations that will come. Most appreciative.

So the first chemical on the agenda for consideration for listing is hexavalent chromium. The staff presentation will be given by Drs. Marlissa Campbell -- oh, and Ms. Amy Dunn.

(Thereupon an overhead presentation was Presented as follows.)

DR. CAMPBELL: Good morning.

There, how's that?

DIRECTOR DENTON: Marlissa, our monitors are not working.

Do you --

DR. CAMPBELL: Oh, I don't -- Cindy is coming.

Do you want me to wait?

DIRECTOR DENTON: Why don't you just wait momentarily.

I think we're good to go.

DR. CAMPBELL: You've got it.

Hexavalent chromium compounds contain the metallic element chromium in its plus 6 valence state. Chromium has six oxidation states with the hexavalent state being one of the most stable forms in the

environment.

Chromium is used in the manufacture of stainless steel and other alloys, as well as in making pigments and in leather tanning and welding. The general public can be exposed to Cr(VI) in ambient area through manufacturing emissions and from cigarette smoke or orally through contaminated drinking water.

Chromium and chromium compounds are absorbed after oral, dermal or inhalation exposure. Most studies of absorption of Cr(III) or Cr(VI), after oral administration to rodents, found that only one or two percent of the administered dose is bioavailable. Whereas, similar studies with humans report somewhat higher numbers, particularly for Cr(VI).

Human and animal studies show that chromium is widely distributed in the body after oral intra-tracheal, I.V. or I.P. administration of Cr(VI). When given by the oral route, chromium levels were particularly elevated in the liver, kidney and spleen, but were only modestly elevated in red blood cells. In pregnant experimental animals, Cr(VI) given in drinking water has been shown to cross the placenta and reach fetal tissues.

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DR. CAMPBELL: Oral exposure of humans to Cr(VI) have occurred through contamination of well water or other

accidental poisonings. Effects include mouth ulcers, diarrhea, abdominal pain, indigestion, vomiting, leukocytosis, presence of immature neutrophils, metabolic acidosis, acute tubular necrosis, kidney failure and death.

Effects of Cr(VI) exposure by inhalation include nasal atrophy and ulcerations, septal perforations, pulmonary function changes and other respiratory effects. IARC, U.S. EPA, NTP and OEHHA have all identified hexavalent chromium as a known human carcinogen.

Similar effects of Cr(VI) have been reported in studies of laboratory animals by both the oral and inhalation routes.

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DR. CAMPBELL: Five developmental toxicity studies were gestation-only exposures to Cr(VI) and drinking water were identified: One in rats and four in mice. Most of these studies use potassium dichromate, although one used potassium chromate. Most of the studies used Cr(VI) concentrations in the range of 50 to 1,000 ppm. And all of these studies reported statistically significant effects on embryo-fetal viability, growth and the frequencies of external and skeletal anomalies. One mouse study used much lower concentrations of 5 and 10 ppm and did not report developmental effects.

There were some reductions in gestational maternal weight again observed in the rat study, as well as in the mouse studies at concentrations of 500 ppm and above. In all cases, this appeared to be explainable on the basis of decreased litter weights. No maternal deaths or clinical or behavioral signs were reported in any of these studies.

In addition to gestational studies, relevant adverse developmental effects may result from exposure of either parent prior to conception. In the pre-gestational exposure studies that are described on this slide, the treatment period for the females ranged from 20 days to three months prior to mating. The treatment ended prior to mating, such that the males were never exposed. In one of these studies, the dams', mothers, were actually the exposed group. And they were exposed to Cr(VI) during gestation and lactation. And then at post-natal day 60, the female offspring were mated with unexposed males. All of these studies used potassium dichromate in drinking water.

Observed fetal effects were similar to those found with gestation exposures, including decreased viability, effects on growth and increased frequencies of external and skeletal anomalies. Effective Cr(VI) concentrations range from 250 to 5,000 ppm with most

studies using a range of 250 to 750 ppm.

In some of the studies, maternal and fetal levels of Cr(VI) were determined and found to be elevated in both the dams and their offspring. Hence, it would appear that chromium accumulated in maternal tissues during treatment remain there during that untreated mating period and then crossed the placenta into the fetuses during gestation.

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DR. CAMPBELL: Data on the potential female reproductive toxicity of Cr(VI) in experimental animals comes from three drinking water studies in rats and five in mice. All of these studies used potassium dichromate. All of the studies in both species gave evidence for adverse effects of Cr(VI) on the female reproductive system at concentrations in drinking water, ranging from 5 ppm, at which ovarian alterations at the ultra-structural level were seen, up to 1,000 ppm, which resulted in complete pregnancy failure in all exposed dams.

Exposure to more moderate concentrations of 200 to 750 ppm was associated with effects, such as lengthened estrous cycles, decreased mating and fertility indices, decreased numbers of corpora lutea, implantation sites and live fetuses per litter, and increased frequencies of pre- and post-implantation loss, as well as increased numbers of resorption sites.

In one rat study, female offspring were exposed to 200 ppm Cr(VI) when their mothers were treated during lactation. Vaginal opening was significantly delayed and estrous cycles were lengthened in the offspring. The numbers of ovarian follicles were also reduced in these animals and their hormone levels altered.

Most of these studies either did not report on systemic toxicity or else reported no systemic effects. One rat study showed increased mortality among treated females. Two rat studies and one mouse study showed decreases in gestational weight gain, which again appeared to be explainable on the result of decreased litter weights.

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DR. CAMPBELL: Sixteen available studies on the potential male reproductive toxicity of Cr(VI) in experimental animals included studies conducted in monkeys, rats, mice and rabbits. The means of exposure included drinking water, feed, gavage, and I.P. injection. Most of these studies use potassium dichromate as the test compound. One rat study used chromium trioxide, another used sodium dichromate, and two used sodium chromate. All but one study showed adverse effects on some aspect of the male reproductive system, regardless of the species or the route of Cr(VI) exposure.

The observations included histopathology findings, altered sperm parameters, altered testicular biochemistry, altered sexual and aggressive behavior, altered testes weights, altered weights of epididymides and other accessory organs, decreases in testicular protein, DNA and RNA, and decreased serum and/or testicular testosterone. Male fertility was tested in only three studies and only one of these reported decreases in embryo-fetal survival in untreated dams mated to Cr(VI)-exposed males.

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DR. CAMPBELL: In macaque monkeys effects were seen in drinking water at concentrations greater than or equal to 100 ppm; in rats 1,000 ppm was an effective concentration; in mice concentrations equal to or greater than 2,000 ppm were effective.

In rat feeding and gavage studies effects were seen at doses ranging from 10 to 60 milligrams per kilogram per day. One feeding study in mice found effective concentrations of 100 to 400 ppm. In a rabbit gavage study, a test dose of 5 milligrams per kilogram per day was associated with male reproductive toxicity.

When given by the I.P. route, the effective concentration of Cr(VI) in rats ranged from 0.05 to 4 milligrams per kilogram per day. In rabbits, the test

dose of 2 milligrams per kilogram per day was associated with adverse effects on male reproductive organs. Most studies either did not report on systemic toxicity or else reported that there was no systemic toxicity.

One monkey study reported deaths after more than three months on 400 ppm Cr(VI) in drinking water. One rat and one rabbit gavage study showed decreased body weight or weight gain at 40 or 5 milligrams per kilogram per day respectively.

The frequency of deaths increased with increasing dose in the rat I.P. study. And a mouse drinking water study found decreased body weights at a concentration of 2,000 ppm.

And that concludes my part of the presentation. And I will hand over now to Amy Dunn, who's going to talk about the human data.

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MS. DUNN: We turn now to the human data available to evaluate chromium's effects on reproduction and development.

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MS. DUNN: The human data relevant to consideration of developmental effects is limited. There are two studies. One study examined associations between chromium in drinking water and adverse pregnancy outcomes.

This study had many limitations, including the fact that levels of chromium were below the level of detection in the drinking water for the majority of women in the study. The odds ratio for stillbirths in relation to chromium levels was elevated, but not statistically significant. The study found no significant associations for any of the outcomes measured in relation to chromium exposure.

The other study was an ecological study of congenital malformations. Soil contamination due to an old chromium processing factory was the potential source. Relative risks in relation to radial distance from the old factory were examined, despite a lack of confirmatory evidence that exposure varied with distance.

This study lacked control for maternal age or alcohol consumption. Relative risks were higher for some segments but not for the area closest to the factory, where individuals were presumed to have had the highest exposure.

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MS. DUNN: With regard to human data on female reproductive effects, there are two reports published in Russian by the same author. The first one published 30 years ago.

Women occupationally exposed to high levels of chromium as measured in urine and blood, experienced

complications during pregnancy and child birth at much higher rates than unexposed women. Due to limited reporting, no conclusions can be drawn as to the role of chromium in causing these effects.

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MS. DUNN: A number of publications are available that consider the potential for male reproductive effects from chromium exposure. Sixteen studies were identified, all of which focus on men occupationally exposed to chromium, primarily due to the welding of stainless steel. Nine studies examined semen quality and seven others looked at fecundability, infertility or male-mediated spontaneous abortion.

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MS. DUNN: In steel welding fumes, much of the chromium occurs as water soluble hexavalent chromium with exposures varying by the method of welding and the material being welded. Chromium levels are higher in the breathing zone for those welding stainless steel as compared to mild steel. Measurement of chromium in workplace ambient area or in urine or blood of workers provide a basis for evaluating an assumption that differences in chromium exposure exist between the groups being compared. Some, but not all, of the studies I'll describe were able to establish such differences.

Levels of exposure also vary across these studies. Although the methods used for measurement were different, and thus the findings are not strictly comparable, consider two examples of air levels measured in studies of semen quality.

The study by Li et al. in China, published in 2001, reported air levels of 235 micrograms per meter cubed for their exposed group and 17 micrograms per meter cubed for their unexposed group, with more than an order of magnitude difference between exposed and unexposed.

Compare this to air levels experienced by the exposed group of stainless steel welders in the studies in Denmark published by Bonde in the early 1990s, who had 2 micrograms per meter cubed in the air of the exposed group.

Despite these differences in levels, for both of these studies and for others that were able to distinguish those with more chromium exposure and compare them to men with less chromium exposure, effects are seen in studies, both those with relatively lower as well as higher exposures.

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MS. DUNN: Of three earlier studies examining semen quality in relation to stainless steel welding, two found no difference in sperm parameters between the groups

they compared. However, in both of these studies, investigators found that the exposed and comparison groups had similar levels of chromium in urine.

The case-control study by Mortensen in Denmark did find an elevated but not significant odds ratio for poor sperm quality. Exposure in this study was based on self-report in a mailed questionnaire with no verification.

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MS. DUNN: This slide shows three additional studies of semen quality all conducted in Denmark. The first two were published in the early 1990s by the same author Bonde, who, with various collaborators, conducted a series of studies on male reproductive effects in relation to welding exposures.

The first study shown here reported statistically significant effects on several different semen parameters, including decreased sperm count and semen volume, decreased percentage of motile sperm and increased percentages of sperm with poor to no motility.

The second study was a follow-up on a subset of the same workers. The author hypothesized that discontinuing exposure would restore spermatogenesis. He examined semen quality before and three, five and eight weeks after a period without exposure, a three-week

vacation.

For stainless steel welders, no significant improvement of semen quality was observed.

The third study was published in the late 1990s and also included Bonde as an author with Hjollund as the first author. This study found no differences in semen quality measures for stainless steel welders, but also reported that they found no differences in urine concentrations of chromium between welders and non-welders or between pre- and post-shift samples. They mentioned that the lack of findings may be due to the generally low exposure of the study base.

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MS. DUNN: This final set of semen quality studies all examined men occupationally exposed to chromium in Asia. Significantly decreased sperm count and decreased sperm motility were found in both the Li et al. study in China and the Danadevi et al. study in India.

Danadevi also found a negative correlation between blood chromium and sperm concentration, that is as blood chromium increased sperm concentration decreased. The Danadevi et al. study also found significantly increased abnormal sperm morphology as did the Kumar et al. study also conducted in India, which examined workers in a chromate factory.

Kumar et al. observed a significant positive correlation between abnormal sperm morphology and blood chromium levels. These studies all had high exposure levels as well as substantial limitations in terms of their design or reporting, with the Danadevi et al. study having the most robust design of these three.

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MS. DUNN: The seven studies that address chromium exposure in relation to fecundability, infertility and male-mediated spontaneous abortion were all conducted in Denmark by Bonde and Hjollund and other collaborators working with them.

Three of these studies examined effects in a population of males identified through the Danish Pension Fund, who had been employed for at least one year in companies manufacturing steel. The comparison was of at-risk years with years not at risk in the same individuals.

In the first study, the investigators found that the probability of a man's spouse having a child was decreased when the man was welding. This was significantly decreased for any welding, but when limited to those who ever welded stainless steel, the value did not reach statistical significance.

The authors of the 1992 study examined

spontaneous abortion in the same cohort of welders, as did the authors of the 1995 study. So all three of these studies are looking at the same group of people. The difference between the '92 and the '95 study was that the source of information on spontaneous abortions was different.

The '92 study used records that included more early pregnancy losses, but lacked the accuracy of dating events that was available in the source used by the '95 study. As we'll see in a minute, early losses appear to be important. And in the case of this cohort, the study that included more early losses, found a significantly increased risk of spontaneous abortion with stainless steel welding, while the other study did not.

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MS. DUNN: Both of the studies shown on this slide were limited due to their design, though in different ways. The 1993 Bonde study based occurrence of infertility on self-report and did not provide details on stainless steel as opposed to mild steel welding exposure.

The 2005 Hjollund study examined a cohort of couples from an in vitro fertilization registry, who may not be comparable to the general population. Also, a concern with this latter study is that 85 percent of the men identified as welders, welded stainless steel less

than one hour per day.

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MS. DUNN: Finally, results of two studies of couples followed in a prospective cohort design provide fairly compelling evidence of male reproductive effects of stainless steel welding. Couples were recruited by mail sent via metal workers unions and other trade unions. These couples included only those without previous reproductive experiences who intended to attempt to become pregnant. Couples were followed for up to six menstrual cycles or until a pregnancy was clinically recognized.

Subclinical spontaneous abortions were detected in an analysis of urine samples via measurements of human chorionic gonadotropin or HCG. The 1998 report provided information on fecundability in these couples, that is the probability of conceiving in a given menstrual cycle. An adverse effect on this measure is seen when the probability of conceiving is decreased. For those currently working as welders of stainless steel, the probability was decreased, an odds ratio of .82. Although, the decrease was not statistically significant.

However, when the length of time the man had worked in stainless steel welding was considered, probability of becoming pregnant was significantly decreased, an odds ratio of .39 with a confidence interval

that excludes 1.0 for those with six or more years of exposure.

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MS. DUNN: The 2000 report describes the findings for male-mediated spontaneous abortion. The risk for spontaneous abortion with paternal stainless steel welding exposure was significantly increased, a relative risk of 2.6. These results include adjustment for potential confounding factors, such as female age, and body mass index, menstrual cycle length, male and female smoking, caffeine and alcohol consumption as well as other factors.

Risk of pregnancy loss increased as years of stainless steel welding increased. All of the spontaneous abortions in spouses of stainless steel welding took place before the 10th gestational week. The authors of this study, having conducted studies for more than 15 years on male reproductive effects of welding exposure, stated that their findings indicate quote, "An increased risk of early spontaneous abortion for women whose partners are engaged in stainless steel welding."

This concludes my presentation.

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DR. CAMPBELL: And just to do a quick summary of both the human and animal data. The evidence on developmental toxicity of hexavalent chromium includes few

and limited human epidemiological studies, which have not provided evidence for significant effects. The animal evidence for developmental toxicity consists of multiple studies demonstrating decreased embryo-fetal viability, impaired growth and increased frequencies of external and skeletal anomalies. Effects were similar whether Cr(VI) exposure occurred during gestation or if exposure of females ended before the mating period.

Evidence on the female reproductive toxicity of hexavalent chromium includes some evidence from human studies of occupational exposures for increased complications during pregnancy and child birth. Effects observed in animal studies included length in estrous cycles, decreased mating infertility indices, decreased numbers of corpora lutea, implantation sites and live fetuses per litter and increased frequencies of pre- and post-implantation loss. Also, ovarian changes at the ultra-structural level.

Evidence on the male reproductive toxicity of hexavalent chromium includes studies of occupationally exposed men, primarily welders, which provided evidence for an association between Cr(VI) and decreased sperm counts and motility, decreased probability of a spouse becoming pregnant and increased risks of male-mediated spontaneous abortion.

Studies in multiple animal species, which identified adverse effects, including testicular histopathology, altered sperm parameters, altered testicular biochemistry, altered sexual and aggressive behavior, altered weights of testes and accessory male reproductive organs, decreases in testicular protein, DNA and RNA contents, and decreased serum and/or testicular testosterone levels.

And that concludes our presentation.

CHAIRPERSON BURK: Thank you.

And are there any questions from the Committee of Dr. Campbell or Ms. Dunn?

COMMITTEE MEMBER JONES: Yeah, I just have one question. I didn't read these two uninterpretable studies in Russian, I will admit. But is it those studies that you base the fact that there are possible effects with high exposure in the human -- in female reproductive toxicity?

MS. DUNN: Yes. Those are the only studies that are available on human female reproduction.

COMMITTEE MEMBER JONES: Yeah. I'm surprised that you say possible effects with high exposure as far as female reproductive toxicity is concerned, based upon those 2 uninterpretable studies. That's the only point I would make.

MS. DUNN: Yeah. I think the intention was just to mention that there were some effects seen and we don't really have good information about the study.

COMMITTEE MEMBER JONES: Okay.

CHAIRPERSON BURK: Please.

COMMITTEE MEMBER HOBEL: There appears to be a gender difference in effect in terms of reproductive toxicity in humans. And in the animal model, did there seem to be a gender difference with a greater effect on the male reproductive system?

MS. DUNN: Sir, I think, in fact, there aren't really good studies of exposed females that the -- all the studies that really provide good data are on males who are welders. So we don't really have anything comparable to be able to exclude the possibility that women would be similarly or somehow adversely affected.

COMMITTEE MEMBER HOBEL: So it's the exposure effects then?

MS. DUNN: I'm sorry, I didn't hear you.

COMMITTEE MEMBER HOBEL: Well, it's just -- there are no -- I guess, women don't do welding, so I guess only men do welding, so it's exposure difference.

MS. DUNN: There could be -- you know, there could be some women, but we haven't seen them in studies.

DR. CAMPBELL: You know, with respect to the

animal data, I mean, there's plenty of positive evidence for both sexes. I mean, the specifics are different, because the endpoints are different.

COMMITTEE MEMBER KEEN: Perhaps it's worth noting, at least when I tried to look at the concentrations, both male and female in the experimental animal model seemed to show similar types threshold levels.

DR. CAMPBELL: Similar -- oh, yeah yeah. Those ranges are similar.

COMMITTEE MEMBER KEEN: In terms of where you see effects are really quite similar. And I have to concur, I went through the human literature very carefully. And the lack of any evidence in the female population because the females haven't been studied who are welders shouldn't be taken as lack of sensitivity. There are a lot of female welders. It clearly is a question that could be answered if one chose to.

CHAIRPERSON BURK: I don't see that we have any public comments, is that correct?

All right. Then I guess we'll just begin our discussion. I think we already have. But I have asked Dr. Carl Keen and Dr. Ken Jones to take the lead on the discussion of hexavalent chromium. So I'll turn it over to them.

COMMITTEE MEMBER KEEN: Well, I'd be happy to say any contrarian suggestions, but as I read the experimental animal literature, it's relatively straightforward. And refreshingly for a change, it's uncomplicated, in the sense that signs of maternal toxicity do not seem to be a principal driver of some of the reproductive toxicity, which is often times the case when some of these agents are looked at such high concentrations.

So I paid particular attention when I went through the literature as to what one observes with, say, 50 to 100 parts per million exposure. And there is a remarkable consistency across the literature that there is not effects to speak of on maternal food intake or weight gain independent the obvious lower weights sometimes that are observed if you have lower concepti burden.

So unless other members of the Committee read the data differently, it seemed to be relatively straightforward, both on males and females.

COMMITTEE MEMBER JONES: I totally agree with Carl, as far as his concern. And furthermore, I was struck by the consistency in the effects from one species to the next, as far as all these different studies were concerned. So I don't think there's much question either.

CHAIRPERSON BURK: Are there any other comments from any other Committee members on any of the endpoints?

Okay. We will be taking a vote on each of the endpoints. And I will read it exactly as it is written. Although -- no, I won't read it exactly as it is written, because I'll tell you, it's written for cancer.

(Laughter.)

CHAIRPERSON BURK: But I'll read it the way I think it's supposed to be written.

Did I get the wrong one? I don't think they were -- actually, I believe it's actually already on the Prop 65 list as a carcinogen.

So, has hexavalent chromium been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity? All those voting yes, please raise your hand?

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, if we could just be really clear on the designation, it should be chromium in paren, hexavalent compounds.

CHAIRPERSON BURK: Say that again, I'll write it down.

CHIEF COUNSEL MONAHAN-CUMMINGS: Chromium and then a paren hexavalent compounds closed paren.

CHAIRPERSON BURK: Okay. I'll read it again. Has chromium (hexavalent compounds) 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 BURK: Seven. And Linda is recusing herself; is that correct?

COMMITTEE MEMBER ROBERTS: (Committee Member Roberts nods her head.)

CHAIRPERSON BURK: Okay. So I have 7 yes, and 1 recusal for developmental.

Again, has chromium (hexavalent compounds) 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?

(Hands raised.)

CHAIRPERSON BURK: Okay. I see 6.

All those voting no?

(Hand raised.)

CHAIRPERSON BURK: One. And again one not voting.

And finally, has chromium (hexavalent compounds) been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity?

All those voting yes, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Okay, 7, and 1 recusal.

Okay. The result then -- it takes 5 yes votes are required to add a chemical to the Prop 65 list. So therefore, chromium (hexavalent compounds) will be added to the list.

Moving right along then. Next on the agenda will be a discussion and a consideration for listing of chlorpyrifos. And the staff presentation will be by Drs. Poorni Iyer and Farla Kaufman.

(Thereupon an overhead presentation was Presented as follows.)

DR. ALEXEEFF: Dr. Burk, I have a comment. This is George Alexeeff of OEHHA. This presentation will be a little bit long. And we apologize for the length, but it is kind of a complicated analysis for both the animal and the human data. So the staff felt it was important and we felt it was important to give you enough groundwork. And we know that in the public comments will also be talking about very specific details. So we felt this was going to be kind of a full discussion of this issue.

CHAIRPERSON BURK: I totally support that. And I hope I'm speaking on behalf of the Committee that take as much time as you need.

(Laughter.)

DR. IYER: Okay. On that note, my name is Poorni Iyer and I'm going to be presenting the -- we are going to be presenting the evidence for developmental and reproductive toxicity. And initially, we're going to be presenting the background and the animal data. And then my colleague, Dr. Farla Kaufman, will be presenting the human data.

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DR. IYER: Chlorpyrifos is an effective broad spectrum organophosphate insecticide. And it is used as an insecticide on grain, cotton, field, fruit nut and vegetable crops, as well as on lawns and ornamental plants.

The general population can be exposed to chlorpyrifos via the oral route in food and water, that is from runoff or leaching, as well as from exposure via the inhalation and/or dermal routes, through volatilization and spray drift for those people living in close proximity to fields treated with chlorpyrifos. Workers who apply or handle chlorpyrifos could also be exposed via the inhalation and dermal routes.

In 2000, nearly all the residential uses were voluntarily cancelled by Dow AgroSciences, but the agricultural use remains.

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DR. IYER: Reviewing the pharmacokinetics for this chemical.

Absorption of chlorpyrifos varies with species - in humans about 70 percent is absorbed after oral exposure. From data in the rat, it is rapidly absorbed and transported to the brain with oral dosing. Chlorpyrifos is rapidly metabolized and highest tissue concentrations were found in the liver and kidney, but the chemical does not bioconcentrate.

Fetal brain metabolite concentration was found to be twice as high as maternal brain concentration. And the mean half-life of chlorpyrifos in humans was about 27 hours.

Excretion was in the urine and no parent compound was detected. Metabolites were detected in urine. And we'll be moving onto the metabolism in the next slide.

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DR. IYER: Chlorpyrifos is bioactivated to the chlorpyrifos oxon via cytochrome P450 mediated desulfuration. Chlorpyrifos oxon is subsequently hydrolyzed by A-esterase to diethyl phosphate and 3,5,6-trichloro-2-pyridinol (TCP) also referred to sometimes in the literature as TCPY, which is also the major biological metabolite and environmental breakdown product of chlorpyrifos.

Now, TCP can undergo Phase II sulfation and glucuronidation. And chlorpyrifos oxon mediates -- this oxon mediates the toxic effects of chlorpyrifos by binding irreversibly with acetylcholinesterase, that deactivates the neurotransmitter acetylcholine, eliciting cholinergic hyperstimulation in the nervous system and in neuromuscular junctions.

This inhibition of the catalytic function of acetylcholinesterase in removing acetylcholine from the synaptic region is generally regarded as the cause of its toxicity leading to observable clinical science.

Now, A-esterase, that is chlorpyrifos oxonase or paraoxonase or PON1 and carboxylesterase are known to play an important role in the detoxification of chlorpyrifos. Reviewing the ontogeny metabolic processes in the young, rat fetuses and juveniles and newborn humans have a lower capacity to detoxify than adults.

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DR. IYER: Since chlorpyrifos oxon has been shown to inhibit brain acetylcholinesterase at about 1,000 times the rate of chlorpyrifos itself, the rate of detoxification can be very important. PON1 is a member of the family of proteins that hydrolyzes the active metabolite, the oxon, and is also referred to as paraoxonase as it hydrolyzes paraoxon the substrate that

provides its name.

Now, there are several polymorphisms of the PON1 gene that influence both the level of expression and its catalytic ability, referred to as the PON1 status. The PON1 status varies across ethnic groups and this will be discussed later on in the presentation.

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DR. IYER: The non-DART, or the Developmental and Reproductive Toxic, effects include the acute, subchronic and chronic effects of chlorpyrifos. So far, it is the inhibition of cholinesterase that is generally regarded as the most sensitive toxicological endpoint following oral exposure, regardless of the exposure duration. The muscarnic effects of acetylcholine resulting from such cholinesterase inhibition can include increased intestinal motility, bronchioconstriction, increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia.

Nicotinic effects include muscle weakness, twitching, cramps and general fasciculations. The classic effects of severe poisoning with cholinesterase inhibitors, such as organophosphate insecticides, typically include slurred speech, tremors, ataxia, convulsions, depression of the respiratory and circulatory

centers followed by coma and death.

In animals, significant inhibition of plasma an RBC cholinesterase occur at doses below that which cause the inhibition of brain cholinesterase.

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DR. IYER: In a recent review, results of numerous mutagenicity short-term assays and genotoxicity were looked at. And chlorpyrifos was found to be not mutagenic in bacteria or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria.

Also, chlorpyrifos did not induce chromosomal aberrations in vitro, was not clastogenic in the mouse micronucleus test in vivo, and failed to induce unscheduled DNA synthesis in isolated rats hepatocytes.

DNA damage in lymphocytes of mice exposed to chlorpyrifos was demonstrated using the comet assay. Given that the comet assay is a sensitive assay for DNA damage, typically additional positive responses in in vivo systems are required to be predictive for carcinogenicity in mammalian systems.

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DR. IYER: Examining what has thought to be its

primary mode of action, this inhibition of acetylcholinesterase results in accumulation of endogenous acetylcholine in nervous tissue and effector organs, muscarinic, nicotinic and CNS receptors are stimulated, with characteristic signs and symptoms occurring throughout the peripheral and central nervous systems as have been described earlier.

The sensitivity varies across species with the dog being most sensitive, followed by the rat and then the mouse.

In most humans and dogs, plasma cholinesterase is predominantly the butyrylcholinesterase, which is more sensitive to inhibition than acetylcholinesterase. While in rats, plasma cholinesterase consists of approximately a 60 to 40 ratio of acetylcholinesterase to butyrylcholinesterase. So it is likely that the human sensitivity for cholinesterase inhibition, relative to rats, is due to species differences between rats and humans in the constituents of plasma cholinesterase.

Given this predominant mode of action of organophosphates, as you will see later on, studies examining the effects of chlorpyrifos on acetylcholinesterase have been used in determining the relationship between cholinesterase inhibition and developmental toxicity.

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DR. IYER: Moving onto the relevant metabolic changes during pregnancy. We note that female rats, particularly pregnant rats, appear to be more sensitive than adult male rats to cholinesterase inhibition. There is a consistent pattern for several key detoxification enzymes that metabolic activity may decrease during pregnancy. While the reductions are not large in magnitude and the importance of these decreases is unknown at environmental exposures, studies suggest the potential for a reduced capacity to detoxify during pregnancy.

Toxicity studies in rats add further support that reduced ability to detoxify chlorpyrifos and/or the oxon effects sensitivity during pregnancy. As mentioned earlier, pregnant female rats had lower plasma, brain and liver carboxylesterase activity than non-pregnant animals.

Another key detoxification enzyme discussed previously is PON1. And PON1 activity is reduced during late gestation to about 76 percent in women.

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DR. IYER: With this background, we move onto the animal data.

Several studies evaluating the effects of

chlorpyrifos on the developmental and reproductive toxicity in animals have been conducted. These include studies conducted to meet with regulatory requirements, as well as studies in the published literature.

Some reported reproductive or developmental toxicity with endpoints, such as resorptions, decreases in pup weight and long-term effects on brain and behavior, while others did not report reproductive or developmental toxicity.

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DR. IYER: Chlorpyrifos was evaluated for its potential to produce developmental and reproductive toxicity in rats following oral exposure. Now, both these studies, as Breslin 1991, were conducted to meet with regulatory agency guidelines and the data was submitted to the California Department of Pesticide Regulation around 1991. And the findings were subsequently published in the open literature as Breslin 1996.

By way of background, in a previously conducted three-generation dietary reproduction study -- developmental and reproduction study, exposing rats to dose levels of 0, 0.1, 0.3 and 1 mg/kg of chlorpyrifos per day -- this is in your HIM materials that you have -- depressions in parental plasma and RBC cholinesterase were observed without effects on reproductive parameters, fetal

development or neonatal growth, survival or histopathology. But the viability index was decreased at the high dose level of 1 mg/kg/day, though it was not statistically significant.

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DR. IYER: Now, actually looking at the results from these two studies in the next slide.

For the developmental toxicity study, reduced cholinesterase levels at 3 mg/kg, that is the mid dose, and cholinergic signs, such as excessive salivation and tremors were noted. Decreased cholinesterase levels and decreased body weight gain was noted at the high dose of 15 mg/kg/day. And no maternal effects were apparent at .1 mg/kg/day, which is the low dose. And for the standard parameters, such as offspring viability and malformations, chlorpyrifos appears not to have an effect at these dose levels.

For the two-generation reproduction study, there was significant inhibition of brain cholinesterase of dams at 5 milligrams per kilogram per day. And pup body weight, there was a decrease in pup body weight and increased pup mortality observed only in the F1 litters.

The neonatal effects observed in F1 generation was not noted in the F2 generation. And no effects on histopathology of reproductive tissues were noted at any

dose level.

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DR. IYER: The effects of gestational exposure on neurodevelopment and behavior was undertaken in this developmental neurotoxicity study submitted as Hoberman 1998 to regulatory agencies and then it was subsequently published as Maurrissen et al. 2000.

In this study, chlorpyrifos in corn oil was administered orally via gavage to Sprague-Dawley, presumed pregnant, rats on gestation day six through postnatal day 11 at 0, 0.3, 1, and 5 milligrams per kilogram per day. The protocol is described in detail in the hazard identification materials. An exposure during postnatal day one through 10 in the rat pup would be equivalent to a continuous in utero last trimester exposure in humans.

Now, here pups from the high-dose group showed increased mortality soon after birth, gained weight more slowly than controls and had several indications of slightly delayed maturation. No overt effects were noted by the authors in either dams or pups at 1 or .3 mg/kg/day. In spite of the apparent delay in physical development, learning and memory as tested on the T-maze spatial alternation tasks, motor activity and auditory startle were not affected in the high-dose animals in the

pups tested just after weaning.

On gestation day 20, the brain acetylcholinesterase of the 1 milligram per kilogram and 5 milligram per kilogram groups were 82 percent and 10.2 percent of the controls.

While the authors considered any patterns observed to be spurious, it must be noted that the apparent reduction of motor activity on postnatal day 14 was accompanied by modest weight -- body weight decrements and was not dismissed by either the U.S. EPA, Office of Pesticides or the California EPA, California Department of Pesticide Regulation reviewers.

According to the authors, the chlorpyrifos produced maternal and developmental toxicity in the high dose of 5 mg/kg/day group, but did not cause selective developmental neurotoxicity.

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DR. IYER: Upon closer review, adverse findings were noted in the adult offspring on postnatal day 66. There were alterations in motor activity, auditory startle response, and of particular interest are the effects on brain structure, such as decreased measurements of the parietal cortex and hippocampal gyrus in the absence of significant brain weight deficits at 1 and 5 mg/kg/day. And this is the first hint of possible adverse outcomes,

as can be observed in the findings on the next slide.

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DR. IYER: The decrements at postnatal day 66 was slightly higher at 5 mg/kg/day than at 1 milligram per kilogram per day. And the changes were consistent with the postnatal day 12 sacrifice results. And accordingly, a careful review by U.S. EPA concluded that, "Adverse findings in the adult postnatal day 66 offspring, that is the alterations in motor activity, auditory startle response and brain structure, that is the decreased measurements of the parietal cortex and hippocampal gyrus in the absence of significant brain weight deficits, observed at postnatal day 66, in the offspring, long after exposure via the dam can be interpreted to represent long-term sequelae of developmental exposure."

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DR. IYER: For the developmental neurotoxicity study therefore, across all studies, the lowest dose tested was .3 mg/kg/day. No behavioral effects were observed in the offspring at this dose level. Brain morphometric changes were seen at one milligram per kilogram per day, but they were not available for examination at the .3 mg/kg/day.

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DR. IYER: From these and other subsequent studies, that is after 2002, in the literature, at the Slotkin/Levin and Calamandrei laboratories that have been described in detail in the hazard identification materials, it appears that adults have persistent behavioral effects following gestational and/or early postnatal exposure in both rats and mice. Some of these studies focused on exposure to chlorpyrifos during specific periods of gestation, targeting specific windows of development and late developmental effects, such as gliogenesis, axonogenesis and synaptogenesis.

Findings from these studies suggest a wide window of vulnerability of the cholinergic systems to chlorpyrifos, that the effects of chlorpyrifos on fetal brain development are fundamentally different for exposure in early, compared with late gestation, and prenatal chlorpyrifos exposure elicits marked alterations that emerge in the postnatal period, specifically behavioral abnormalities were observed when pups were tested in adolescence and adulthood.

These studies used slightly different protocols, such as the route of exposure and a vehicle, leading us to consider other relevant issues.

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DR. IYER: And these issues will be presented in the following slides. And they include use of DMSO as a vehicle for chlorpyrifos administration in animal studies; the differences between developing animals and adults; distribution and metabolism in pregnant females and conceptuses and other possible mechanisms of developmental toxicity.

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DR. IYER: Concern for the use of DMSO as a vehicle in studies has been raised due to the possibility of either DMSO's effects on development or its role in interaction with other chemicals. However, there was concordance observed between studies that used DMSO at a vehicle and those that did not for the parameter of cholinesterase inhibition. And also from the recent work of Marty et al. Cmax, area under the curve, and the half-life values for subcutaneous administration in DMSO was similar to bolus oral exposure in a milk vehicle. So this underscores the effects of chlorpyrifos in pups subsequent to maternal exposure.

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DR. IYER: As with many organophosphate pesticides, developing animals appear more susceptible to

the acute toxic effects of chlorpyrifos than adults, primarily because of lower levels of detoxifying enzymes such as carboxylesterases, which stoichiometrically degrade the chlorpyrifos oxon and A-esterases, which actively hydrolyze the oxon.

This decreased capacity to detoxify has been associated with increased sensitivity. Specifically, in rats, A-esterase activity is virtually nonexistent in the fetus and increases from birth to reach adult levels around postnatal day 21.

Also, given the net increase of more than four-fold in fetal brain cholinesterase activity from gestation day 14 to 18 in control animals, and the fact that maternal brain cholinesterase was inhibited more than fetal brain cholinesterase only in a repeated dosing regimen, researchers have concluded that the fetus is not genuinely protected from the toxic effects of a given dose of chlorpyrifos as the fetal brain cholinesterase could simply be able to recover more fully between each dose, as compared to the maternal brain cholinesterase, giving the illusion that the fetal compartment is less affected than the maternal compartment.

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DR. IYER: The dosage to nursing pups was much

reduced compared to the dams exposure. From the developmental neurotoxicity study of Hoberman earlier on and other modeling, it can be concluded -- it has been concluded that at the high dose, a nursing pup's exposure would be about .1 to .5 mg/kg/day of chlorpyrifos.

What was noted was that in spite of exposure via milk, the cholinesterase levels of all tissues of the high-dosage pups rapidly returned to near control levels by postnatal day 5.

Since immature animals actually recover more rapidly from cholinesterase inhibition than do adults, measurements of cholinesterase activity alone may not be sufficient for the assessment of adverse effects. Besides, the precise time of measurement of cholinesterase would also be critical and one would also have to take into consideration the time for distribution of the chemical into the milk and other pharmacokinetic considerations.

Hence, chlorpyrifos-induced neurochemical and neurobehavioral changes may or may not be related to the cholinesterase inhibition as has been measured in the studies to date. And so the vulnerable period for adverse effects of chlorpyrifos is likely to extend into childhood or adolescence.

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DR. IYER: While inhibition of cholinesterase by its active metabolite chlorpyrifos oxon was once considered the lone mechanism for chlorpyrifos neurotoxicity, recent studies have presented additional possibilities. There is evidence that chlorpyrifos directly targets events that are specific to the developing brain and that are not necessarily related to the inhibition of cholinesterase.

And these include:

Effects on the developing brain, such as cell division; interference with RNA synthesis during differentiation; interruption of cell signaling; interference with important nuclear transcription factors involved in cell differentiation; impairment of cholinergic synaptic function during development; effects on the catecholamine system in the developing brain; oxidative stress in the developing brain; interference with gliogenesis and axonogenesis. And all those could happen in the absence of clinical signs and brain cholinesterase inhibition.

Also, neither the magnitude nor the timing of the changes observed in these studies was predictive of the cholinergic defects, rather it appears that the cellular effects may actually result from defective synaptic

transmission.

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DR. IYER: According to the authors, taking a number of studies, the findings show that the hippocampus appears to be adversely affected by chlorpyrifos, regardless of whether the exposure occurs in early or late brain development, and defects emerged in adolescence or adulthood even in situations where normative values were initially restored in the immediate post-exposure period. This is probably because the alterations may be late emerging and not a result of an initial deficit that continues into later life.

Also, based on the disparate mechanisms by which chlorpyrifos perturbs neuronal and glial cell development, there is extraordinarily broad critical period for adverse effects on brain development with a shifting target set of consequences dependent upon the period of exposure.

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DR. IYER: Since the behavioral effects noted in the studies were seen long after immediate cholinergic responses, even transient cholinesterase inhibition may alter the complicated progression of development in the nervous system, which could result in long-term changes,

even after the inhibition has recovered.

Accordingly, prenatal chlorpyrifos appears to elicit delayed onset alterations, disrupting the program for emergence of cholinergic activity. The functional significance on the later-occurring neurochemical anomalies is also corroborated by behavioral deficits in cholinergic contributions to working and reference memory that emerge in adolescence and adulthood after fetal chlorpyrifos exposure, and the same pattern is elicited by prenatal exposure to nicotine. Researchers therefore speculate that these long-term alterations reflect disruption consequent to elevated cholinergic activity during a critical period in fetal development.

What is really unknown is whether protection against cholinesterase inhibition, even transiently at any time during development, is adequate to protect the developing organism. And thus relying on cholinesterase inhibition may not be the appropriate upstream marker or event for protecting the fetus or developing individual.

In other words, cholinesterase inhibition may not be the upstream marker of choice for regulating exposure of a developing individual to chlorpyrifos.

And in the subsequent material that was presented to the Committee, at the Scientific Advisory Panel meeting in September this year, at the U.S. EPA -- the scientists

at the U.S. EPA have accordingly stated that, "Although these studies raise many questions, and each took a different approach with regard to dosing and behavioral assessments with different behavioral techniques, when taken together, they provide a basis for concern for susceptibility of persistent effects of chlorpyrifos on neurodevelopment."

Moving onto the next endpoint here.

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DR. IYER: According to generally accepted principles, changes in offspring growth or milk quantity and quality may constitute a female-specific endpoint or reproductive toxicity. Hence, the presence of chlorpyrifos in the milk may be considered as affecting lactation, an essential component of female reproduction.

On the whole, the animal data both from studies conducted for regulatory purposes per FIFRA guidelines, as well as those from peer-reviewed literature, demonstrate lactational exposure and the effects observed from the presence of chlorpyrifos in the milk.

Reproductive effects included reduced pup weights and increased pup mortality in rats, but only at dose levels that induced parental toxicity as evidenced by inhibition of plasma, RBC and brain cholinesterase activities.

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DR. IYER: Taking a look at the effects on the male reproductive system. No effects on the histopathology of reproductive tissues were observed at dose levels below the levels that resulted in significant cholinesterase inhibition. And severe testicular damage resulting in reduction in sperm count and fertility were noted in another study, but they were at much higher dose levels, and they seem appropriate for the dose levels exposed.

Typically, studies in laboratory animals focus on fertility or sperm abnormalities and do not examine DNA damage per se. The findings of DNA damage noted in few of the studies conducted for evaluating genotoxicity may support the findings in the human studies; however, similar endpoints were not examined in the animal studies.

And now I'm going to turn it over to Farla Kaufman who's going to present the human data.

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DR. KAUFMAN: Most of the human developmental studies come from three large prospective cohorts, the Columbia Center For Children's Environmental Health, the Mount Sinai Children's Environmental Health Study, both of which were conducted in New York City, and the CHAMACOS

Study, which is an acronym for the Center for the Health Assessment of Mother And Children Of Salinas set in the agricultural area of the Salinas Valley here in California.

In addition, there is a cohort study conducted in Sri Lanka, a case control study of neural tube defects, case reports, as well as a related study of brain tumors.

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DR. KAUFMAN: The Columbia prospective cohort included African American and Dominican women residing in specific areas of New York City, definitely considered inner city. Pregnant women were enrolled by the 20th week of gestation. There was a total of 314 mother newborn pairs.

Measures of exposure included maternal and umbilical cord blood, chlorpyrifos, as well as maternal personal air levels monitored during the third trimester. Multiple birth outcomes were examined, as well as neurodevelopmental outcomes.

And a unique feature of this cohort was that it spans a time over which chlorpyrifos was cancelled for residential use and analyses were conducted which examined pre- and post-differences.

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DR. KAUFMAN: So in this cohort, we see -- I'm

going to be discussing some slides showing updated and additional analysis that were conducted for the U.S. EPA in their current reevaluation of chlorpyrifos.

This slide shows chlorpyrifos in personal air samples monitored during pregnancy by year, as we can see on the right. There was a large -- well, chlorpyrifos was detected in almost 100 percent of the samples in most years. There was, on your left, you can see a large decrease in mean levels in 2001, which corresponded to the cancellation of the pesticide for residential use. The cancellation was completed in December 2001. During this time, there was ongoing exposure to other pesticides, such as diazinon and propoxur.

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DR. KAUFMAN: Here you can see the levels of chlorpyrifos in maternal blood and cord blood. Samples were taken at delivery by year of birth. Again, there was a large decrease of chlorpyrifos in these levels seen during the phase out of the use of the pesticide due to the cancellation.

So levels of chlorpyrifos, that you can see this in the yellow, in 2000 decreased greatly to 2001. And levels of chlorpyrifos in cord and maternal blood were highly correlated at .79.

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DR. KAUFMAN: Results from Whyatt et al. from this cohort showed significant decreases in birth weight and length associated with chlorpyrifos levels. In infants born before the cancellation, birth weight among those with the highest chlorpyrifos exposures averaged 215 grams less than those with the lowest combined cord plasma chlorpyrifos and diazinon exposures. This is a statistically significant finding with the confidence intervals not encompassing 1 and a P value of .01.

When examining chlorpyrifos alone, that is for each log unit increase in chlorpyrifos -- over here -- in infants born before January 1st, 2001, that's before the cancellation, there was a 67 gram decrease in birth weight or an average deficit of 210 grams, which was highly statistically significant.

In infants born after the date of the cancellation, January of '01, there was no significant association between chlorpyrifos and birth weight. Only one infant fell into the highest exposure group here.

Similar findings were seen for birth length, where there's a statistically significant decrease before January of '01, but no significant association after January of '01.

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DR. KAUFMAN: These are updated analyses prepared

by Whyatt at the request of the U.S. EPA. There is a large sample size in the group born after the cancellation, so we can see the updated analysis. The before ban is pretty similar, but the end in this group is now 193 versus 77 from the previous analyses or the previous slide. The findings are similar to the previous slide, where there was a significant decrease in birth weight in the infants born before the cancellation, but no effect in infants born after.

All these analyses controlled for a number of covariates including active and passive smoking, ethnicity, parity, maternal pre-pregnancy weight and net weight gain during pregnancy, gender and gestational age of the newborn as well as season of delivery.

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DR. KAUFMAN: Additional analyses were also prepared where imputed cord blood values were omitted and additional potential confounders were evaluated. Imputed cord blood was originally used where there were missing cord blood levels and values were imputed for maternal blood samples since the two had been so highly correlated. When the imputed cord blood levels were omitted, the values for chlorpyrifos on birth weight and length remained statistically significant with a slightly smaller beta coefficient of 64.5 compared with the 67.3 that we

saw earlier.

These additional analyses also included the evaluation of other potential confounding factors, such as those related to socioeconomic status, housing disrepair, material hardship, maternal satisfaction, prenatal alcohol consumption, prenatal exposure to polycyclic aromatic hydrocarbons and lead.

Diazinon and propoxur were previously controlled for, as well. In addition, for these pesticides to be confounding factors in the pre/post cancellation analyses, they would need to vary along with the chlorpyrifos exposures. Since there was no cancellation on these pesticides at the time, this would seem unlikely.

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DR. KAUFMAN: These are the results from some additional analysis by Dr. Rauh presented to the U.S. EPA in September, which showed the effect of high chlorpyrifos exposure on the odds of small for gestational age. The proportion of infants born small for gestational age is on the Y axis. And we can see that there are -- there's a higher proportion of these infants born in the high chlorpyrifos exposure group as opposed to the low-exposure group.

The adjusted odds ratio for this comparison is 2.5, which is statistically significant. So fetuses who

were more highly exposed to chlorpyrifos basically had a two and a half times greater odds of being born small for gestational age. Again, these analyses were adjusted, in this case, for maternal short stature, maternal low body mass index, net weight gain in pregnancy, race/ethnicity and exposure to secondhand smoke.

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DR. KAUFMAN: Rauh et al. in their publication examined neurodevelopmental outcomes in this cohort. And they used the following standardized tests:

The Bayley Scales of Infant Development II, to assess mental or cognitive and psychomotor development at 12, 24 and 36 months of age;

The Childhood Behavioral Checklist measured behavior problems;

And the Home Observation for Measurement of the Environment tool to measure the quality of the caretaking environment.

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DR. KAUFMAN: This table presents the odds ratios of the effect of high exposure to chlorpyrifos on neurodevelopmental outcomes. High chlorpyrifos exposure was defined as a blood concentration of greater than 6.17 picograms per gram based on the findings of Whyatt et al., which reported, at this level, a decrease in birth weight.

The results in this table show that there are no significant delays in mental or psychomotor development at 12 or 24 months of age. There were statistically significant effects at 36 months of age in children with high exposure to chlorpyrifos, where they had more than twice the odds of being delayed -- this mouse is finicky -- being delayed in their mental development, and more than four and a half times the odds of being delayed in psychomotor development.

In examining behavioral disorders, children had odds ratios of 11.26 for attention problems, 6.5 for attention deficit hyperactivity disorder, and 5.3 for pervasive developmental disorder, all being statistically significant. Inclusion of diazinon in these analyses did not reduce the effect of chlorpyrifos on these endpoints. In addition, ongoing analyses presented to the U.S. EPA have indicated that these deficits persist in children tested at 5 and 7 years of age.

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DR. KAUFMAN: In the Mount Sinai cohort conducted in New York City, the subjects included women and children who were Puerto Rican Hispanic, African American and Caucasian. The pregnant women were enrolled by the 20th week of gestation. There were 404 mother-newborn pairs in the cohort. Exposure measures included urinary TCPY

levels and dialkyl phosphate metabolites, which are organophosphate metabolites not specific to chlorpyrifos. The enrollment of the Mount Sinai cohort overlapped with the cancellation of the residential use of chlorpyrifos.

However, in these publications, the researchers had not evaluated the impact of the cancellation on health outcomes. A unique feature of this cohort is the measurement of the PON1 genetic status and activity in these women.

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DR. KAUFMAN: So some of the findings from this cohort includes a publication by Berkowitz et al., which showed that significant reductions in head circumference at birth were associated with detectible maternal levels of TCPY in the urine and low maternal PON1 activity. There was no association with PON1 activity or TCPY and birth weight or birth length.

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DR. KAUFMAN: Some of the studies that I will discuss are considered related studies, since they did not examine chlorpyrifos levels or TCPY, the metabolite specific to chlorpyrifos, but looked at other metabolites, such as the total dialkyl phosphates, the diethyl phosphates or diethyl thiophosphate in urine. These metabolites can be formed from exposure to other

organophosphates as well as to chlorpyrifos. Therefore, for purposes of Proposition 65, they're not given the same consideration when examining the evidence of toxicity of chlorpyrifos.

As seen in Berkowitz et al., this related study by Wolf, reported that head circumference was inversely associated with maternal PON1 activity statistically significant. There was also significant decrease of 163 grams in birth weight, between the extremes of the interaction of fast activity-PON1 genotype with low sum of diethyl phosphate, and the slow activity-PON1 genotype with some of the high diethyl phosphate levels.

A similar effect was seen between the extremes of the interaction of the PON192 genotype with the diethyl phosphate.

In another related study from this cohort, Engel et al. looked at infants whose mothers had total diethyl phosphate levels above the median. And the ones with higher levels had 2.3 times -- were 2.3 times more likely to have at least 2 abnormal reflexes.

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DR. KAUFMAN: Again, it's significant.

So we move onto the CHAMACOS study where this cohort was comprised of mothers and children from farm families living in Salinas valley who are predominantly of

Mexican descent. This cohort is exposed to many pesticides, including multiple organophosphates from multiple pathways, such as occupational exposures and take-home exposures as well.

In this cohort, the urinary -- I'll go through it. They were also enrolled at 20 weeks gestation and the cohort included 488 mother-child pairs. They measured the TCPY levels, specific and total dialkyl phosphate levels in urine. And in this cohort, there were associated -- the dialkyl phosphate levels were associated with multiple birth and neurodevelopmental outcomes.

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DR. KAUFMAN: So the specific publications include Eskenazi et al. in 2004, which saw no association between TCPY levels and parameters of fetal growth or gestational age; decreases in gestational duration were associated with increased urinary dimethyl phosphate levels; and decreased levels of cholinesterase in umbilical cord blood.

In Eskenazi 2007, no associations were observed between two TCPY levels and the mental or psychomotor developmental index scores or with the childhood behavior checklist. Elevated odds ratios were seen between total dialkyl phosphates and pervasive developmental disorder.

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DR. KAUFMAN: Young et al., in a related study, observed a positive association between higher diethyl phosphate levels and the number of abnormal reflexes. Similar associations were also seen with the total dialkyl phosphates and dimethyl phosphate levels. These findings are similar to those reported by Engel et al. in the Mount Sinai Cohort between the diethyl phosphate levels and abnormal reflexes.

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DR. KAUFMAN: We move onto another cohort study by Samarawickrema et al. conducted in Sri Lanka. Pregnant women were exposed to pesticides during the spray season in this study, as compared to women who were pregnant in between spray seasons. Chlorpyrifos was detected in only one maternal cord blood sample. However, this may not be surprising as the limit of detection in the assays used were very high.

Lower mean cord blood butyrylcholinesterase activity was seen during the spray season compared with the between spray season. And there was also evidence of increased oxidative stress and DNA fragmentation in the cord blood obtained during the spray season.

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DR. KAUFMAN: This slide compares the three prospective cohorts that we saw before. The studies that

use dialkyl phosphates, the nonspecific metabolites of chlorpyrifos as the exposure measure are not included here. The three cohorts differ in population, setting and exposure measures.

As we can see, the ethnic differences between the studies are on the left. Since there's a large variability in polymorphisms of the PON1 enzyme by ethnicity, there indeed may be large differences in the susceptibility of exposure to chlorpyrifos in these populations. PON1 status has been shown to vary up to 165-fold within a population of Mexican American women and newborns.

The environmental settings also varied between these studies. In the two inner-city environments, pesticides were sprayed inside the home in New York City. While in the agricultural setting of CHAMACOS very little exposure came from home use of chlorpyrifos. Chlorpyrifos may persist much longer indoors due to environmental conditions, such as diminished filtered sunlight, reduced moisture, reduced air movement and surface areas are also variables, as well as the lack of soil microorganisms.

Therefore, the ratio of the concentration of parent pesticide to the less biologically active environmental degradants -- in this case such as TCPY -- is likely to be higher in the indoor settings than in the

outdoor settings. The results of Whyatt et al. in the Columbia study showed that pesticides were persistent in the home with very little variability in the air concentrations over a two-month period.

The exposure measures used as seen in the center of the column, here, include TCPY, which is easier to measure as there is greater concentration of TCPY in urine than there is chlorpyrifos in blood. However, the urine levels of this metabolite do not differentiate between exposure to chlorpyrifos, exposure to TCPY in the environment or exposure to chlorpyrifos-methyl.

Thus, the exposure to TCPY directly from the environment would result in exposure misclassification and would decrease the ability to detect a true effect of exposure if chlorpyrifos -- if one were present in exposure to chlorpyrifos.

As you can see, the median TCPY levels were higher in the Mount Sinai cohort than in the CHAMACOS cohort. In actuality, since the limit of detection was about five times higher in the Mount Sinai cohort, the difference between the actual exposure may be even greater between these two studies.

These exposure levels cannot be compared with the Columbia cohort since Columbia measured the parent compound chlorpyrifos in blood.

Blood chlorpyrifos is considered the best biomarker of exposure with cord blood being in direct conduct with the fetus. Since the levels of chlorpyrifos in blood depends somewhat on the equilibrium between its concentration in adipose tissue and blood, the blood concentrations are best evaluated both with a concentration basis and a lipid basis. The exposure levels from the Columbia study included levels for only the concentration basis.

The only study reporting PON1 data in relation to birth outcomes was the Mount Sinai study, which found decreases in head circumference. Only the Columbia study examined the differences between pre- and post-cancellation of chlorpyrifos use in residential settings, which showed decreases in birth weight and length and increases in small for gestational age, as well as delays in mental and psychomotor development and behavioral disorders, including attention deficit and AD/HD and the pervasive developmental disorder.

No effects were seen in the CHAMACOS study in relation to exposure to TCPY. As noted earlier in all these studies, there was exposure to multiple pesticides, some of them being other organophosphate pesticides including diazinon, which diazinon, in fact, in the Columbia study was actually controlled for in the

analysis. It's also noted, though, that there could be early childhood exposure to lead, which may also be a confounder that was not controlled for.

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DR. KAUFMAN: So moving on out of developmental and into female reproductive studies. These two female reproductive studies in humans were identified on the basis of examining the presence of chlorpyrifos in breast milk. As mentioned earlier by Poorni, according to the U.S. EPA, changes in offspring growth or milk quantity and quality may constitute a female-specific endpoint or reproductive toxicity.

So what we see in Wagner et al. in Germany, they examined various samples and detected chlorpyrifos in 1 out of 11 human blood samples and 3 out of 11 cervical fluid samples. Chlorpyrifos was not detected in follicular fluid. In a study by Sanghi et al. Bhopal, India, chlorpyrifos was detected in all of the 12 breast milk samples. Estimated intake, as calculated from these measured levels, was more than four times greater than recommended intakes by the World Health Organization.

Other pesticides detected included endosulfan malathion and methyl-parathion.

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DR. KAUFMAN: On to male reproductive studies of

chlorpyrifos in humans.

We see six male reproductive studies, one case-control and five cross-sectional studies by the same group of researchers, Meeker et al., as well as two related studies, one in vitro and one of an agricultural study of multiple pesticide exposure.

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DR. KAUFMAN: So when we look at the case control study by Swan et al., subjects were chosen from men who participated in a multi-centered study of semen quality in fertile men. The men were chosen from Missouri and Minnesota reflecting urban and rural areas. And cases were defined as men having poor semen quality. Numerous pesticides were examined. For TCPY, the odds ratio for low semen quality in men from Missouri was 6.4 versus -- sorry -- versus 0.5 for men from Minnesota, but neither were significant, as you can see with the confidence interval encompassing 1.

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DR. KAUFMAN: The five cross-sectional studies by Meeker et al, included males from sub-fertile couples attending an andrology clinic. The exposure measure was TCPY in the urine. The study included 360, mostly Caucasian men, with a mean age of 36 years. And men with urine samples whose specific gravity values were outside a

range were excluded from the analysis.

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DR. KAUFMAN: The results from these five studies include the following:

Most of these associations are examining an increase in interquartile range in TCPY. Using the comet assay, there was statistically significant associations between higher TCPY and two measures of DNA integrity, thus suggesting DNA damage in human sperm. There were suggestive associations with higher TCPY levels and decreased sperm concentration, sperm motility and straight-line velocity. No association was seen with follicle-stimulating hormone, leuteinizing hormone, inhibin B, or sex hormone binding globulin.

And there is a mistake on this slide. There was an association with higher TCPY levels and lower free androgen index. Higher TCPY levels were also associated with lower T4 levels and higher thyroid stimulating hormone, but no association was seen with T3. Estradiol levels were also lower in men with higher TCPY levels. And no change in prolactin was seen.

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DR. KAUFMAN: There are two related studies. The first one looked at the effects in vitro exposure to sperm samples from healthy males with normal semen quality

parameters. Samples were incubated with different concentrations of 3 organophosphate pesticides, methyl-parathion and chlorpyrifos, as well as diazinon, and their corresponding oxon metabolites.

The results showed that the oxon -- the organophosphate oxons, and to a lesser degree, the parent compounds have the ability to damage matured sperm chromatin and particularly the DNA.

In the cross-sectional study by Perez and Herera, the authors examined the role of PON1 -- the PON1Q192 polymorphism on the susceptibility of sperm quality and DNA integrity to organophosphate toxicity in agricultural workers in Mexico.

Semen samples were acquired along with questionnaire data, including a history of pesticide use. Participants were exposed to a mixture of pesticides, mostly organophosphate pesticides. And the study reported that sperm DNA integrity and semen viability, motility and morphology were modified by this polymorphism, the Q192R polymorphism, where the men with the 192RR genotype were more susceptible to adverse effects on exposure -- of exposure -- from exposure.

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DR. KAUFMAN: The summary slide. So for developmental toxicity endpoints you've seen throughout

this presentation, the animal data reported no malformations or effects on viability or birth weight. For neurodevelopment findings from studies with oral exposures were indicative of effects on behavior and brain morphometry. In the subcutaneous exposure, there were cholinergic and cellular effects on the hippocampus and cerebral cortex, as well as biochemical changes affecting synaptic nerve terminals and synaptic activity.

From the human side of things, there were decreases in birth weight and length, as well as decreased head circumference in association with PON1 activity. In the neurodevelopmental, delays were reported in the mental and psychomotor indices, as well as increases in behavioral disorders, including attention deficit disorder and pervasive developmental disorder.

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DR. KAUFMAN: From the female reproductive data, we saw animal studies demonstrating the presence of chlorpyrifos in milk. Also, reduced pup weight and an increase in pup mortality was noted in the F1 rats at the high dose in a two-generation study. And chlorpyrifos was also detected in the breast milk in humans.

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DR. KAUFMAN: And finally, the effects on male reproductive system show that DNA damage was noted in

genotoxicity studies in the animal data. There were no effects of the histopathology of reproductive tissue at doses -- or at dose levels below the levels that resulted in significant cholinesterase inhibition.

In the human studies, there were inverse associations with a number of sperm parameters, as well as the male reproductive hormones including testosterone and free androgen index. Significant associations were also seen with lower T4 levels and higher thyroid stimulating hormone, but not with the total T3. Estradiol levels were lower, but prolactin levels were not.

And that concludes our presentation.

CHAIRPERSON BURK: Thank you. Are there any questions from the Committee for the presenters?

We are speechless at the moment.

But are there any public comments? I haven't gotten -- let's take a look and we'll see how the timing looks here. This is the order. So we have three. And the first one is requesting 30 minutes. Oh, it's 30 minutes for all of them. I think we should go for it.

How are you doing?

THE REPORTER: I'm fine.

CHAIRPERSON BURK: So I think what we'll do is we'll go with this and then we'll take a break after that.

So very good.

COMMITTEE MEMBER JONES: Dotty, can I ask one question?

CHAIRPERSON BURK: Oh, absolutely.

COMMITTEE MEMBER JONES: In the studies in which there was an inverse relationship between PON1 and the exposure, was the exposure documented to be just chlorpyrifos or was it all of the organophosphates?

In other words, was that a, so-called, related study, the PON1 study or was --

DR. KAUFMAN: No, it wasn't --

COMMITTEE MEMBER JONES: -- it a specific study related to --

DR. KAUFMAN: It was a specific study with TCPY.

COMMITTEE MEMBER JONES: It was?

DR. KAUFMAN: Um-hmm.

COMMITTEE MEMBER JONES: Okay.

COMMITTEE MEMBER KEEN: As we're getting some things clarified, I just want to make it clear in my own mind. As I look at the milk data, often times I've interpreted the original EPA as if you see a change in production -- and I see no data that the production is affected -- or the composition, and often times that's been interpreted as it's something other than the compound you're studying, because otherwise virtually anything that shows up in the milk, you'd say okay well, that's an

effect. So was there any compositional changes in the milk by the exposed animals, exclusive with the compound being studied?

DR. IYER: No. I think it's just the question that they did detect it in the milk, because this was part of the companion developmental neurotoxin.

COMMITTEE MEMBER KEEN: Yeah, I appreciate that. But there's a distinct difference between saying the composition of quality of the milk has changed versus merely the compound being detected.

DR. DONALD: Right. If I could add to that, Dr. Keen. It's perfectly correct in the way that that's normally been interpreted. But also, we have to bear in mind the specific constraints of Proposition 65 that -- the guidance that Dr. Keen is referring to encompasses postnatal exposures to chemicals as contributing to developmental toxicity. And there's really no reason to distinguish whether an effect that results from the presence of a chemical in milk as a developmental effect or a female reproductive effect.

Since Proposition 65 is interpreted to exclude postnatal exposures, in this case, we're at least putting forward for the Committee's consideration that the presence of chemical -- that interpreting the presence of the chemical in the milk is not inconsistent with the

generally accepted guidance that changes in the composition of the milk can be considered a female reproductive effect.

COMMITTEE MEMBER KEEN: Yeah. I think, Dr. Donald, you raise a good point there, but is there any data that you're aware of, just for kind of tidying it up, that cross-fostering studies would suggest that exposure to the compound of the milk is associated with any problems?

I looked for it and couldn't find any, but perhaps you have.

DR. DONALD: In the case of this chemical, no. No such data exists as far as we know.

COMMITTEE MEMBER KEEN: Thank you.

CHAIRPERSON BURK: Are there any other questions?

I'm sure we may have some later, but let's continue. The first speaker is Christian Volz, McKenna, Long and Aldridge. Maybe you should introduce yourself and make sure.

MR. VOLZ: Before I start speaking on behalf of Dow, we would offer to let other speakers who have just recently submitted their intention to speak go ahead of us, that would help us to know how much time we have. We have a rather lengthy collective presentation to make.

CHAIRPERSON BURK: The only other request to

speak is requesting two minutes.

MR. VOLZ: Should we let her go first?

CHAIRPERSON BURK: No, I think you can go right ahead since you're there.

(Thereupon an overhead presentation was Presented as follows.)

MR. VOLZ: Do I have a clicker or do I say, "Next Slide"?

MS. OSHITA: Next slide.

MR. VOLZ: Okay.

Well, good morning, Dr. Denton, Chairperson Burk, fellow members of the Committee.

CHAIRPERSON BURK: Could you pull the mic closer?

MR. VOLZ: Is that better?

DIRECTOR DENTON: Why don't you try putting it up on the podium and see if it's better.

MR. VOLZ: How's that?

DIRECTOR DENTON: Better.

MR. VOLZ: On behalf of Dow AgroSciences, thank you for this opportunity to address the Committee on the subject of the scientific evidence about the potential developmental and reproductive toxic effects of chlorpyrifos and for the opportunity to present our case that the weight of evidence does not support listing.

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MR. VOLZ: Our agenda is as follows: I will just have some brief comments about the standard for listing under Proposition 65, both with respect to the statute itself and more particularly with respect to this Committee's written guidance criteria for making listing decisions.

I won't take long. The great majority of Dow's presentation this morning will be presented by two scientists, one an epidemiologist and the other an animal toxicologist. Dr. Carol Burns is an epidemiologist with the Dow Chemical Company, and she will address the human data on chlorpyrifos. And she'll be followed by Dr. Juberg who will address the animal data.

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MR. VOLZ: You know the statutory standard very well. It's been quoted several times this morning. Still, you know, we think it's important to emphasize that the statute sets a stringent criteria for listing. It requires that a chemical be clearly shown, through scientifically valid testing, according to generally accepted principles in order to be listed.

You know that. But the reason why we think it's worth mentioning that is just listening to OEHHA's presentation this morning, we heard a bunch of phrases which don't really add up to that. We heard reference --

you know, the standard isn't that the chemical might cause reproductive toxicity or that there's some evidence. It certainly isn't that there are uncertainties. Some of the phrases that we heard earlier just without pretending to be comprehensive or get them all, we heard a hint of positive outcome. We heard speculation about possible mechanisms, and about novel modes of action. We heard that some studies may or may not show an effect. We heard that other studies raise concerns or raise questions. And finally, we heard that some create suggestive associations.

Well, those are all perhaps legitimate observations, but none of them individually or collectively add up to a clearly shown standard. So we ask you to please keep that in mind.

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MR. VOLZ: The regulations under the statute follow the statutory definition, precisely word for word. And so the Committee's job today, as you know, is to render an opinion about whether, on the basis of all of the evidence, chlorpyrifos has been clearly shown to be a developmental or reproductive toxin.

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MR. VOLZ: As you know, the statutory criteria, and while stringent, is not specific, and so the DART

Committee has its own guidance criteria for listing, which are considerably more specific.

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MR. VOLZ: You know your criteria well. And I wouldn't presume to lecture you on them. What we've done instead is to selectively highlight certain provisions of the criteria that we think are particularly relevant to chlorpyrifos and to the scientific data that you will be weighing and that our scientists will be discussing. These particular criteria in your guidance document will be referred to specifically by Drs. Burns and Juberg when they come up to the podium.

In terms of general principles, as indicated on this slide, the two principle -- the two most important principles are, first of all, that a weight of evidence approach should be taken evaluating all the science. And second, in the case of quite a few studies, it's important to focus on biological plausibility. And like I said, Drs. Burns and Juberg will elucidate the particular studies where those issues are important.

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MR. VOLZ: The guidance criteria specify that in order to be listed, the chemical has to be shown as reproductively toxic or developmentally toxic by either sufficient evidence in humans or sufficient animal

toxicology data or both. And they also provide guidance to help the Committee decide what constitutes sufficient evidence.

With respect to epidemiology studies, the guidance criteria specify that sufficient evidence requires studies that show convincing evidence to support a causal relationship between exposure and effect. Such a convincing evidence of a causal relationship requires accurate exposure classification and proper control of confounding factors and bias.

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MR. VOLZ: The guidance criteria concerning human studies also emphasize weight of evidence considerations. They emphasize that, in general, an effect should be reported in more than one human study for a chemical to be listed based on human data.

They go on to point out that data from a single well-conducted study could support a listing, but only where there are not equally well-conducted studies which do not show that same effect, and therefore call into consider its repeatability.

In her presentation, Dr. Burns will explain how these criteria and these factors indicate that the human data don't support a listing of chlorpyrifos.

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MR. VOLZ: With respect to animal studies, the criteria specify that to be considered sufficient evidence to support a listing, animal studies in most cases, you know, have to satisfy the following criteria. They have to have a proper experimental design. They have to involve a route of administration that's relevant to expected human exposures. They should involve enough dose levels so that a dose response relationship can be established. And it's important that issues of maternal and systemic toxicity be considered.

In his presentation, Dr. Juberg will explain how these criteria affect and apply to the animal toxicology data on chlorpyrifos.

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MR. VOLZ: Finally, and this was mentioned earlier by OEHHA staff, so it's uncontroversial, Proposition 65 has been interpreted not to affect or not to regulate postnatal exposures. This is a factor that comes up with respect to quite a few of the studies, both animal and human. And it needs to be taken into account.

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MR. VOLZ: Thank you. And with that, I will turn the podium over to Dr. Burns.

DR. BURNS: Thank you. Good morning. It's my big test.

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DR. BURNS: Well, I'm going to talk to you about the epidemiology data. And I think we can agree that it's a little bit confusing.

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DR. BURNS: So I'm going to just focus on a few studies and really today just focus on the developmental toxicity as well. We've heard a review of the three cohort studies. The study by Rull et al. on neural tube defects. They found no significant elevation with chlorpyrifos in the cases, so I won't be discussing that anymore than is in the HID document.

And then as we heard previously, there are several publications that are not specific to chlorpyrifos. The Sri Lanka study focused on analyses by cholinesterase inhibition, the Wolf, Engel and Young also used the nonspecific metabolite for OPs. And the Serles Nielsen study in addition to not finding an association with pest treatment, was not specific to chlorpyrifos. So I won't be talking about those in anymore detail today.

Like I said, I'm going to talk about developmental toxicity. But very briefly, I think it's important to mention the Meeker studies, because they were presented quite a bit in detail just before me.

In the HID document, it discusses that that is

just a one-time urinary measurement and may not be reflective of the three months prior to that. Furthermore, I think it's important to notice that the levels, even though they talk about high and low, were all within the range of normal in the CDC NHANES data. And that may be reflective of its just an exposure to TCP itself and not to the chlorpyrifos parent.

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DR. BURNS: So quickly, I'll move onto the other developmental studies, the clinical -- the case reports, the four cases by Sherman. Reviews in the literature have indicated there's no syndrome in those four cases and not a consistent pattern to the anomalies.

And then the attempted suicide, clearly very high exposure. And perhaps suicidal behavior beyond just the ingestion of chlorpyrifos.

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DR. BURNS: So in preparing my presentation today, I looked at the standard for listing to look at the weight of evidence criteria and try to match my interpretation of the data with that standard for listing.

And that includes that the effect should be seen in more than one human study. And if there is some super study, that you would use that unless there were not equally well-conducted studies.

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DR. BURNS: Feel free to jump in and stop me at any time if you have any questions, but I'll forge ahead nonetheless.

Thank you for presenting the tale of two cities and the story of three cohorts, so I can kind of go through this more quickly. I will try and talk about publications by the authors and not the study, but I may go back and forth.

I think's important to recognize they're very similar in their sizes. Because the cohorts are dynamic in identifying the mother and birth pairs, some publications have 372 and some have 414. So the number of study participants varies with each publication. And I list the number of publications on this slide to give you an idea of the scope, that these studies are broad and go well beyond our discussion today for chlorpyrifos.

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DR. BURNS: I would like to talk about one study in particular. And I took this language from the website of the CHAMACOS study. Although, it's kind of been suggested that a weakness of this study is that the myriad of pesticides that these participants may be exposed to, I think it's also important to understand that the scope of this study was to look at farmworker populations.

In addition to just Epi, it was also trying to evaluate exposures, learning how to reduce exposures in using pesticides effectively. So it has a multiple component to it besides just the epidemiology.

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DR. BURNS: And just quickly, I want to talk about some strengths of this study. Again, it focused on pesticides. And I don't think that's a weakness. Epidemiology is designed to evaluate the environment that we have exposure, whether it's pesticides and lots of different pesticides or if it's the inner-city environment. But this one is very specific to the issue today.

The study conducted was very robust. And I just give you a couple of examples of what they did to try and make the study conduct really good. They didn't just use bilingual people, it was bicultural interviewers. They interviewed the moms twice during pregnancy and they collected urines at both times. And when it came time to evaluating the children, they didn't just use a graduate student and say this is how to do it. They used psychometricians.

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DR. BURNS: And then I think it's important to talk about their use of the urine metabolite TCP. Now

we've heard discussed that this could be exposure to the metabolite and there may be some weaknesses to that. On the other hand, the blood method used in the Columbia study has been viewed as a strength. And I don't disagree because you're evaluating the parent. However, we, at Dow, we're in conversations with Dana Barr at CDC to try and do some other studies, getting the methods so we could look at our workers and maybe, you know, some other populations, so we could look at the blood lipid factor.

Well, she let us know the method has changed already. And so the ability to replicate and test this method is unavailable.

The nice thing about the urinary metabolite in the CHAMACOS study is that then we can compare it to other studies. You know, what are these moms exposed to to compare to other populations, both occupational and residential.

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DR. BURNS: Every Epi study has limitations and that's what we like to do is point them out. And I think realistically, it's important to notice that this study probably isn't representative of all Californians. The high percentage that are Mexican born and about a quarter were field workers.

On the other hand, if you're going to study

pesticides, you should study the group that are probably most highly exposed.

Another thing to consider is what do we really know about in-utero exposure. And some mention was made about misclassification bias. We really don't know if the day that they provided their urine was a representative day of their whole pregnancy, were those exposures higher or lower. I don't think we can necessarily assume that it was non-differential though. There's been recent papers out that bias may not always be toward the null.

And lastly, because these were field workers in a farm-worker community, it's very highly that after they had the baby, they went back to their regular lifestyle and there may have been some subsequent exposures after birth.

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DR. BURNS: So what I'd like to do is similarly summarize the results, only put everything together in a single slide.

So what you see here are the papers by Eskenazi, Berkowitz and Whyatt on birth weight. And as we've seen before, there are two studies for which birth weight -- that's the positive indication -- birth weight increases with increasing exposure, whether it's urinary metabolite or the nonspecific metabolite or even reported use.

However, for the Whyatt paper, and you see the negative indication, birth weight decreases with increasing cord blood, so that would be a bad thing.

And the yes indicates statistically significant, and we only see that for cord blood in the Whyatt paper.

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DR. BURNS: The same format looking at birth length. Again, birth length increases with increasing exposure in the Eskenazi and Berkowitz papers. It decreases in the Whyatt publication. And here we see two yeses. We see a positively significant association for the nonspecific metabolite in the CHAMACOS study. And a positive -- a statistically significant in the negative direction for the CHAMACOS -- the Columbia study. I'm going to get mixed up here. I better slow down.

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DR. BURNS: All right. Then head circumference. And this is a little less clear. Head circumference increases for the CHAMACOS study. And I think it's worth pointing out that when you don't talk about PON1 in the Berkowitz paper, the means are equal by TCPY level. And with respect to PON1, if it's greater than the limit of detection, it was statistically significant. But I think it's relevant to point out that when you look at the means for less than the limit of detection, they're very, very

similar. The pattern is the same.

So it would suggest that the PON1 results are correlated with head circumference irrespective of exposure to TCPY.

And then lastly, head circumference decreases with increasing cord blood, but is not statistically significant for the Whyatt paper.

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DR. BURNS: So quickly we'll put everything together. And if we just look at the yeses, that's the statistically significant associations, for the CHAMACOS study, for the nonspecific metabolite birth length and head circumference increase with increasing levels.

And for Whyatt et al. in New York City, they decreased significantly for birth weight and birth length.

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DR. BURNS: Now, let's talk about what happens when the babies get a little older. Both studies of CHAMACOS by Eskenazi, and Columbia by Rauh et al. reported on the Bayley scores for mental developmental index. And you can see here by the nose, that none of them was statistically significant at 12, 24 or 36 months. And so far we have not seen results for the kids at three years of age in the CHAMACOS cohort.

Now, quickly I'm just going to introduce the

concept of the R-squared for the nonepidemiologist. It's just an indication of when you're doing a multiple linear regression model and you're throwing all the confounders in there, you want to look to see if your variables are statistically significant individually. But then you really want to see how well does your whole model altogether explain the variability of your continuous variable from low to wherever.

And like most percentages, the bigger it is, the better your explanation is. So what we see is very low R squareds for the Rauh paper. Unfortunately, Eskenazi didn't report those R squareds.

As an anchor in comparability, there's a birth weight paper I looked up looking at cocaine use. And they had their R squared of about 70 percent when they controlled for maternal stress and home life and everything else.

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DR. BURNS: And then with the physical developmental index, we see that the Rauh et al. study did show a statistically significant finding for the children out at three years of age. However, the R squared was only a .11 or 11 percent. And I included the factors that they included in their model. ETS is Environmental Tobacco Smoke, secondhand smoking.

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DR. BURNS: Home score is a calculated variable indicating home life.

There was quite a bit of discussion both in the written comments and the presentation today about the Columbia study and evaluating results over time. So I thought it would be important to discuss that today, my point of view on that.

I think we can all agree from the slides presented that the cord blood levels really went down by a lot. You can use whatever adjective you want, "a lot", "dramatic", whatever. And the public health question is, does health improve? You have a natural experiment. You have some kids when you enroll them in the study, chlorpyrifos was prevalent in the home and in the environment. And indisputably it's not for the kids enrolled later.

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DR. BURNS: And this is taken from the 2005 paper. And as we saw today, that by 2001 and 2002, they're right at the limit of detection. And in those later years that there weren't any that were above the limit of detection for cord blood. And just keep in mind, although this says over time, these are different kids. They aren't measuring the same kid going down. It's kids

born in '99 were higher than kids born in 2002.

Now, a lot of discussion has been made about if you stratify this down the middle, that those 200 plus children born prior to 2001, the results are statistically significant, and the ones born after are not.

The question is, and in none of the 60 papers or the additional reports by the investigators, does it say are the babies bigger. We know statistically significant and we know modeling. But we wouldn't expect it to be statistically significant, because there's no exposure.

The question is, do the babies get bigger, longer, better?

And there's no evidence in any of the papers that tell me that. What they do show, however, is in their 2006 paper, they do show mean scores over a three-year period that correlate with the change in exposure.

And if you read the written comments, this looks a little different, the lines are bars and the bars are lines, but essentially it's the same. For example, for the kids born in 2000, that bar up around three and a half picograms per gram, they were three years old in 2003. So that's their mean level. The red bar is the mental development score and the blue car is the physical development.

So you see, their exposure was less and they are

statistically better -- their scores are better than the kids born the year before them. However, even though exposure drops down to the limit of detection, the kids born the next year don't have even better scores. Their scores are about right there in the middle of what the other kids were.

So, to me, this says that all things being equal, you've taken away the exposure, but nothing dramatic has happened.

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DR. BURNS: Just quickly to have a little slide on biological plausibility, and I think the previous speaker went -- talked about this very well about cholinesterase inhibition and how it's been viewed in the past.

Keep in mind, that although we talk low and high about these human studies, these are too low to inhibit cholinesterase. So if there's a mode of action, it's not cholinesterase in these populations.

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DR. BURNS: So the key points for my talk today are that the three birth cohorts that we've been discussing, myself and other speakers, the CHAMACOS study is the one study that did focus on pesticides and farm workers and they found no significant findings. The

Columbia study is the only study to report statistically significant adverse effects.

And, in my view, the natural experiment does not support a cause and effect. Exposures are low and unlikely to inhibit cholinesterase.

Just to remind myself how I viewed the weight of evidence criteria, that the effects should occur in more than one study, and only rely on one study if there aren't others that are well conducted and I don't see that there's a consistent pattern across the three studies. And the effects don't occur. There are well-conducted studies that don't show an effect.

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DR. BURNS: I'd be happy to answer any questions before I turn it over to Daland Juberg.

CHAIRPERSON BURK: Are there any questions?

Okay, thank you.

DR. KAUFMAN: Actually, I'd like to take this opportunity to clarify something. Can we go back a little bit.

As Carol Burns mentioned, this was a graph that was submitted in the written comments form by Dow. And I had some question about this graph, because I couldn't understand where the data was coming from. So I asked Dr. Rauh to verify my concerns, and essentially she did.

The data that was taken from the paper, Rauh et al. 2006, in this context is ecologic data. So that means that there's no individual data, so the scores that you're seeing are not related, in any way, to that individual's blood level. So that's one point on this graph.

Also, none of these are adjusted for any of the confounders or potential confounders or covariates that we've mentioned that could be so important. So this is unadjusted data.

In addition, Dr. Rauh felt that it was kind of not really logical to expect to see the kind of change that we saw in birth weight over time, because this is a neurodevelopmental outcome. And as Dr. Burns noted, the variability in neurodevelopmental outcomes that could be related to chlorpyrifos is a very small percentage of the variation. So one would not expect to see large changes in these outcomes. And it's certainly not unless one was adjusting for all the potential covariates that we know influence neurodevelopment.

So I think this slide is a bit misleading.

DR. BURNS: May I comment?

Certainly not my intent to mislead. And these numbers are taken verbatim from the 2006 paper from their discussion.

I only present the two together just to

demonstrate the dramatic decrease in chlorpyrifos over time. That certainly if, as public health decision makers, that removing exposure to chlorpyrifos will solve any problem or if this is highly correlated with the effect, ecologically, you may or may not see effect. But I'm just presenting the results from their paper, that they did not show that the scores were -- you know, improved over time.

DR. KAUFMAN: I thank you for clarifying that.

I just also want to clarify that Dr. Rauh added the comment that she did conduct the analysis between exposures to chlorpyrifos in the blood levels and the neurodevelopmental outcomes and that's what she presented. These values were included in the paper, but not intended for this use. As she said, it would be completely under-powered to be able to, if you looked at it by year, because of the numbers and the covariates that had to be included. So they haven't looked at the analysis by year. They've looked at the effect by chlorpyrifos levels. They feel that it just wouldn't be possible.

I mean, if you do the calculations, it's not possible to analyze it properly by year, as what you've presented here.

DR. BURNS: Okay.

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DR. JUBERG: Okay. How do I get to the first slide?

Is this on and can you all hear me or should I not -- it is?

Okay.

I was all prepared to say good morning, but I'm going to have to say good afternoon --

(Laughter.)

DR. JUBERG: -- to you all. My name is Daland Juberg. I'm the toxicologist responsible for chlorpyrifos for Dow AgroSciences. I want to begin my presentation by thanking Dr. Iyer and the OEHHA for giving us the opportunity -- me the opportunity to speak to you today on our scientific views on the animal data. I also want to express my appreciation to the DART Identification Committee for considering these views.

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DR. JUBERG: Briefly, my background today -- outline is going to be a brief one slide on chlorpyrifos and its mode of action. I will then move into some discussion of the developmental toxicity studies focusing in on the guideline studies that we've conducted and other registrants have for FIFRA purposes. I will talk briefly about some of the studies included in C.2.2 of the HID, some of these other studies that Dr. Iyer has discussed.

I would then like to share a view or two on the developmental neurotoxicity study that Dow conducted on this molecule back around the year 2000. I will then talk about reproductive toxicity and the studies we have available for review and finally some conclusions.

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DR. JUBERG: First of all, this is a molecule that has an extensive toxicological database. We have conducted over 3,600 studies not all on toxicology. But, in fact, many of those hundreds have been toxicology studies. And we know a bit about its developmental and reproductive toxicity potential. As with other organophosphates, it's toxicological mode of action is through cholinesterase inhibition. And I point this out because this has been, over the 40-year history of its use, the most sensitive effect that's been determined through a number of different studies.

And just so I give you some context to that, before we inhibit plasma cholinesterase, there's a tiered layer of protection that goes on beginning with portal of entry metabolism continuing on with protein binding. We then have a hepatic metabolism. All these A and B esterases. So before we even begin to get to plasma and RBC inhibition, we have these layer protections. And I know a lot's been made of PON1. We certainly acknowledge

there's a genetic polymorphism.

But PON1 doesn't come into play. It's a high-dose modest detoxification mechanism that really doesn't play a role in environmental exposures. This has been supported in a mouse model, Kohl et al. It's also been supported by the PBPK model that's available by Chuck Timchalk out of Battelle Northwest.

So it's something to keep in mind, before we even get to those layered -- or before we get to brain cholinesterase inhibition is where you really begin to see toxicity, cholinergic effects. We've got a tiered system of protective devices.

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DR. JUBERG: Moving onto the developmental tox studies. There is a rich database for chlorpyrifos relative to the design and the conduct of studies that we have for FIFRA purposes. We have the fortune of having four studies in three different animal species. These have all been conducted according to U.S. EPA guidelines. These are comprehensive studies, meaning that if we are going to look for some developmental effects, we are likely to see these through these studies. These are designed over multi years through a multi-stakeholder process. And they're designed to determine and detect effects. These are what I would consider scientifically

valid, according to generally accepted principles.

What are some of the significant findings amongst these studies? And there is consistency. No developmental toxicity in the absence of maternal toxicity. More importantly, and I would emphasize, there's really little or no developmental toxicity even at doses that produced substantial maternal toxicity, including tremor, salivation and even death.

We do not see evidence of teratogenicity in any of the three species. And, again, as I alluded to earlier, cholinesterase inhibition is the most sensitive endpoint and has been determined in all of these studies -- in fact, in some cases, you don't establish a maternal NOEL because of inhibition of cholinesterase.

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DR. JUBERG: Now, to illustrate just one of the studies in this lack of developmental toxicity, I've highlighted the Deacon et al. study. This is the mouse developmental toxicity study. And I just raise this, because I want to take you through three dose levels.

At the low dose, we saw evidence of maternal ChE inhibition but no developmental toxicity. At the 10 milligram per kilogram day does, we saw increased evidence of maternal toxicity, but, again, no developmental toxicity. It was only at the high dose where there was

severe maternal toxicity, including death, did we begin to see evidence of developmental toxicity in the offspring.

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DR. JUBERG: Moving onto some of the other studies. And I've taken a look at the studies that were included in the HID C.2.2., and there are a number of studies. There are 18 others that OEHHA has evaluated and I applaud them for their accurate description of some of these. They've pointed out some of the limitations.

But before I get to those, some of the DART criteria that are used for developing a sufficient evidence in experimental animals is based on adequacy of the following: Experimental design, route of administration needs to be relevant to expected human exposures; we have to have a number of dose levels that are evaluated; and, in fact, 11 of the 18 studies that I looked at had fewer than -- two or fewer dose levels, such that a dose response could not -- relationship could not be evaluated; and finally, consideration of maternal toxicity.

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DR. JUBERG: Now, looking at some of these studies, they provide value, in terms of investigation into unique and interesting aspects of chlorpyrifos, under perhaps different routes of exposure and so forth. When

you look at the sum total of these, some of the deficiencies I see as a toxicologist are the following:

In fact, 13 of 18 used either a subcutaneous intraperitoneal route of exposure. Some involve postnatal day PND exposure only. Those were 4 of 18. I've mentioned the inadequate dose groups. And OEHHA did a good job of pointing out where there are limitations with each of these studies.

I want to pause on the next, because I think it's been under appreciated the significant role that dimethyl sulfoxide has and is known to affect on neurotoxicity effects of its own. There's some very recent evidence. But going back, there's a growing literature on the effects of this particular solvent. It affects a number of different things.

And let me just read a couple of these things that DMSO on its own will affect: Structural changes in peripheral nerves, reduction in nerve conduction velocity, spontaneous changes in exploratory behavior, altered sleep behavior. The point is not only can DMSO do these, but the CAR and Kneel recently has shown that the volume of the vehicle can cause dramatic effects, not only on birth weight, but also on brain cholinesterase inhibition.

The DNT study guideline from OECD specifically calls out and says the vehicle should not be -- should not

interfere with interpretation of the data nor should it be neurobehaviorally toxic. And so I think in a number of these studies, and many of these employed DMSO, we have a major confounding issue that has to be worked through.

Finally, numerous of these studies -- and this is a sentinel point relative to the noncholinergic effects. A number of these studies claim effects on offspring below a threshold for maternal toxicity, but, in fact, when you begin to look at some of these studies, rarely is concurrent cholinesterase inhibition measured in dams.

More importantly, we've done some evaluation. Maternal body weight gain is often not reported. Differences in body weight are. But if you were to look at weight gain, often there's an incremental difference of greater than 10 percent. And in a typical developmental tox study, we would consider that adverse.

So these are a couple things that once you get into the details of these studies, I think, really need to be looked at.

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DR. JUBERG: Moving on then to the developmental neurotoxicity study, we do have a study that was conducted back in the year 2000, and this was conducted in conjunction with EPA. It followed the current -- the guideline design at the time. We even met with agency

toxicologists to incorporate a particular design to measure memory in learning.

I will acknowledge this did encompass both prenatal and postnatal exposure. And I understand the significance of excluding postnatal exposure. But what I want to offer is the following: In this study, there was no evidence of developmental toxicity in the absence of maternal toxicity. There were no effects on birth weight, except at maternally toxic -- the top dose of 5 milligrams per kilogram. There were no effects on learning and memory even at the top dose. There was no evidence -- and these are the author's conclusions of selective developmental neurotoxicity following exposure to chlorpyrifos.

The one piece of information that's very critical to review that's probably not been included in the OEHHA HID nor in a number of other things, is what's called Supplement 3, which when after this thinning of the parietal cortex. This is what Dr. Iyer referred to earlier. The situation was at the time when this study was conducted, there were no historical control data. What Argus Laboratories did was review after they conducted another four studies, they submitted, what they called, Supplement 3. And this is available. It's been submitted in our written comments. And I can show you a

slide. And it's not here. But, in fact, what it did was bring those parietal cortex, that thinning, the five percent thinning in the top and middle doses, into perspective.

And I hope to have the opportunity to show you, if you would like. What this basically showed is that the thinning of the mid and high dose were well within historical range, high and low. And so there's essentially no difference in this thinning of the cortex. The effects were not shown in males. And so this is why the authors concluded, as they did, there's really no evidence of selective developmental toxicity.

I'd be happy to show you that after I'm done here.

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DR. JUBERG: Moving onto reproductive toxicity, and I quote from the HID, "No effects on the reproductive or fertility indices or on the histopathology of reproductive tissues were observed in animals at dose levels that resulted in significant cholinesterase inhibition. Severe testicular damage resulting in reduction in sperm count and fertility was noted in a study at higher dose levels."

The one study that's referred to here is the Joshi et al. study. This does have some challenges, I

believe, as a toxicologist. And none of these effects have been reported or confirmed by others. And I would remind myself and the panel that we have dog data for up to two years, no effects on testicular function or histopathology. We have rat data and we don't see any effects of reproduction in our multi-gen studies.

But specific to this particular study, some of the challenges were that these were high exposures, well above where cholinesterase inhibition occurs. Toxicity was reported at all dose levels, but it was not well characterized. And then importantly, mating data were not included in this study, so we don't have a real good way to get a handle on the characterization of reproduction function.

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DR. JUBERG: What we do have available though is the Breslin study. And this is what I would characterize as the most robust multi-gen study we have. We do have three others and those are alluded to in my final bullet up there. But these were all conducted at lower dose levels.

But what the Breslin study showed is that there were no effect on fertility or histopathology of reproductive organs at the highest dose. No neonatal effects in the absence of maternal toxicity. And I also

then went back to our oncogenicity chronic studies, because it's important to look both in the long-term rat and mouse studies, gee, were we seeing any evidence of histopathology, organ weight changes in reproductive structures? The answer is no.

And then I alluded to there are three other multi-gen studies, albeit these were at lower dose levels, but they essentially confirm the absence of reproductive effects.

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DR. JUBERG: In conclusion then, as the toxicologist for Dow AgroSciences who works with this molecule familiar with the database, it's my perspective that studies representing scientifically valid testing, according to generally accepted principles, do not indicate developmental toxicity across a number of species in the absence of maternal toxicity.

And I think we're seeing consistent evidence across studies, which demonstrates fetuses to be less sensitive than dams. There was a companion study that was attached to the DNT study that specifically looked at differential sensitivity and this did not show any.

Point 3, the weight of the scientific evidence does not demonstrate that chlorpyrifos produces male or female reproductive toxicity in animal studies. And

collectively and conclusively then, I would submit that the scientific data indicate that chlorpyrifos has not been clearly shown to cause developmental or reproductive toxicity.

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DR. JUBERG: On behalf of my colleague Dr. Carol Burns and Dow AgroSciences, I would summarize then that chlorpyrifos has not been clearly shown, through scientifically valid testing, according to generally accepted principles to cause either developmental, female reproductive or male reproductive effects, and this predicated on a lack of evidence in both humans and experimental animals.

That's all I have today. And I'd be happy to answer questions if I could, if you have those. Or if you want me to show you the one bar graph, I'd be happy to show you the control data for that study. But Supplement 3 is a very critical part of the assessment of the DNT study.

CHAIRPERSON BURK: Yes. I thank you for bringing that up, because I was a little confused on it here in our materials. I don't need to see the details necessarily, but I just wanted to verify that with the data that we had, we had a study called Hoberman and that's where they found the morphometric differences. And then you're

saying that the published study that came later was after this Supplement 3?

DR. JUBERG: The published -- actually, Dr. Burk, it did not have that conclusion. And so even the published study didn't have the benefit of that. Subsequent to that though --

CHAIRPERSON BURK: Because that wasn't mentioned in the published study, was it?

DR. JUBERG: It was not. It was not. These were submitted four months after the EPA actually reviewed the data back in 2000. And so it's one of those things as a toxicologist, I just like to keep bringing up, because it's pretty insightful to the overall DNT study, and at least should be thrown into the mix of the discussion I believe. Historical control data can be invaluable in cases like these. And, in fact, it shows this five percent thinning to be right in the middle of where you would normally expect control animals to be.

COMMITTEE MEMBER JONES: I'd like to see your data.

DR. JUBERG: Okay. Do we have that?

It's slide 53.

And will you all work it from there or will I operate it?

MS. OSHITA: We will get it up and you can do it.

DR. JUBERG: Okay.

Again, this was a finding of about five percent seen in the mid- and high-dose animals, females only. And when Alan Hoberman at Argus did then was to bring in the data from four other DNT studies in conjunction with our study, the 5th. It's the 10th -- middle on the -- yeah, there you go.

I don't know if we can highlight that. What we're demonstrating here is parietal cortex thickness, again, measured at two months out, day 66. And you can see either by the bar graphs or the tabulated data there, you can benchmark it against the percent historic mean, where we basically are running from a high of 105 down to 95. But if you look at the 1 and 5 milligram per kilogram per day -- these are the mid- and high-dose levels -- those numbers fall right at the historic low is 92.4.

But looking at the bar graph, they're just right in line with where these effects -- or where parietal cortex thicknesses will be.

Dr. Hoberman and others went on to bring a number of facets of this thing -- a number of findings before saying, you know, given a 5X difference in dose, if the effect were treatment related, we certainly should have seen it in the males as well. So it was not reported in the males at all.

DR. IYER: I'd like to add that I did talk with the U.S. EPA reviewers about this. And, A, they were -- you know, they thought that you have -- concurrent controls have more value than historic controls. And given that, you know, it's a matter of semantics, these may not have been historic, because these were actually done afterwards, so there's some question about that. But they did take that into account and they still felt pretty strongly that for the concurrent controls, there was an effect. It may be just a hint of that this is maybe happening. They actually looked at it though and found it, even in the mid-dose. I think that's what really kind of convinced them. Seeing it at the high dose would have been one thing.

And then they didn't have the benefit of looking at the low dose, because that wasn't done, so they couldn't tell what was happening. So that was their view on looking at this closer examination, because at first glance, it doesn't look like there's an effect. But when you look at it again, you see that there is actually an affect by their estimation.

DR. JUBERG: I would note, there were no histopathological effects associated at any dose level. So while they had this thinning effect, its histopathology wouldn't support that there was any finding. But Dr. Iyer

makes a good point.

Thank you.

Any other questions?

Thank you all very much.

CHAIRPERSON BURK: Thank you.

And next we have Dr. Gina Solomon, NRDC, two minutes.

DR. SOLOMON: Sure. I don't have a PowerPoint prepared. Thank you for your patience and for going into your lunch time. I'm Gina Solomon. I'm a senior scientist with NRDC, the Natural Resources Defense Council. I'm also an Associate Clinical Professor of Medicine at UCSF, where I'm an Associate Director of the Pediatric Environmental Health Specialty Unit there.

And so I was just listening to this and it's sort of striking to me how -- well, first of all, I also wanted to thank the staff, because I thought that the presentation were really very strong, very well done and reflected a lot of work.

And this is a chemical that I've been interested in for quite a number of years. And it, I think, is a testament to a new improved priority-setting process that you're now getting really meaty interesting chemicals with quite a lot of data to chew on. And it was sort of interesting to me to see how a chemical with such a strong

data set, that is really so consistent when you look at the developmental neurotoxicity data in animals. And, of course, cortical thinning is not a super-sensitive endpoint. It's pretty gross histology. But if you look at both the animal toxicity and the human data, you really see very much the same kinds of effects. You see really very nice dose-response relationships in many, many studies.

And, of course, folks can point out issues with individual studies and sort of make the whole thing seem more confusing than I actually think it is.

But I, of course, am not a toxicologist. So my expertise is more in the epidemiologic area. And I have spent a fair amount of time looking at the CHAMACOS study, the Mount Sinai study and the Columbia study and really feel that they're not inconsistent with each other when you take into consideration some of the dose metrics used.

In other words, whether they're looking directly at chlorpyrifos, directly at cord blood versus a metabolite in urine; when you look at the dose differences that were found in those studies, so that you have higher doses. Certainly, I think in both of the New York studies that's a little hard, as Farla mentioned, to compare the two.

But there's no reason to think that populations

would be that different between Mount Sinai and Columbia in terms of, you know, the exposure pathway, because it was all indoor extermination.

So we see much lower exposure levels in CHAMACOS in a much less dramatic effect. But still something that is completely consistent with what we see in terms of neurodevelopmental toxicity.

And just going back to the R squared question. I don't think that any of us are saying that chlorpyrifos is as potent a developmental toxicant as cocaine. I think we're saying that it is -- you know, we're seeing really pretty dramatic data showing developmental neurotoxicity, not something that will swamp everything else like, you know, cocaine or lead, but certainly something that is an important developmental neurotoxicant that is very much within the purview of this Committee to designate as such.

And so I'm just asking you to look at the big picture, look at the consistency and to designate chlorpyrifos as known to the State to cause birth defects or reproductive harm or whatever the big picture is. I'm actually not going to speak to the male reproductive endpoint, because it's not something I've looked at at all.

So thank you very much.

CHAIRPERSON BURK: Thank you.

And I think this is a time to take a break.

How long do you recommend?

What time should we reconvene?

Oh, absolutely. We do have a full agenda left. We have to discuss this and we have other things. So 1:30?

No later than 1:30. We absolutely will start right at 1:30.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, I just wanted to remind --

CHAIRPERSON BURK: Yes, Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- the Committee Members not to discuss this issue or any of the others that are on the agenda while they're at lunch. So we need to keep it in the public forum.

Thank you.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON BURK: Well, good afternoon, everyone. I'd like to call the meeting to order again. Five minutes later, but -- well, maybe this clock is fast, but for whatever reason.

At this point, I think the Committee will begin discussing chlorpyrifos. And I have asked Dr. Hillary Klonoff-Cohen to take the lead on the discussion of the epidemiological studies. And somehow by default, I will take the lead on the discussion of the animal studies. So I'll turn it over to you, Hillary.

COMMITTEE MEMBER KLONOFF-COHEN: Thank you.

Well, I thought I would start with looking at the guidance criteria that was provided to the Committee. And so I just wanted to touch on that very quickly.

So for the people who don't have a copy of this, basically what it says is for sufficient evidence in humans in the case of epidemiology studies, they should provide convincing evidence to support a causal relationship between exposure to the chemical in question and the effect in question.

And for epidemiological studies, we have various types of study designs and certainly we're very fortunate to have prospective studies to actually look at with this particular chemical. We have three, in fact. And as

well, we also have case control studies and cross-sectional studies. But I think in terms of establishing a causal relationship, the prospective study certainly does that.

The next point is that it requires accurate exposure. Now, in terms of accurate exposure, I think that these studies, all three of them, were designed very well, to be honest. They might actually measure different metabolites or use different mediums, whether it be blood or urine. But in terms of the accurate exposure, I think that they certainly do that.

As far as the confounding factors, for all three studies -- I've been on this Committee a long time. I've not seen such a long list of confounders for particular studies. And I'll just read a few of them just to give people the idea.

But for the CHAMACOS study, some of the potential confounders are maternal education, marital status, parity, county of birth, poverty, smoked during pregnancy, caffeine use. So you can see that they certainly have adjusted for a great deal of confounders.

As well for the Columbia study, the same thing and even more I might add. So they have a lot of demographics in terms of maternal age, race/ethnicity, et cetera, et cetera, maternal IQ, environmental tobacco

smoke, season of delivery, home environment, marital status. So once again -- and I'm just reading a partial list. So I think they've also done an excellent job of the confounders that they considered.

And last of all for Mount Sinai, they also had looked at in maternal age, race/ethnicity, infant sex, gestational age, et cetera.

So in order to address the criteria in terms of the studies, I think the studies are rigorous studies, and I think that they are designed very well.

Now, having said that, there are certainly differences within the studies. And the beauty of doing research is that we tend to look at studies and improve upon them and do different things. So the fact that the CHAMACOS and Columbia and Mount Sinai aren't absolutely measuring the same things to me is not necessarily a flaw.

I want to start with the ethnicity or the racial breakdown in terms of these three studies. And I wanted to say that CHAMACOS was looking at the low-income Latino pregnant women. Whereas, Columbia was looking at a African American and Dominican women and Mount Sinai was looking at African American, White Mexican and Puerto Rican.

And I have to say that having sat on this Committee for a long time, a lot of the studies have been

primarily Caucasian. So this also, I think, is a plus.

If you look at the demographics for CHAMACOS, you'll see that 82 percent of the women are married and 81 percent had less than a high school education. But what was nicely balanced and yet different in the other studies were that only 25 to 29 percent of the women were actually married. And that 35 percent -- 32 to 35 percent had less than a high school education.

So differences sometimes are good, because when you look and compare and contrast studies, it helps to explain things. So as well, it's been brought up that the New York studies were, of course, measured indoor in terms of the exposure assessment. Whereas, the CHAMACOS study was outdoors. Certainly, there are a whole myriad of other pesticides that were taken into account, but I think that the studies acknowledge those limitations.

So to me, at the end of the day, you really have to somehow combine these studies and be able, after thinking and acknowledging the limitations of each and every study, what does it all mean, and whether or not there is, in fact, an effect.

And so what I've done, which is fairly similar in terms of the wonderful presentation we had, was to basically separate the study designs by prospective case-control cross-sectional and just basically tabulate

what the different outcomes were just for my own personal understanding, because there is a lot of literature and it's hard to actually, at the end of the day know what it all says.

So I will start with the prospective studies, and looking at the effects, in terms of the neonatal characteristics. So Berkowitz was the one who found a decrease in head circumference. So there was one study on decreased head circumference. There were two studies on decreased birth weight, and those were from Whyatt, who was from Columbia and Wolf from CHAMACOS. There was two studies for decreased birth length, one from Whyatt, one from Wolf. And then there was an increase SGA from Whyatt. So those are basically the summaries of all of the neonatal characteristics.

Now, when we go onto the developmental characteristics, we have one study by Rauh, who found a decrease in psychomotor development index, and as well a decrease in the MPI. There were two studies by Whyatt and Eskenazi that had an increase in pervasive developmental disorders. And as well, Whyatt found an increase in Attention Deficit -- ADHD. And there were three studies that found abnormal reflexes and those were Young, Eskenazi and Engel. So that sort of covers those characteristics.

Now, when we go onto the sperm DNA, those are all cross-sectional studies. And for people that are in epidemiology, they know that cross-sectional studies don't necessarily establish the temporal situation as well as prospective studies.

Certainly, in terms of the Meeker studies, there were five studies and they were all on the same study sample. Having said that, he found a percentage tail, where there's a percentage of the DNA in the comet tail, there was an increase. He found an increase in DNA damage and Perez found a decrease in motility and viability and integrity.

So I could sit there and sort of tease out in terms of who used what, whether they used maternal blood or they used urine or if they used DAP or DEP or CPF. But at the end of the day, you have to say to yourself what are the characteristics that they found and whether or not it is important.

And so I think if you take together with the animal studies, of course, with the caveat that there are certainly variations in the outcomes that all of these studies looked at, because they chose the outcomes they wanted to choose to look at. And certainly how they measured their exposures and what confounders they used were their own choices. But as I said, taken together

with the animal studies, there is concern for this.

So that's what I have to say.

CHAIRPERSON BURK: Is there any discussion, I hope?

Questions?

Shall I go ahead and talk about the animal studies and give you more time to think?

(Laughter.)

CHAIRPERSON BURK: All right.

DR. BURNS: Can I ask a question?

CHAIRPERSON BURK: I guess so sure. Come on up.

DR. BURNS: Carol Burns again. Thank you for that interesting summary.

I have a question about accurate exposure assessment when the nonspecific metabolites are used. I mean, I need to know where we are on that? Could you explain that?

COMMITTEE MEMBER KLONOFF-COHEN: In terms of for each of the studies in terms of --

DR. BURNS: Well, if you, for example, the -- I'm getting them mixed up in my head, but --

COMMITTEE MEMBER KLONOFF-COHEN: When you're talking in terms of for instance like DAP and DEP in the urine versus if you're using the blood of the cord blood versus --

DR. BURNS: When one publication of the Mount Sinai study, the Berkowitz paper, did evaluate the specific metabolite. And then I think it's Wolf for Mount Sinai that was nonspecific. So --

CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me. I just wanted to point out that this is the time for the Committee to do their deliberation and their discussion.

CHAIRPERSON BURK: Okay. Carol, so in other words, this is our discussion time now.

CHIEF COUNSEL MONAHAN-CUMMINGS: We already had the public comment period. And so if it's not a clarification of something that was said during public comment and it's just a question about what you just said, I'm not sure that that's an appropriate thing to do at this point. This is the time when the Committee is deliberating and discussing among themselves.

CHAIRPERSON BURK: All right. We will do that.

When it comes to the animal studies, there were many. A lot to read. A lot to wade through. After getting through them all, kind of put them into three categories, which, I think, are consistent with the way it was discussed earlier, we have the standard developmental tox type of studies, that are mostly done for registration purposes. And in those cases, they were pretty much all negative or finding effects only at maternally toxic

doses, if -- as that's defined as inhibition of cholinesterase activity. So I don't think the evidence is very strong for a listing just based on standard developmental tox.

The next sort of group of studies or the ones that look at neuro and behavioral toxicology, and these are much more interesting. And it's nice to actually have some. It's not something we've talked about that much on the Committee yet, so it's a little bit of a new thing for us. And I'm certainly not an expert on this, but, you know, I looked at what we were given, the Hoberman study first, which was using the standard EPA procedure at the time at least. And although they considered that their results were spurious, there were a number of findings, morphometric changes and behavioral changes.

Again, the follow-up to that, I guess, the published study appeared to be negative, and we heard about this other thing about the historical controls versus the concurrent controls. But nevertheless, I mean, I think in light of the human findings, I wouldn't totally dismiss these findings. Again, by themselves, I'm not sure it would be, you know, strong enough, but certainly it's an adequate study and to be considered.

Then there are a whole bunch of studies that I found the most fascinating, because I'm interested in

mechanisms, and, you know, what's actually going on. And so I spent perhaps too much time reading those, but those were the ones from the Slotkin lab. And many of them -- and I had to go in the back to try to figure out who all works in that lab. It must be quite an enterprise.

But the criticisms there, of course, are the route of exposure and the use of DMSO and all that. Again, I would not, on the basis of those alone, find support, but I do think that their findings lend support to the human data. So particularly looking at the windows of vulnerability, you know, different times of exposures, the behavioral alterations emerging later times during adolescence and adulthood, certainly suggesting there may be another mechanism other than cholinesterase inhibition.

Again, I don't think these studies alone would be adequate to support a listing, but I'm kind of looking holistically at the weight of the evidence here. And I do see support for the human findings, particularly the Columbia study. There are other issues to be considered that, you know, were mentioned before, all of which I guess are designed to have us think well, this study doesn't count, this doesn't count, this doesn't count, but I still try to look at this more globally.

So I cannot give you, you know, a checklist of positive studies that make this very clear. I can only

say that there's a vast amount of information, all perhaps with limitations, but that in kind of the big picture on the weight of the evidence, I think we should discuss it seriously.

So I will ask for comments now on the whole picture.

COMMITTEE MEMBER KEEN: Just a -- I guess it's not even the whole picture. I can't help but wonder if we'd flipped it around and we'd done the experimental animals first, because what I'm impressed by is there are clearly, in my opinion, are some effects. Where the confusion comes in is over to what extent are they driven by maternal toxicity.

And when I went through the papers, and then went through the papers that were cited in those papers, I became very much impressed with the fact that maternal toxicity seemed to be an overarching problem in the vast majority of cases.

And if we then used the strict, sort of, guidelines that we've largely used in the past, we'd say well then we have to be very cautious here.

So if one starts from that, I would agree the animal data do not disagree, assuming one takes the interpretation of the human literature that there is in effect, that they don't argue against it, but the only way

that could happen if you saw absolutely no effect with the animal data.

Given the maternal toxicity there, I would almost tend to view it as maybe being a draw. We're missing the critical set of data, and that is something which is below evidence of maternal toxicity, then do we see effects?

If so, I would argue that would buttress my view of the human data is it's not overwhelmingly strong. And, in fact, I think that was pretty well what I heard in your -- you have to take it in totality and you can say well it seems like the suspects are all there. But I do wonder if we -- unless we can point to some data on the animal side where maternal toxicity isn't a major factor, is the right conclusion to say, we're just not going to get anything useful here. And we shouldn't arbitrarily say we'll use it to support that human data. Either the human data should be strong enough on their own or they shouldn't be. That's kind of -- I'd love to hear other's opinions on that.

CHAIRPERSON BURK: I would like to hear from those that -- just relative to the human data, is it strong enough on its own?

Dr. Hobel

COMMITTEE MEMBER HOBEL: Yeah. I think that the human data is great for characterizing the fact that there

is concern about hazard to this chemical. And that puts us in a frame of mind that this is something that we need to seriously consider. But then when I go to the animal studies, it seems to be somewhat overpowered by a much higher focus on toxic levels, which do seem to affect various things in biology.

So I'm finding it hard to compare both to convince me that this is a serious problem at this time. My greatest concern is that with all the new techniques available to look at the epigenetics of the effect of an environmental substance, there are a lot of new tools that can be used today to focus more on really what is happening by looking at certain biomarkers.

So I don't think we're really at the stage yet where we can really make a major decision about listing this drug or this chemical compound.

COMMITTEE MEMBER WHITE: I'm just going to mention, I do agree. I'm not quite convinced that we're there yet. I see the hazard as well, but I can't personally look at the data and say, well, yes, this is a hazard and we need to -- I mean, not a hazard, but this is definitely something that could truly affect reproduction and maternal fetal health. I'm just quite not there yet. I don't see it.

And it's still a little bit confusing for me too,

because of the animal data. So I would agree, I just don't think we're there yet to be able to list it.

COMMITTEE MEMBER JONES: Can we ask Hillary to say whether she thinks the human data, from an epidemiologic standpoint, stands on its own.

COMMITTEE MEMBER KLONOFF-COHEN: Does it stand on its own?

I guess I was interested in hearing the summary of the animal data, because from the presentation, it seemed very striking that the animal data was supportive. But hearing what -- but it sounded very supportive. I don't get that strong a sense now hearing what's been discussed at this point with the animal data. And on it's own, the human data without the animal data...that's a...

CHAIRPERSON BURK: I think this is one of these difficult ones, where we think there's something there, but we don't perhaps quite have what actually would make it crystal clear.

I do think the animal data supports it, but I think what supports it is actually the studies that look at a different mechanism than cholinesterase inhibition, and that would be at a much lower level. But they're not done in the standard way and all that, so therefore we have these kind of limitations that we're looking for the standard type of studies done in the accepted way, and you

know all that.

But I think finding out more about mechanisms other than cholinesterase inhibition, which you would consider maternal toxicity is, would be really important.

So, Ellen.

COMMITTEE MEMBER GOLD: I just want to ask a question again about the human data. Because there's this concern in the animal data about the effects of it being mediated through maternal toxicity, what about the male effects that were observed in the human data?

COMMITTEE MEMBER KLONOFF-COHEN: I think that it's a good question. I think the hesitation I have about the male data, I think the results are very interesting and very exciting.

The difficulty is that it's the same data sets, so it's multiple publications by the same gentleman. And so that's why it sort of tempers my -- if somebody else had come and done a similar study with a different study sample, I would feel more excited.

It's basically five studies by the same gentleman.

CHAIRPERSON BURK: There was one positive animal study for male repro effects. Although, there were quite a number -- well, at least three that were not. And in that one, that's the Joshi 2007. There were reduced

testes weights, reduced testicular sperm counts, degenerative changes in the seminiferous tubules, and 85 percent negative results for fertility in the high-dose group. But, again, it's at the high dose, so that makes it less than crystal clear unfortunately.

Other comments? We didn't talk about the female repro. I think, earlier when you asked about the lactation, Carl, you were probably saying you didn't think that was going to fly. But the one thing I wanted to point out, and again it's a constraint that we have, is that a number of the neuro and behavioral studies need to go from gestational times into the early part of postnatal development. And that's the way they're set up, because that actually corresponds to a third, say, trimester in the human, which I think is a valid model and shouldn't be discounted either. But we do have that issue.

If it comes via breast milk in the -- or directly to the pups on the early days after birth, is that female reprotox? You know, is it or -- you know, you could sort of stretch it, I think, and would say that --

COMMITTEE MEMBER KEEN: Yeah. I would have no trouble moving out of the harbor and saying yes, it is, if I saw data cross-fostering. The dilemma here is we're not seeing that information. I mean, so, you know, I see an awful lot of suggestive evidence. But if we use the

strict interpretation that we're charged with -- you know, is it really conclusive -- that's what I -- in my mind, it seems to be a little short.

COMMITTEE MEMBER HOBEL: A quick comment. I think that we're all dealing with this issue of timing. I look at things in a life-course perspective. The information that was mentioned about the effect on testes and sperm, this happens very early in the continuum. There's a lot of interest now in looking at genetic changes, methylation changes that occur in sperm early in the reproductive cycle. And these can now be monitored and measured.

But then later on, I'm really thinking about the mechanism that we're dealing with here. And I don't think it's necessarily affecting an enzyme system that affects nerve transmission. It's -- I think there's something going on here that might need to be carefully looked at. And you have to look at it very early in reproductive life. You have to look at it during pregnancy, and then also during the infancy. So with a constant focus on really what is the mechanism.

CHAIRPERSON BURK: Any other comments?

Any other comments?

Does anyone -- I feel like -- we want to make sure we've discussed this thoroughly because it's a

serious issue.

Does anybody think that the human data can stand on its own?

You're not willing to go out on a limb there. Because I really do think that the Columbia data set is impressive to me, but I know it's only one study and -- all right, so are we ready to vote, one last chance.

Speak up.

COMMITTEE MEMBER GOLD: Well, I'm just going to be thinking out loud here. But if we want to take the totality view rather than saying it -- putting our weight on one study, can we look at the totality and get a sort of gestalt of leading us in a certain direction, both human and animal. Rather than saying we'll, I'm really convinced by one study. So I would raise that question to the two primary reviewers.

CHAIRPERSON BURK: Yes. Well, I mean, I think there's two things you're asking. One, are we permitted to do that? And I know earlier we were shown something that said you had to have sufficient human or sufficient animal or sufficient both. I think the sufficient both could be a -- I don't know how -- a totality type of -- yes. Well, Carol, why don't you comment legally on what that means.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. One thing I would point out to you is that when you're talking about all these criteria, those are your criteria that the Committee developed. They're not a mandatory -- you know, they're not part of the statute or the regulations. Those are certainly important, but they -- what we're -- what you need to rely on is your own expertise. That's why you're put on the Committee and what you're feeling is on all of the evidence. And certainly under your own criteria, you can look at both the animal and human evidence together. You don't have to have separate -- you know, it's only based on animal or only based on human. In fact, one of the items on your criteria says that you can list based on limited evidence or suggestive evidence in humans supported by sufficient experimental animal mammalian data. Okay. So, you know, you can kind of look at it in terms of all of it together. And it is a weight of the evidence argument. It's not beyond a reasonable doubt.

CHAIRPERSON BURK: Does that make it any clearer?

COMMITTEE MEMBER KLONOFF-COHEN: Ellen, I just want to say that when I presented it, I tried to give a total presentation to be honest. So when I was listening and it wasn't based on one parameter or one outcome, I tried to sort of present all of the outcomes that were

described in all of the studies to try to get a sense if there were findings where more than one study had found those, but to also give a sense of what all the neonatal characteristics, all of the neuropsychological.

Okay, so --

COMMITTEE MEMBER GOLD: I do have one other thing. So if we divide this up into sort of developmental female and male, maybe that helps us a little bit. And then if the animal and human data, although we don't have a single study that we'd like it to stand on, do they together help us reach a decision in each of those three areas? Personally, I would find that a more helpful approach.

And with regard to the one study where it's the same study population for the male data, but they've got multiple publications, if we thought that that was a really excellent study, it wouldn't particularly bother me that it was multiple publications on the same study population. So if you want to comment on what you think the quality of that study is, that would also be helpful.

COMMITTEE MEMBER KLONOFF-COHEN: So I'm just looking to see in terms of Meeker's -- let's see. His sample was anywhere between 260 and 322. What he was doing was he was looking at environmental exposure to other things, for instance, like carbaryl and other

things.

To be honest, I don't have any limitations down for him, so it's not like I didn't like the study. But would I pass it based on his study alone, is that the question?

COMMITTEE MEMBER GOLD: No.

COMMITTEE MEMBER KLONOFF-COHEN: Okay, good.

I have to say honestly to me, since it was brought up, and I was really looking at, in terms of where it says where epidemiology data are suggestive, and I do think that the human data is highly suggestive. I think it's a good word. Do I think it's overwhelming? I don't think it's overwhelming. I think it's suggestive. I think that is definitely what it is.

It says, "A listing must be supported by sufficient experimental animal data." So to me, to be honest, that was my approach was I thought the human data was very suggestive. There were a lot of really important endpoints that were established in a multitude of studies. And I was going for the fact that in combination with the animal studies that was how we would consider it.

COMMITTEE MEMBER HOBEL: I think that based on all the information available, one could sit down and design a very good study. And just to give you an example, we've been able to demonstrate there is some data

on the effect of the chemical on sperm and genetics. And you have to keep in mind, that during pregnancy, the genes don't -- genome of the infant and the placenta is a combination of the mother and father. So that if something happens in the father during pre-gestation and during gestation, then that can influence what happens to the pregnancy.

And one can actually begin to look at the genetics of the placenta, which is a combination of the woman and the father. And that's where these changes can begin to be passed onto and affect the pregnancy, early in pregnancy, during pregnancy or then even affect the child. So I think that's really where something like this has to go to be studied. Because all the pieces are there, but you can't connect them, unless you study them.

CHAIRPERSON BURK: Other comments?

I actually agree that the Meeker studies are very suggestive. The main problem I have there -- it's not a problem, but I'm kind of balancing that against a negative Epi study that we also were given, the Swan study. So obviously they're not measuring the same thing. And I see that DNA damage is serious business. But do you think it was a limitation that they only measured things at one time point, too. I think you said -- right.

COMMITTEE MEMBER KLONOFF-COHEN: Yeah,

absolutely.

CHAIRPERSON BURK: Any other discussions?

I don't want to draw it out, but I also don't want to cut anyone off. So I think we're ready to vote.

And I will, again, read this for each of the three endpoints. Has chlorpyrifos been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity? All those voting yes, please raise your hand?

(Hand raised.)

CHAIRPERSON BURK: And I'm voting yes, but I'm the only one.

Okay, all those voting no?

(Hands raised.)

CHAIRPERSON BURK: Six no. And, again, Linda recusing.

Next one. Has chlorpyrifos 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?

Zero.

All those voting no, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Seven.

Has chlorpyrifos been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity? All those voting yes, please raise your hand?

(Hand raised.)

CHAIRPERSON BURK: Okay, one.

All those voting no, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: She changed?

Okay. So we're making that two.

Anyone else?

So now we're on the noes?

(Hands raised.)

CHAIRPERSON BURK: Okay, 2 to 5.

And we had one abstaining for each one.

Okay. So the result then is chlorpyrifos will not be added to the Proposition 65 list for any of the 3 endpoints, because we did not get five yes votes.

All right. So moving along in the agenda, the next portion will be two chemicals to discuss relative to prioritization for developmental reproductive toxicant identification -- well, recommending they be moved on for hazard identification material production, I guess you call it.

So the first one are trihalomethanes. And the

staff presentation will be given by Dr. Francisco Moran. Oh, and Jim Donald.

(Thereupon an overhead presentation was Presented as follows.)

DR. DONALD: If I could just introduce the item briefly. At the Committee's last meeting in December 10th of last year, eight chemicals had been identified as potential candidates for consideration through OEHHA's current prioritization process were discussed. And while all eight chemicals were recommended by the Committee as candidates for development of hazard identification materials, two of the chemicals also prompted discussion of additional related chemicals.

Bromodichloromethane or BDCM was one of the eight chemicals discussed. BDCM is a trichloromethane or THM and the Committee noted that the data for total trihalomethanes in drinking water would likely be stronger than for any individual THM alone.

The Committee requested that OEHHA prepare the same prioritization materials for total THMs as had been prepared for other potential candidates.

OEHHA has done so and Dr. Francisco Moran will, in a moment, present a brief overview of the materials.

All of the abstracts previously included in the prioritization materials for BDCM are also included in the

current materials, along with abstracts of studies on other THMs and mixtures of THMs. Two points to note are that although the search terms used OEHHA encompassed all THMs, only data on chlorinated and brominated compounds were identified.

The second point is that the epidemiological screen of two analytical studies of sufficient quality was not reapplied to this data set, since it had already been established that the screen was met by BDCM alone and hence would necessarily be met by the larger data set that encompassed BDCM.

So in the meantime, OEHHA is proceeding with the development of hazard identification materials for BDCM. And we published a request for relative information for inclusion in the hazard identification materials.

Some members of the Committee may also recall that chloroform, another individual THM, was previously considered by the Committee on November 4th of 2004 and not listed. Since that consideration, one additional study of chloroform has been identified and is included in the abstracts provided to the Committee.

So, in summary, we're seeking your recommendation as to whether the information we've provided to you on THMs merits the development to full hazard identification materials on THMs as a group or on a subset of THMs, such

as the chlorinated and brominated THMs as a group or if you wish to consider some or all of the chemicals individually.

If you recommend proceeding with a broader group of THMs, we presume you would want us to merge the hazard identification materials we're preparing on BDCM into the larger package on THMs, so that you could make a listing decision encompassing the broader group. If you recommend that we do not proceed with the broader group, we will still bring BDCM before you as an individual chemical for a listing decision, pursuant to your recommendation at last year's meeting.

So to summarize, we're asking your advice concerning whether to, one, prepare HIMs for total trihalomethanes or, two, prepare hazard identification materials for certain trihalomethanes, for example, the chlorinated and brominated trihalomethanes. A third option is to prepare hazard identification materials for each of the four trihalomethanes with available data. Or, finally -- the final option is to not proceed with hazard identification materials for any trihalomethane other than BDCM.

And with that, I'll turn it over to Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good afternoon. The comments you received concerning prioritization of the

trihalomethanes raise some legal and scientific issues about whether it would be proper for this Committee to list chemicals as a group or a class or whether you are required to consider and list each chemical individually.

While this is not a new issue, I thought it might be helpful for you to clarify the issue prior to your discussion of the next two items on the agenda, as they both relate to classes or groups of chemicals or mixtures.

Proposition 65 applies to "chemicals", quote unquote, known to the State to cause cancer or reproductive toxicity. But the law does not provide a specific definition of the word "chemical".

OEHHA and the Attorney General's office have interpreted this language not to be limited to individual elements or compounds, but rather to apply to a range of substances, including groups of related chemicals, mixtures of chemicals and substances made up of a variety of different chemicals, so long as the mixture or group of related chemicals meets the requirements for listing.

This is consistent with the practices of other authoritative bodies and agencies that identify chemical hazards, such as IARC, NTP, NIOSH and U.S. EPA among others. Accordingly, existing Prop 65 listings include chemical groups and mixtures, such as PCBs, which were listed by this Committee, anabolic steroids, cadmium and

cadmium compounds, conjugated estrogens, estrogen steroidal, coke oven emissions, tobacco smoke, oral contraceptives combined, unleaded gasoline (wholly vaporized) and diesel exhaust, for example. And these are all found in Title 27 of the Code of Regulations 27001.

Although you are not being asked today to make a listing decision concerning trihalomethanes or particulate matter, which is the next item, if you were to eventually list a group or class of chemicals, such as all trihalomethanes, the substances in the class must be sufficiently well-defined so that the public has reasonable notice as to what is included in the listing.

In addition, this Committee would need to conclude that the scientific evidence, even if it comes only from a subset of the chemicals in the group, persuades the Committee that all chemicals within the group are clearly shown to cause reproductive toxicity.

In making this determination, the Committee should consider all of the appropriate evidence before it, including the member's scientific judgment as to the similarity of all chemicals and the extent to which results of a study of one or more of the chemicals would apply to other chemicals within that group or class.

Similarly, if this Committee were to decide at a future meeting to list a chemical mixture, such as

trihalomethanes, as disinfection byproducts in water, you would need to conclude that the mixture itself is clearly shown to cause reproductive toxicity.

Because a mixture may vary in its exact composition, the Committee would need to conclude that any variation of the mixture, so long as it still falls within the definition of the mixture used by the Committee, is clearly shown to cause reproductive toxicity. This conclusion can be based upon studies of the mixture or of individual chemical components of the mixture.

Again, the question before you today is not whether you should list any of these chemicals. We are simply asking your advice concerning how you wish to have some or all of them presented to you at a future meeting. I hope this helps clarify the issue for you.

Does anyone have any questions on that?

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So we can go ahead and proceed.

DR. MORAN: Good afternoon.

I will present evidence that -- it's not on?

I think it was on.

Okay. Good afternoon. I will present the evidence that we have for prioritization of trihalomethanes.

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DR. MORAN: The major source in the environment of trihalomethanes are produced mainly as byproducts of water disinfection with halogenated compounds.

The most common THMs are bromodichloromethane, BDCM; dibromochloromethane, DBCM; tribromomethane, bromoform; or trichloromethane, commonly known as chloroform.

I will present the data for the whole class and separated for the four members from this group.

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DR. MORAN: The epidemiology data research found that six epidemiologic studies reported increased risk of adverse developmental or reproductive outcomes.

Also, five studies reported no increased risk were identified, as well as 11 other related studies or meeting presentations.

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DR. MORAN: In the four member -- more common members for this group we found that for BDCM four studies reported increased risk, as well as four studies reporting no increased risk of adverse developmental or reproductive outcomes. And also four related articles or meeting abstracts on BDCM were identified.

For DBCM, one study reported increased risk, as well as one study reported no increased risk of adverse

developmental or reproductive outcomes, as well as one related study were identified.

For the chemical bromoform, we have two studies reported no increased risk of adverse developmental or reproductive outcomes.

For chloroform, we have five studies reporting increased risk and three studies reporting no increased risk, as well as four related or meeting abstracts were also identified.

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DR. MORAN: Among the most common reported effects for the epidemiologic data, we have the THMs, in general, produced ventricular septal defects, cleft palate, and anencephaly, stillbirth, small for gestational age, and effects on ovarian function, such as short-cycle length, especially on the follicular phase, also spontaneous abortion is a common effect.

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DR. MORAN: On our search for the animal data, it was pointed out that for total trihalomethanes one study was misclassified, so there were two animal studies reported adverse developmental or reproductive outcomes is only one. The other studies were classified under the chloroform-only group. One study also reported no increased risk of adverse developmental or reproductive

outcomes. And six animal-related meeting abstracts were also identified for total trihalomethanes.

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DR. MORAN: For the animal studies for each of the four members of this group that we found information, five studies for BDCM reported increased risk and five studies reported no increased risk of an adverse developmental or reproductive outcomes, as well as nine related articles or meeting abstracts were identified.

For DBCM, we have the three studies where no animal studies -- with no effect were identified.

For bromoform, two studies reported increased risk and three reported no increased risk of adverse developmental or reproductive outcomes, as well, three related articles or meeting abstracts were identified.

For chloroform, we have the three studies reported increased risk of adverse developmental or reproductive outcomes and one related article or meeting abstract was also identified.

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DR. MORAN: The most common effect in the animal studies for these chemicals, in rats we have this fetotoxic response; there is developmental toxicity -- oh, I didn't press the slide -- thank you. Fetotoxic response; developmental toxicity; pregnancy loss; and also

resorption in rats. Testicular histopathology and sperm parameters also were found as a common effect. Decreased serum progesterone and luteinizing hormone (LH) levels in vivo were altered and disruption of the LH secretion and disruption of the corpus luteum ability to respond to LH among the effects of THM.

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DR. MORAN: And the last slide is just a summary table that was created with the intent of clarifying how there was the distribution of the abstracts found. So we have it separated by categories. The human studies and animal studies reporting high increase, no increase or the animal studies in positive or negative. And to your right, we have several columns where THMs and the four members of this group with a number of particular abstracts for each one.

So that pretty much will tell you a little bit of the distribution of the abstracts. I hope that will help recognizing the number of the studies involved.

That concludes my presentation.

CHAIRPERSON BURK: Thank you. Are there any questions about the presentations?

No.

Are there any public comments?

I guess there are.

Okay. We have two. The first one is Rebecca Sutton of the Environmental Working Group.

DR. SUTTON: Can you guys hear me?

All right. So my name is Dr. Rebecca Sutton. And I'm a senor scientist with Environmental Working Group. I'd like to thank you guys for considering trihalomethanes, because we're very concerned about these chemicals, especially because of the epidemiological data related to spontaneous abortion.

We think it makes a lot more sense for you guys to consider these chemicals in aggregate, because that's the way we're exposed to them. So we'd like to recommend that you guys move forward in that direction.

Thank you.

CHAIRPERSON BURK: Thank you.

And the next speaker is Dr. Jay Murray and Dr. Robert Tardiff on behalf of the -- well, you can say the Chlorine Chemistry something.

DR. MURRAY: Thank you, Dr. Burk and Committee Members, and good afternoon. I'm Jay Murray. I'm speaking on behalf of the Chlorine Chemistry Division of the American Chemistry Council. So I appreciate why you didn't want to tackle that one.

What I'm going to cover are the reasons why you should not prioritize any additional THMs, either

individually or as a group. In other words, we're urging that you go with option number 4 that was described to you, which is stick with BDCM.

And as was pointed out already, this issue did not come to you through your normal process. It didn't come through the prioritization process. It came out of a discussion that your committee had a year ago when you were discussing BDCM. So I'm going to summarize the reasons. And I'll be followed by Dr. Robert Tardiff who is going to focus more on the science and the scientific evidence, including the epidemiologic studies.

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DR. MURRAY: This is an overview of the reasons. And I'm going to go through this very quickly. I have a slide or two on each one of these bullets.

First, THMs do not meet the 2004 prioritization criteria. There are a couple reasons for that.

Prop 65 regulates chemicals and not groupings. And I appreciate Chief Counsel's comments on that and I'm going to go through that very quickly.

The category of THMs is loosely defined. You've got some guidance here today that the background materials focus on the four chlorinated or brominated THMs.

Individual THMs are not clearly shown to cause reproductive toxicity. And this is important, because if

you listed THMs as a group, you're essentially saying that all THMs have been clearly shown to cause, and that's definitely not the case.

And then the final point is it would be impossible to establish a NOEL or MADL for THMs as a group.

So let me start with the prioritization process.

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DR. MURRAY: The 2004 prioritization process says, "It is unlikely that chemicals will be proposed that have been recently reviewed by an authoritative body and found to have insufficient evidence of reproductive toxicity."

And that is exactly what you have. U.S. EPA is an authoritative body. And the second quote is what EPA said in 2006. "EPA concludes that no dose-response relationship or causal link has been established between exposure to chlorinated drinking water or disinfection byproducts and adverse developmental or reproductive health effects."

And DBPs, disinfecting byproducts, include THMs. So this alone would be reason enough to stick with just BDCM, but there's more.

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DR. MURRAY: And one of the other things from the

prioritization procedure, is it says it's important to weigh positive and negative studies. And this one is easy, especially for the animal studies. Dr. Tardiff is going to talk about the epidemiology studies. But for the animal studies, there are no animal studies of THMs as a group.

And I know this is a little different from what you read in the background materials. It said there were two positive, one negative. But as has already been pointed out, those two positive studies of total THMs are -- first, they're not studies of total THMs. The first is an in vitro study of three solvents, one of which is a THM, chloroform. The other two are not THMs at all.

And those compounds were given individually. They were not given as a mixture or in combination. The second study is a conventional developmental tox study in rats where they looked at each of the four chlorinated or brominated THMs individually. So none of those -- neither of those are positive studies of THMs as a group. They're studies of individual THMs. And the negative study, the same thing. It's not a study of THMs as a group. It's a study of one or more individual THMs.

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DR. MURRAY: Prop 65 regulates chemicals, not chemical classes or mixtures. And this was the issue that

you heard about just a few minutes ago from Ms. Monahan-Cummings. And what I'm going to do, I'm going to go through this very quickly.

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DR. MURRAY: This is the language of the statute. And I'll let you read it for yourselves and that's where this issue comes from about whether Prop 65 applies to chemicals or groups of chemicals. But what I want to repeat, and I'll encourage Chief Counsel to correct me if I misstate, but what I heard her say was if you list a group of chemicals, all chemicals in the group would have to be clearly shown. And we're in agreement.

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DR. MURRAY: This was a slide that had the duties and responsibilities, render an opinion as to specific chemicals. You actually saw the same quote earlier this morning, so I'm going to breeze over that one as well.

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DR. MURRAY: The category of THMs is not clearly defined. It was clarified by Dr. Donald that what you are being asked to weigh in on is THM -- the four brominated or chlorinated THMs as a group or individually or combinations of individual THMs. And you just want to be sure if you do anything with THMs, be very clear, because there are over 20 THMs. The brominated and chlorinated

THMs are the most common. And that's what most people think of when you talk about THMs. But in the world of chemistry, THMs are trihalomethanes and there are five different halogen groups and so it gets you to more than four chemicals real quick.

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DR. MURRAY: Now, neither prioritizing nor listing THMs as a group is scientifically appropriate. And this was the point about if you list a category, THMs, for purposes of Prop 65, it means that you're determining that each and every THM is clearly shown to cause. And from Dr. Moran's last slide, it was the table of animal studies and human studies, it should be obvious that the data are extremely limited for some of the individual THMs.

And the one that I've used as the example here is the DBCM. And I'm just telling you what's in that table. There are no animal studies. There's one positive epidemiologic study, one negative epidemiologic study. The one positive Epi study I'm going to read you the author's conclusions.

It says, "These findings suggest that THM exposure..." -- not DBCM exposure, THM exposure... -- "...may affect ovarian function and should be confirmed in other studies."

So that one Epi study is not going to be enough to meet the prioritization criteria and certainly isn't going to come close to meeting the clearly-shown standard. So you want to be careful about tackling this as THMs as a group, because you're going to have some individual THMs that will miss by a long shot.

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DR. MURRAY: I missed one. How did I do that? There we go.

Listing THMs would be unworkable. And there's a real practical problem here. And that is, if you were to list THMs as a group, then there is no NOEL for THMs as a group. We just said there are no animal studies of THMs as a group. And the problem with the Epi studies is it just doesn't lend itself for a dose response, where you can say well here's the NOEL from the epidemiologic studies. And if you don't have a NOEL, there's no way to establish a Maximum Allowable Dose Level under the law.

And the consequence is that there's no defense available to say that exposure is below the MADL. And the upshot is that all THM exposures, no matter how small, would require or potentially require a known-to-cause-reproductive-toxicity warning. So the bottom line is THMs, as a group, is unworkable.

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DR. MURRAY: This is my last slide before I turn things over to Dr. Tardiff. Our recommendations are to advise OEHHA that you do not wish to consider the potential group listing of THMs. Simply said, choose Option 4. BDCM and chloroform are off the table. You've already decided by a 4 to 3 vote to go forward on BDCM. Chloroform was evaluated by your committee in 2004. You chose not to list chloroform.

So it really only leaves two others. The data just are not there with the two others. Neither of them made it through the recent prioritization process with good reason. There's just not sufficient evidence for them to go through.

So, look, no one is telling you to limit the relevant evidence when you consider BDCM. You can look at any evidence you think is potentially relevant. So you're not going to miss anything scientifically. If you want to look at other studies as you look at BDCM to make a decision about whether BDCM is clearly shown to cause, there's nothing that precludes that.

So the bottom line is, you know, I urge you not to prioritize any additional THMs, either as a group or individually. Stick to BDCM.

Thank you.

Questions, before I turn it over to the other

speaker?

Yes, Dr. Roberts.

COMMITTEE MEMBER ROBERTS: I get to turn on my microphone now.

(Laughter.)

COMMITTEE MEMBER ROBERTS: In the comments submitted by Dr. Tardiff and yourself, and I don't expect you to memorize them, but on page 10, there is a sentence that says, "While Waller et al. 1998 reported a statistically significant increase for spontaneous abortion, Savitz et al. 2005, in a much more sensitive and sophisticated study, found no such association and EPA disqualified the Waller et al. study as a positive finding." Can you elaborate on why the Waller study was disqualified?

DR. MURRAY: I tell you, I'm actually going to shift the question to Dr. Tardiff, because we each sent, you know, comments in. And I think the one that you're reading from was actually Dr. Tardiff's question. And he's more up to speed on the epidemiology than I am. So we'll go to the A Team.

Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me, before Dr. Tardiff speaks, can I just clarify a couple of things based on Dr. Murray's comments.

The prioritization procedure that he was referring to is for OEHHA. We developed it for our process to bring chemicals to the Committee. While it's, you know, of interest to you and we've discussed it with you, it's certainly not binding on this Committee at all. You can bring up chemicals as you did at the last meeting and they don't have to meet any of the criteria in the prioritization process. You can decide that you want to look at any chemical that you want to look at. Just so you're clear on that.

And also, in terms of the question on the MADL, as you probably know MADLs are not required by the statute. They're something that OEHHA develops and puts out to help people comply with the requirements of the act. And, at least, it's my understanding that even though one MADL may not be able to be developed for a group of chemicals, that we can develop them for chemicals within the group. And so it's not -- it wouldn't be impossible to do that. I just wanted to clarify those two things.

DR. DONALD: And if I might add to that. If some subset of THMs was identified by this Committee, we also believe that it's quite feasible that we could develop guidance for considering whether or not a warning had to be provided for mixtures or THMs, rather than individual

THMs.

COMMITTEE MEMBER KEEN: Can I ask a quick question, since you just raised something that was a little unclear to me.

If, hypothetically, we said, yes, we want to look at them as a group, now looking sometime in the distant future, would we then vote on them as individual compounds or vote on them as a group, because that makes a large difference, potentially.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's one of the choices you have. And that's one of the questions that we're asking you, is do you want them presented to you as individual compounds?

COMMITTEE MEMBER KEEN: But, if hypothetically, we said we wanted to see it as a group, when it comes down to the time to vote, can we deconstruct that group or do we, by definition, work on the group?

CHIEF COUNSEL MONAHAN-CUMMINGS: You could do either one at that point. You would say, you know, I don't think that we should list these as a group. I think there's only enough evidence for three, one whatever. So, at that point, we can talk about what the different choices might be and how you could frame that. What I had mentioned before is we just want to be clear to the public what category or what chemicals you're referring to when

you do the listing so they know. But you can do that at the later point once you see all of the evidence.

COMMITTEE MEMBER KEEN: Thank you.

DR. MURRAY: May I respond to two quick points. On the prioritization procedure, I was pretty sure that all of you are familiar, this is the one that went into place in 2004 and you are all asked to review. And I certainly didn't mean to imply you are stuck with following that and can't deviate and can't do anything other than that. But I thought it was important for you to note that these other compounds presumably went through that prioritization process and didn't spit out at the end.

The other thing I want to comment on was what Dr. Donald just said. And I think it's not so simple to come up with a MADL for THMs as a group. And EPA just tackled this recently in the Stage II Disinfection Byproducts Rule. And I'm going to read you part of the quote. It says, "A combined MCLG..." -- MCLG is Maximum Contaminant Level Goal or limit goal -- level goal, thank you. It's a drinking water goal, like a public health goal in California.

And it says, "A combined MCLG for THMs..." -- and they're talking about the four brominated and chlorinated THMs -- quote, "...is not appropriate because the THMs

have different modes of action and health endpoints." So I don't think it's going to be that easy to come up with a MADL for THMs as a group.

But more importantly, I think what you've got to look at is what the Chief Counsel said. Is if you list THMs as a group, you've got to be sure that every THM in that group has been clearly shown to cause. And I don't think the data is there.

Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Let me -- I'm sorry to keep doing this, but let me just say again, what I said about listing a group. So if you decided to list a group in order to make a determination that that group is known to cause reproductive toxicity, "The Committee would need to consider all the appropriate evidence before it, including the member's scientific judgment as to the similarity of the chemicals and the extent to which results of a study of one or more of the chemicals would apply to the other chemicals within that group or class." That's different than saying that every single chemical within the group has been individually clearly shown. I mean, if that's the case, then you don't need to list the group.

So I just wanted to clarify that, that you can list groups and they have been listed that way, because

there's evidence on members of the group that can be applied to the others, based on your own scientific expertise.

DR. MURRAY: May I ask a question of clarification?

If you list a group, all the members of that group would be treated, for purposes of the law, as if they had been clearly shown to cause. Am I right?

CHIEF COUNSEL MONAHAN-CUMMINGS: And that's the finding that they would make, is that the group is known to cause. But what I'm saying is that the evidence can be from members of the group.

DR. MURRAY: So you would be able to tell from other members of the group that --

CHIEF COUNSEL MONAHAN-CUMMINGS: Maybe they have the same mechanism, they have the same makeup, they have whatever. They have to be similar enough and they would need to understand that. But it's not --

DR. MURRAY: So the mode of action would be the same and then, you know --

CHIEF COUNSEL MONAHAN-CUMMINGS: Or something like that, right. I'm not going to say exactly the scientific criteria you would use, because I'm not a scientist. But what I'm saying is that you wouldn't have to find every single chemical, whether it's 20 or 100, in

a particular group is separately, clearly shown in order to list a group.

DR. MURRAY: Thank you.

CHAIRPERSON BURK: Before you begin, there's one more question.

COMMITTEE MEMBER GOLD: I actually have two questions now, because this partially applies to the next thing that's going to come up. So if chemicals tend to occur together, they might have different mechanisms, but you can't separate them out because they occur together. What are our options in that circumstance?

And secondly, do we have a copy of what you read to us, because I would find it helpful to have it in front of me.

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't have -- I didn't make copies for you, but I can give it to your -- it will be in the transcript. But what you're talking about, the question is about a mixture, which is different than a chemical class or group. And what I mentioned to you on the mixtures, which is more related to PMs, but could be considered a mixture in terms of the THMs as well, would be that you would have to conclude that the mixture itself is clearly shown to cause reproductive toxicity. And because the mixtures can vary in their exact composition, you know, they may have different

levels of different chemicals or components, the Committee would need to conclude that any variation of the mixture, so long as it still falls within the definition of the mixture that you define, is clearly shown to cause reproductive toxicity.

And that conclusion could, once again, be based on studies of the mixture as a whole or individual components within the mixture. Okay. It's like ETS or diesel exhaust or any of those where there's a lot of different things in it and we know that the -- that mixture causes harm, but we may not know every piece of the mixture individually would cause that harm.

COMMITTEE MEMBER GOLD: Thank you.

Could I just say one thing that probably in post-prandial confusion --

(Laughter.)

COMMITTEE MEMBER GOLD: -- I may ask you to repeat the options again when we get to the next one.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, actually we gave them to Dotty so she has those.

DR. TARDIFF: Ready to proceed?

CHAIRPERSON BURK: Yes, go ahead.

DR. TARDIFF: Okay. Dr. Denton, Dr. Burk, members of the DART Committee, thank you very much for the opportunity to address you this afternoon about this

subject.

I'm going to, in deference to Dr. Roberts, just jump ahead to try to answer her question now rather than for fear that I might forget it a little bit later.

The Waller study was a very well done study for that particular period of time. They looked at pregnant women during the course of their pregnancy to see what kind of water they were getting from the different water systems using traditional water data. They used three different water systems within northern California.

And it was only out of one water system in which, despite the fact that they were the same levels of exposures from one water system to the other, that they found that there was a statistically significant increase in spontaneous abortions.

That study, while well done, was actually replicated several years later by Dr. Savitz in his research group, work that was funded by the Environmental Protection Agency. The improvements that were made was to increase significantly -- first of all, they did another three water supplies with the same kind of underlying brominated and chlorinated substances from the chlorination of drinking water.

Then they took about twice as many people in the cohorts as there had occurred in the prior study. They

looked at far more refined information about exposure. So they were able, because of EPA's input, able to get much more information than the standard rolling three month averages that were normally available for many of the studies that had been looked at over the past 15 and 20 years.

And they looked at far more confounders and were able to control for them much more tightly. And the bottom line was that this study was negative. There were not statistically significant findings associated with them. And it was believed that that would actually co-opt or supplant, if you will, the results that had been obtained by Dr. Waller and her team.

EPA took a look at that with the Science Advisory Board. And the conclusion was pretty, in a sense, kind of startling. They basically said that it disqualified the Waller study, that this was so much better. That the negative finding was the one in which we should place the greater degree of confidence.

And Dr. Savitz even went so far as to say that this issue has been so heavily studied now, not only from his experiments but others, that there needn't be any further epidemiologic investigations associated with those particular endpoints. Again, another unusual outcome.

So if I could just return to my script for a

moment. And I'll entertain more questions as we go along and finish up.

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DR. TARDIFF: My purpose today is to try to provide you with some help in making your decision about whether to prioritize trihalomethanes as a group. And I do believe that there really isn't any evidence that would suggest that you should prioritize it for the consideration, as a group certainly or even for some of the other individual elements within the four-compound class, because you're already pursuing bromodichloromethane anyway. So that one is somewhat off the table.

The evidence that I want to summarize from the submission that we submitted to your group earlier on falls into basically three categories. One is we do have U.S. EPA and WHO who have come out and spoken on this particular issue. They've looked globally at the extent to which there is or is not evidence to support causation. And their conclusions I will read to you in a few moments.

Secondly, we've taken a close look at those abstracts and the studies behind the abstracts that were submitted to you for your consideration by the OEHHA staff at your request.

And third, we have basically been responsible, my

team has, for doing two major reviews, one in 2001 and 2006. And then we've taken into account the fact that there have been additional studies since that time. And we want to give you a sense of what the overall evidence suggests in this regard.

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DR. TARDIFF: Okay. So let's, first of all, talk about the abstracts that were provided by OEHHA in the background document.

There are actually six epidemiology abstracts that are listed. And I've just highlighted the main features of these. We have the Hwang study, which is the most recent in 2008. It was not significant for three endpoints. But it was significant for one thing, the cluster of all birth defects not isolating any one particular birth defect. It occurred only at the low dose and not at the other two higher doses, which is a very peculiar phenomenon. There was an opportunity to see dose response, if, in fact, the effect were biologically plausible, but none was seen.

Other studies have examined this particular issue and there are five of them that found, for the same endpoint, no statistically significant findings. So the weight of evidence for that would really suggest that there really isn't any association between trihalomethanes

and these particular outcomes.

The Toledano study in 2005 was found to be not significant for a variety of endpoints, because the lower confidence interval was well below one, and, in fact, they were not able to accomplish statistical significance.

There were significant findings however for low birth weight and very low birth weight. But the difficulty in interpreting those findings is that the association was really with low socioeconomic status of the cohort that they had. And they were unable to adjust for that in their calculations. So you can't tease apart whether it was trihalomethanes in the drinking water or that it was some other factors within the lifestyle and background of the individuals.

And the statistical significance was only in one water supply where the other two were actually negative. And when they tried to combine the results from all three supplies to try to enhance the power of the study, they found that there was no statistical significance associated with that.

If you take a look at the larger body of evidence, which I tried to submit in my written comments, you find that overall for low birth weight, there are two positives and five negative studies. So basically the data bounced around and the two positive studies are

really marginally positive, but very low odds ratios.

A similar finding was noted also with regard to very low birth weight, when there was one positive finding and three negatives.

In the Wright study, we have a significant finding for small for gestational age. Again, it was a single dose. The other doses were negative. There was no dose response. There are 11 studies that have looked at small for gestational age and all didn't find any. There are three that are positive, which would suggest that this is also probably a spurious outcome.

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DR. TARDIFF: If we look at the Windham study in 2003, it looked at the effect on menstrual cycle. They didn't find it. They had very poor participation. There were recorded self-reporting errors. So that study, in and of itself, simply doesn't meet the criteria for a suitable design.

The King study in 2000 was probably one that caught the greatest degree of attention, since it dealt with stillbirths at the very high levels of exposure, at 150 parts per billion and that was the comparison that was statistically significant. All of the other comparisons that they made across the exposure spectrum were negative and they couldn't find any dose response. Of all the

studies that had been reported so far, we've got now two positives, including the King study and two negatives. So there's no consistent finding of positive associations with these.

The Waller study I already described a few moments ago. And basically that one, at this point, is not really in play and is supplanted by the Savitz study.

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DR. TARDIFF: Now, some of the considerations that we brought to bear on evaluating these studies, included the chemical structure of THMs. We've had a lot of experience in the work that we've done over the past decade or more, with structure activity relationships with regards to both reproductive outcomes as well as cancer.

And we've looked at those particular structures. And, in fact, I've worked on trihalomethanes, by the way, for 35 years, toxicologically and looked at all the different factors associated with modes of action.

These particular structures do not permit one to extrapolate from one compound, let's say, BDCM to the other compounds in the class. Nor does it allow us to say that the other compounds in the class are likely to be reproductive toxicants when the neighboring compound is not.

Probably, one of the best illustrations that I

can give you about how structure activity relationships can lead one astray, is just to take a look, for those of you perhaps who already have, is the difference between toluene and benzene. Benzene is a clear leukemogen, but, boy, you tack on another molecule associated -- another carbon and you lose that particular toxicological effect associated with it. So trying to make that jump is pretty difficult.

And we've looked at that for these four trihalomethanes, and we don't think that there's any commonality that would allow what General Counsel suggested as an option for you. To say that just because one is a reproductive toxicant, then let's say BDCM were judged to be so in the future, you couldn't say that chloroform necessarily is or bromoform.

Now what about metabolites? We've only been talking about the parent compounds. Well, we've looked at the metabolites for the compounds for which they've been reported, and that is for three out of the four.

And even though those metabolites don't provide any indication whatsoever that they could, in fact, impair the reproductive process or slow down or delay development in the offspring, even at high doses, there just is no way to make that conclusion.

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DR. TARDIFF: I mentioned earlier that we've got some support for these conclusions from the Environmental Protection Agency in 2006, as part of its activities with the development of drinking water standards. This was in the Stage II DBP rule. And they concluded that a causal link between adverse reproductive health effects and exposure to chlorinated drinking water or DBPs has not been established.

Now DBPs -- I'm not sure how much of a background you have. And I apologize if I'm getting into too much detail. But the reality is that chlorination byproducts really span over 200 substances at one time. THMs that have been identified by OEHHA are only four of those. Those four, in some cases, happen to be there at higher concentrations than other substances. But some people incorrectly conclude that they are also the ones with the highest toxic potency. That, in fact, we know not to be true. They're haloacetic acids, such as DCA, which are far more toxic, in some cases, in the reproductive system, I might add, which may send them chasing after something.

Secondly, we also know that there are now some chlorinated nitro-organic substances that are produced from chlorine that are also considered chlorination byproducts. And those have a very high degree of toxicity and are now in the process of being investigated more

fully by EPA and its various grantees.

Now, the World Health Organization produces, every five or six years or so, its water quality guidelines. And it looks at all the different kinds of chemicals present in drinking water. And it said in 2000 that the, "...existing epidemiological data are insufficient to allow the importance of observed associations of chlorinated water or THMs and adverse reproductive outcomes to be assessed." So that the information simply did not rise to the point where they could draw some conclusions with regard to that.

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DR. TARDIFF: I mentioned that the third part of the information that I was going to provide to you was our examination of all of the updated data.

We've now published two major reviews, the last one in 2006. And the conclusion is there. It's very similar to the other two that I read to you a moment ago. And just to give you a sense of how much data are out there and what they say, I've given you this very brief summary, obviously backed up by the documentation that was provided earlier, of the -- there were 29 endpoints in the various studies that were examined. That's not 29 studies. That's 29 endpoints and a variety of studies with some people having examined those endpoints in

different designs. No statistical association with those.

We have eight endpoints in which you can't make a distinction between THMs and chlorination byproducts.

Why can't you do that?

Well, very simply, because people were doing epidemiology studies as a screening tool. They would basically say, give me a chlorinated drinking water supply and an unchlorinated drinking water supply, probably a groundwater supply. And let's see if there's a difference in morbidity rates or perhaps even mortality rates. And if there is, then there's an opportunity to do some further research to explore what might be the cause of it.

Well, those studies exist. They certainly need to be considered. And they basically don't tell us that THMs are likely to cause any kind of reproductive or developmental toxicity.

We have three endpoints in which the data are inconsistent, and I mentioned some of those earlier. You have one positive study, no dose response, but then you have other studies in which they're completely negative. And then we have finally one in which a very novel outcome was determined, in which there has been no confirmation, despite a number of other studies able to find it, no replication, no dose response. What is it? It happens to be an anatomical defect in the esophagus. Very unusual.

Usually, we're finding, if there's going to be effects, there's skeletal effects or other behavioral effects and the like. And this one has yet to be confirmed in any particular way.

So it simply doesn't provide any confidence that we can say that THMs, as a group, produce reproductive or developmental toxicity.

There are comprehensive factors that we looked at, which doesn't support prioritization. I wanted you to have a good sense of this is we've taken a look at positive and negative studies and brought them all together, at one point. We've looked at all the major study types. We haven't excluded any from our process. All of the studies combined produce over 40 endpoints that have been looked at, which means that the investigators have been out there beating bushes pretty hard to try to find something that's associated with THMs. We've looked at the quality of the studies. They varied considerably not surprisingly. Some have looked at confounders with a great deal of precision and accuracy, others less so.

We've looked for dose response as a measure of internal consistency. And it's been extremely rare that any of that has ever come to the table. We've looked at the way they've statistically analyzed the data. And we've looked also at what kind of criteria we would use

for describing positive associations.

That last one is a little bit tricky, in a sense, that epidemiologic studies that are marginal in their results will often times lead to investigators saying, "I saw an increase, but it wasn't statistically significant."

In my training, that doesn't count as a positive, but it obviously certainly should raise hypotheses and suggests whether or not people should be doing additional work, but it doesn't lend credence to causation.

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DR. TARDIFF: The toxicological weight of evidence for THMs, as a class, there are none. Nobody has ever done a study of the four compounds that are being considered by this group this afternoon. And so, there's just no evidence. That means, you know, you have to take that into account.

Are there studies of individual compounds? You bet. Can you extrapolate from the potent -- reproductive potency of a compound to another one in the same class? I don't believe that you can with any degree of confidence.

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DR. TARDIFF: So my conclusion is that there just is insufficient evidence to prioritize any additional THMs, either as a group or individually. We know BDCM is going to go forward. You're already dismissed chloroform.

So now the question is what do you do about the other two for which there is little or no data.

I'd be happy to take your questions.

Yes, sir.

COMMITTEE MEMBER HOBEL: Sir, you mentioned the U.S. EPA study in 2006, or recommendations, and the WHO in 2000?

DR. TARDIFF: Indeed, yes.

COMMITTEE MEMBER HOBEL: And you failed to mention the Canadian study in 2006. Why didn't you mention that study?

DR. TARDIFF: The Canadian -- well, there's a Canadian -- the latest Canadian activity is in 2008. And it's reported, I believe, in my written report to you. That one dealt exclusively with bromodichloromethane. And I'm not sure if that's the same one you're alluding to.

COMMITTEE MEMBER HOBEL: Yeah, that's why I'm asking you the question, because they made it very clear they sort of set drinking water guidelines for total THMs to 1,000 micrograms per liter. Yet, when they looked at DBCM, they set it at 16.

So why did they take that action? They must have been concerned.

DR. TARDIFF: They were then. But the conclusion has been reversed in 2008. I was, in fact, part of the

study group a couple of months ago that was up in Ottawa looking at this issue.

As I understand it -- I was not part of the 2006 review. In 2006, there was, I guess, a matter of urgency that was concerned about the possibility that short-term exposures could lead to reproductive malfunctions, which would include the possibility of developmental toxicity.

The evidence -- well, at that time, the precautionary principle, which was originated in Europe, was what probably pushed the conclusion to increase the concern and to set a not-to-exceed limit.

In the meeting that we had a couple of months ago, the conclusion was reversed to indicate that there are no associations any longer, and that, in fact, the not-to-exceed concept should no longer be applied to bromodichloromethane.

COMMITTEE MEMBER HOBEL: Okay. Thank you.

DR. TARDIFF: You may want to revisit bromodichloromethane based on that and other considerations. I don't know.

Yes.

COMMITTEE MEMBER ROBERTS: The Narotsky paper though from 2006, that used the four trihalomethanes, didn't it?

DR. TARDIFF: I'm trying to remember which --

that was -- I think that was the in vitro study?

COMMITTEE MEMBER ROBERTS: It's on page 48 of our section. It's Effects of Defined Mixtures of Trihalomethanes and Haloacetic Acids on Pregnancy Maintenance and Eye Development Fischer 344 Rats.

I believe it's only shown here as an abstract.

DR. TARDIFF: Right. I don't think that it was ever published afterwards. And it was a mixture of trihalomethanes and haloacetic acids.

COMMITTEE MEMBER ROBERTS: Yes. And I've assumed that his THM --

DR. TARDIFF: There was no positive control like -- or no negative control, whichever you want, with THMs, per se, as I recall.

The finding suggests that haloacetic acids cause pregnancy loss in the Fischer 344 rats.

COMMITTEE MEMBER ROBERTS: Yeah. About half way through -- let me see, they dosed on gestation day 6 to 20. It says for the THM-4 mixture, pregnancy loss was seen in 0 of 14, 0 of 25, 11 of 14, and 12 of 13, of the dams at 0, 307, 613 and 925 micromoles per kilogram.

I'm sorry. I'll repeat it.

It says about part way down through the abstract, for the THM4 mixture, pregnancy loss was seen in 0 of 14, 0 of 25, 11 of 14, and 12 of 13 of the dams at 0, 307, 613

and 920 micromole per kilogram respectively.

DR. TARDIFF: Yeah. What's not apparent in the abstract is the high doses all produce substantial maternal toxicity.

The reality is that in all of the animal studies for the individual THMs, invariably people pushed the envelope to try to get some toxicity in the mother. And, of course, they're always examining the fetuses or examining fetal resorption, if they all die.

But when you get down to those doses that don't produce maternal toxicity, you don't get any injurious consequence.

Yes.

COMMITTEE MEMBER HOBEL: Could you explain to us, is there any way to alter the chlorination process so you don't get certain compounds in the mixture? Is that controllable?

DR. TARDIFF: No. Well, yes and no. You can do a variety of different kinds of pre-treatments. And if you go to the southeastern part of the United States, where they have a lot of naturally occurring bromine and bromides, you can pre-treat for the reduction -- it's not complete removal -- of the bromides, so that you get fewer brominated and chlorinated species afterwards. That's more than THMs, by the way.

The other thing that you can do, when there isn't much of a background of bromine, is reduce the amount of organic material going into the treatment plant prior to chlorination. And, in fact, that's being practiced very actively today. So depending upon what kind of organic materials there are, if it's just humic substances coming out of the river, for example, you can actually use a very strong precipitant and you can actually put an accelerant into that process, so everything precipitates out. You've got, you know, very small amounts of total organic carbon that now can come in contact with the chlorine to produce chlorination byproducts, and so you can reduce them appreciably.

Can you change anything like if you wanted to target -- there's a compound called MX, highly potent carcinogen and mutagen, there in small quantities. You want to target getting rid of that, that becomes more difficult. You now have to start playing around with the pH. But when you change the pH, you change a lot of other characteristics that might not be so favorable. If you go too low on the pH side, you start corroding the pipes on the other end. So trying to balance out to get a win-win situation is not easy for the water quality engineers.

But EPA has really done a great job, in my view. It's spear-heading ways to engineer out and constantly

reduce the level of contamination contaminants that may get into drinking water. And that's what the, you know, the chlorination byproduct rule -- disinfection byproduct rule has been. It's just a steady decline, so that there's less and less of the material and less and less chance that anybody could get injured.

Now, at this point, you know, we're down to such low levels in many water supplies, not all. We're probably at the point where the human body has got plenty of detoxification and other defense mechanisms to be able to handle them, even though there are chlorine and bromine species associated with them.

COMMITTEE MEMBER HOBEL: Thank you.

COMMITTEE MEMBER KEEN: Yeah. Actually, I'm going to make a few observations and then I have a question for Dr. Donald.

I'm feeling just -- while I appreciate the presentations we just had, I'm feeling a little uncomfortable, because I get the sense we're being asked to analyze data without seeing the data, so we're getting distillations. An example of that, for example, while the BDC I think clearly we want to look at, you know the idea that we wouldn't want to look at chloroform because in 2004 we said we don't think the data is sufficient.

I'm reminded that this Committee, at one time,

looked at the second-hand smoke data set and said it's insufficient for it to be listed. New data occurred, and then we said, of course it should be listed.

Time marches on. So the shear fact that the Committee previously has said there's insufficient data, in my opinion, should not, in any way, be interpreted as a reason we wouldn't look at it again. The key question is whether or not there has been substantial new data that's emerged, and sometimes that could be a single publication, which was the case with the secondhand smoke.

The question to Dr. Donald that I'd like to pose is, what I'm hearing is it could be a significant staff workload associated with trying to assemble the data for these individual compounds. Where clearly we have some reason to suspect there's a level of urgency that we, at least, look at one or two.

If, by bundling them together, would that significantly delay the process? I'm not too worried about the bundle after the counsel has informed us that we can deconstruct the list. If when we look at it, you know, whenever at time X and say look, we don't see any real evidence for two or three of these compounds, then frankly many of the arguments I've heard against looking at the class, to me, seem to evaporate.

But of much more serious concern is that if by

bundling them together, it causes a significant delay because there's simply no resources, which I know OEHHA often times is faced with severe constraints. So to the best you can, if you could give us a little help here, that would be of value, at least to me.

DR. DONALD: Well, clearly, there are more studies to be considered if we look at THMs or a subset of THMs than if we look at individual ones. On the other hand, if you asked us to look at all of the individual ones, then the workload would actually probably be higher than it would be to look at them as a group.

At this point, we believe we've identified the majority of the studies. We realize there may be other relevant data out there that may come to light, if we prepare hazard identification materials.

But I think the short answer to the question is, it probably wouldn't significantly delay the process if you asked us to prepare materials on the group, compared to preparing materials on individual THMs.

COMMITTEE MEMBER KEEN: Thank you.

CHAIRPERSON BURK: That was a good question. And I kind of observed maybe you two -- I asked Linda and Calvin to take the lead on this, but aren't a lot of studies the same ones and they're just put in these different categories because they looked at more than one

of the trihalomethanes. So I'm not looking for work for you, but I'm just saying some of them you might as well do it and it covers several at the same time.

Did you have another comment, either of you or any edification here?

COMMITTEE MEMBER ROBERTS: I just, in trying to look it over, tried to kind of summarize -- condense it and specifically look at the trihalomethanes data as well as the individuals, and it was a really nice way that this was laid out by OEHHA. And as was shown, there are both positive and negative epidemiology studies and positive and negative animal studies.

One of the complications on the human studies, I think, is that the level of exposure is by drinking water and what one person says is high might be 20 micrograms per liter and that might be in another study's low group and their high group might be 75 micrograms per liter.

Epidemiology studies tend to have more statistical power if they have larger sample sizes. And so the number of negative studies in there, one of the things I looked at -- and I'm not an epidemiologist -- and the abstracts really didn't go into, you know, confounders and how well those are controlled -- were whether or not the negative studies were the smaller studies and maybe couldn't have picked anything out.

That was not particularly the case. The sample sizes went from not being clarified in the abstract to being a couple thousand to, in one case, they said it was in essence 2.6 million birthes in their records. So, some of the negative studies were a large size. They may be completely crummy in terms of their design, but they at least had plenty of material.

The biggest group actually had a quote in their abstract that there was little evidence of trihalomethane exposure and birth defects. There were a couple of analyses that came up with birth defects that were statistically significant. One of them was in a meta-analysis for ventricular septal defects in the Hwang study, which is a Taiwanese population.

The other one, and I'll mispronounce this, was Nieuwenhuijsen, for VSDs also. And that was in a population of England and Wales. But they said overall when they looked at birth defects, they didn't consider the finding. If where there were positive findings and there are also negatives to these, this positive findings tended to be small birth weight or stillbirth. And those adjusted odds ratios tended to somewhere around 1.1 to 1.9. So they're not huge, but they had some. And then they also had the others where the confidence intervals were not different from null.

The animal data is kind of interesting. And they did have that one study where the four trihalomethanes were exposed. And they appeared to me, at least from the abstract, to have an appropriate control group. But in that one, they used the Fischer 344 Rat, which is typical for EPA in North Carolina to use, but not too typical for other people to use.

But they found with BDCM, the bromodichloromethane, that there is a really strong strain-specific difference in sensitivity. Sprague-Dawley rats don't respond to the full litter resorption for BDCM. Whereas, the Fisher 344's do.

They have some mechanistic data that suggests that there's something there in terms of altering progesterone secretion and progesterone seems to rescue it. That's specific to the BDCM, which we're going to see anyway. That hasn't been shown with the trihalomethanes.

And I know that one of the slides said that there was testicular histopathology and altered sperm parameters. But the only one I spotted from the abstracts was a change in sperm motility, and that was for the BDCM rather than the trihalomethanes as a group. So it looked to me overall like we could get a lot more data to look at by looking at the trihalomethanes, but not necessarily that we get a clearer picture.

(Laughter.)

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER JONES: I must admit, I am not for looking at this as a group, but rather looking at it as individuals. And I think there's been plenty of experience, as far as this is concerned, at least in terms of specific categories of medications and their effect on human pregnancy. That it's very appropriate to look at individual drugs within the category, rather than look at the category as a whole in terms of teratogenicity.

So I really am against the concept of looking at this as a drug. And, you know, when I reflect back on this prioritization exercise that you and I went through in 2004, and we came up here on three or four occasions and set up this way to prioritize things, we made it -- one of the things that we looked at was you looked at agents that have good human epidemiologic studies first. And we've got some of these agents in here. And it seems to me that by looking at this entire group, we're just going to be spending a lot of time looking at a lot of agents that there is no good data on.

So I would say we should be looking at the drug that we -- or the agent that we have already agreed to look at. And I would agree with Carl, we should be looking at chloroform again or at least we should be

considering it. And I don't think we should be looking at the other agents in this category.

COMMITTEE MEMBER ROBERTS: Yeah, I would agree. Chloroform and the bromodichloromethane, I think, have sufficient data. There wasn't -- we just wouldn't be there with bromoform or DBCM.

CHAIRPERSON BURK: Let me review what the choices were here, the four possibilities. Oh, Jay -- well, we're in our discussion phase, but if it's really, really short.

DR. MURRAY: Let me tell you what it is and then you decide.

I wanted to answer Dr. Keen's question about additional chloroform data and suggest he ask the same question of Dr. Moran who reviewed the data recently. Is that okay? I don't want to be presumptuous.

COMMITTEE MEMBER KEEN: Actually, I would almost cut it short. I was saying it's a matter more of principle. If the argument is made the Committee has looked at something in the past and found it's wanting, there's no need to revisit, that is not a correct principle.

DR. MURRAY: Right. I agree with you in principle. I'm saying that you don't have the same situation here that you did with ETS.

COMMITTEE MEMBER KEEN: We might have a different

committee now though, Jay, who might come up with a different decision and keep the same data set.

(Laughter.)

DR. MURRAY: Well, it is possible. But, you know, if you're trying to set priorities, you want to think about do you really have, you know, enough new information. And my understanding is, in the case of chloroform, you don't, but I was going to suggest you ask Dr. Moran and see if he could answer that question for you as well.

Thank you.

DR. DONALD: Well, actually to reiterate what I said in my introduction, there is one additional study of chloroform that we've identified that was included in the abstracts that were provided to you.

DR. TARDIFF: Can I ask a question. I'm not sure what study you're talking about.

DR. MORAN: On page 41 of the abstract summary results, 2004 Lim et al. endocrine.

Do you have it?

COMMITTEE MEMBER HOBEL: What page is that on?

DR. TARDIFF: Page 41.

DR. MORAN: Yes, it was the newest abstract that we found. The next one is 1998 and then '83. There were only three.

DR. TARDIFF: If I could.

That's the one that deals with the whole issue of blood glucose. And they really didn't find any effects. They had postnatal growth problems, but the main hypothesis that they had was, you know, glucose homeostasis was not changed by chloroform treatment at high doses. Yes, it's a chloroform study, but it isn't a positive study.

CHIEF COUNSEL MONAHAN-CUMMINGS: This is not the time to have a discussion with Dr. Moran about the study.

DR. TARDIFF: Sorry. He reflected it as a positive.

COMMITTEE MEMBER WHITE: No, he didn't. He just said it was a new study.

CHAIRPERSON BURK: All right. Well, I think we need to make a decision here and I'll review the four possibilities that we will vote on. One would be to prepare hazard identification materials for total trihalomethanes.

Number two was to prepare them for certain trihalomethanes, which, as I read it, would be, for example, chlorinated and brominated trihalomethanes, is that what you're saying.

Okay, the third one would be for each one of the four trihalomethanes.

And the fourth one was not proceed with hazard identification materials other than BDCM.

So the fifth one is -- well, that would be certain ones, but two certain ones, right.

So, I would -- yeah, I guess that would be a fifth. All right, so we'll make a number five, which would be to proceed with chloroform and, of course, continue with DBCM.

All right. So I need to go through each one of these. Is everyone clear on what they are?

COMMITTEE MEMBER KEEN: What's unclear to me though is how we vote, because hypothetically I can see my -- I know what my number one choice is, but if I don't get that, I might go for number two.

(Laughter.)

CHAIRPERSON BURK: Well, you know, that's a good point, because --

COMMITTEE MEMBER KEEN: Are we allowed to make --

CHAIRPERSON BURK: -- we have five choices. If we each pick one of them, we might not get much of a consensus.

COMMITTEE MEMBER KEEN: Would we be allowed to make a motion here or a suggestion?

DIRECTOR DENTON: Well, you know, this is not a listing decision where we have to be very prescriptive on

the language and exactly what the chemical is. I think the Committee, in whatever form and however you want to take a vote, can give us your advice on what you think would be the best thing to do. And if you want to ignore the outline that we've provided, that would be fine. We just need your clear advice on what the Committee thinks that is the appropriate approach.

COMMITTEE MEMBER KEEN: That's great, because that allows me then to make a suggestion. And I would like to propose that we do BDCM and chloroform, those two. Because, as I look at it, the totality of the evidence is most informative in those two cases.

CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me, just to clarify what you're saying. Are you saying separately, but you'd probably want to consider them at the same meeting?

COMMITTEE MEMBER KEEN: That's correct, yes. That's just a suggestion for the Committee to ponder.

CHIEF COUNSEL MONAHAN-CUMMINGS: No, that's fine.

COMMITTEE MEMBER ROBERTS: Would it be possible to vote yes or no on each of those individually? So, in other words, following with what Carl suggested, someone could vote on BDCM yes and chloroform no, if they wished or vice versa.

CHAIRPERSON BURK: Yeah. Well, BDCM we don't

have to vote on that because it's already there. So what we're really just saying is do you want to add chloroform or do you want to add the whole group or any other individual one?

COMMITTEE MEMBER WHITE: I guess my question would be so have we decided not to look at them as a total group? We haven't discussed that part of it. So my recommendation would be that we make that decision and then go from there. I think that would be a more organized way in my brain to consider it.

CHAIRPERSON BURK: I'm willing. Is that okay with you?

So that's voting on the number one here, so that's the only thing up for consideration right now.

So the question is do you advise OEHHA to begin preparation of the hazard identification materials for total trihalomethanes? All those advising yes, please raise your hand.

(No hands raised.)

CHAIRPERSON BURK: Zero.

All those advising no, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: So I'm assuming that's going to be the full eight.

Now, you feel like -- okay, we've got that one

out of the way. And now can we proceed to Carl's motion. And that one would be, do you advise OEHHA to proceed with BDCM, and, in addition, chloroform? All those advising yes, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: So I see six.

And no?

(Hands raised.)

CHAIRPERSON BURK: Two, okay.

Is there any other thing you two would want us to vote on? This is not a certain number carries. It's just a recommendation. But, at this point, I see it 6 to 2 to continue with BDCM plus revisit chloroform.

All right.

Are you okay?

THE COURT REPORTER: I could use a break.

CHAIRPERSON BURK: How long do you want?

THE COURT REPORTER: Ten minutes.

CHAIRPERSON BURK: Ten-minute break. Okay, ten minutes.

(Thereupon a recess was taken.)

CHAIRPERSON BURK: Well, in the interests of some people that have flights back to southern California, let's reconvene.

And the next chemical to consider, is the

prioritization of Particulate Matter. And, again, we have Dr. Francisco Moran, and, again, I assume we have Dr. Jim Donald to start off.

(Thereupon an overhead presentation was Presented as follows.)

DR. DONALD: Yes, again, brief introductory remarks.

During the Committee's discussion of sulfur dioxide at the last meeting, it was noted that sulfur dioxide commonly co-occurs with particulate matter as components of air pollution. The Committee requested that we prepare prioritization materials on particulate matter and Dr. Moran will, in a moment, present a brief overview on these materials.

Once again, since there is substantial overlap between the data sets for sulfur dioxide and particulate matter, and since the epidemiological screen was met for sulfur dioxide, the screen has not been reapplied to this data set.

Also, OEHHA is currently proceeding with the development of hazard identification materials for sulfur dioxide and has published a request for relevant information for inclusion in the hazard identification materials.

But specifically we're seeking your

recommendation as to whether the information provided to you on particulate matter or on particulate matter and sulfur dioxide together as components of air pollution warrants the development of full hazard identification materials.

Sulfur dioxide is a separate entity from particulate matter and one to which exposures can occur independent of exposures to particulate matter. So if you were to recommend that we prepare hazard identification materials for particulate matter and sulfur dioxide together as components of air pollution, we would still prepare a separate set of hazard identification materials for sulfur dioxide and present them to you for a listing decision.

DR. MORAN: Okay.

--o0o--

DR. MORAN: I will present the evidence available for prioritization of particulate matter (PM). PM is of particular concern as an air pollutant, where it occurs in combination with other chemicals of concern, such as sulfur dioxide and carbon monoxide.

--o0o--

DR. MORAN: Particulate matter epidemiologic data is summarized as follows:

We found 30 epidemiologic studies reporting

increased risk of adverse developmental or reproductive outcomes; four meeting abstracts reporting increased risk of adverse developmental or reproductive outcomes were also identified; four epidemiologic studies reporting no increased risk of developmental or reproductive outcomes were identified; and 12 related studies were also found.

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DR. MORAN: Particulate matter epidemiologic effects summarized as low birth weight in both pre- and term-born infants; intrauterine growth retardation; and pre-term birth.

--o0o--

DR. MORAN: In the animal data search we found that 11 animal studies reporting reproductive or developmental toxicity were identified. Also, two studies reporting no reproductive or developmental toxicity, as well as three related articles were identified.

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DR. MORAN: Among the particulate matter animal effects, we have found that in rats it suppresses testicular function, especially spermatogenesis and sperm motility. In mice it can influence the glutathione oxidation deoxidation system, GSH, and cause DNA damage in male reproductive system and may also affect development of the oocyte.

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DR. MORAN: That concludes my presentation.

Thank you.

CHAIRPERSON BURK: Thank you. I've asked the other end of the table here, Drs. Gold and White, to take the lead on discussing this.

CHIEF COUNSEL MONAHAN-CUMMINGS: Do we have any public comments?

Do we have any public comments?

CHAIRPERSON BURK: Do we have any public comments?

I forgot about that.

CHIEF COUNSEL MONAHAN-CUMMINGS: I just want to put that on the record.

CHAIRPERSON BURK: Yes. I need to ask, but I didn't see any blue cards, so I guess not.

COMMITTEE MEMBER GOLD: Okay. So as it was stated, particulate matter is an air pollutant. And when it's less than 10 micrometers in diameter, it can penetrate into the thoracic part of the airways and have adverse effects. The particles may deposit in the upper airways.

A large part of PM10, that is less than 10 micrometers, is actually comprised of fine particles, that is those that are less than 2.5; and the distribution

which -- spatial distribution of PM2.5 and PM10 are often similar, because PM2.5 is such a large fraction of PM10.

And PM2.5 particles can penetrate in the inner-most portions of the lung. And a fraction of them can cross the lung epithelially and reach the blood circulation.

So fine particles are of concern when they occur in combination with other chemicals, such as nonorganic compounds, like sulfur dioxide, nitrous dioxide and certain metals, elemental carbon, carbon monoxide and organic species, including polycyclic aromatic hydrocarbons. And several biologic mechanisms have been suggested as to how they might lead to intrauterine growth retardation, such as hypoxia, reduced maternal placental blood flow, inflammatory process, genetic and endocrine disruption and so forth.

So, as described, there were 30 epidemiologic studies showing a positive relation with particulate matter to adverse developmental and reproductive outcomes, along with four meeting abstracts. Four additional epidemiologic studies showed no increased risk, two of which were median abstracts and 11 animal studies showing relation of PM to reproductive and developmental toxicity were identified, in addition to the two showing no effects.

Most of the studies examined PM10, but several examined smaller particles, PM2.5. Most of the studies examined and found an adverse effect on birth weight as a continuous variable, low birth weight, although the definitions varied, and pre-term birth.

A few studies examined intrauterine growth retardation, small for gestational age, birth defects, stillbirths, head circumference and intrauterine mortality.

Most of the positive epidemiologic studies reported relatively modest relative risks, but a few showed fairly large effects. Some of the studies assessed personal exposures, but most assess ambient county- or area-level exposures on routine monitoring. Most of the studies adjusted for some confounding factors and were factors that were considered different from study to study.

Some of the studies observed dose-response effect. Although most of the studies did not record it in their abstracts, at least they identified that they didn't analyze the data in this way. And some of the studies found adverse reproductive and developmental effects of PM10 independent of other pollutants.

So I think based on this, I'd love to hear further discussions from the Committee, but I would be

supportive of giving it priority for further investigation.

COMMITTEE MEMBER WHITE: I agree. In looking at the -- there was at least three 2004 studies in Pennsylvania and Michigan. And the PM10 and sulfur dioxide were really the pollutants that sort of ferreted out from the others, with respect to low birth weight and pre-term delivery, really taking a look at those. And so we're really looking at this as a mixture of pollutants, I mean.

But in examining the studies and reading these abstracts, those two, particularly PM10 and sulfur dioxide, were the two that seemed to have the most, for me, not so much compelling, but to something else to just look at, to look at those two.

And then looking at the studies with respect to southern California, because, you know, the Los Angeles area, et cetera, there's a lot of pollutants -- it holds a lot of pollutants. If you've ever lived down there and seen a pair of lungs, you can honestly say that they look like smoker's lungs. But if you can imagine fetuses being exposed to those kinds of pollutants, it would have an impact.

And I feel as though, yes, this needs further -- we need to take a further look at this, particularly those

two, PM10 and sulfur dioxide.

CHAIRPERSON BURK: I have just one question, would you want to distinguish between PM10 and PM2.5? Would that be possible or is that --

COMMITTEE MEMBER GOLD: I think the literature suggests that they co-occur so much that you probably -- I mean, you could try, but I don't think it's worth focusing on.

CHAIRPERSON BURK: Right. So we're talking particulate matter including both of those. And sulfur dioxide is already in the hopper.

So is there any other discussion on this?

COMMITTEE MEMBER KEEN: If I could just get a clarification. I fully endorse it as well. 2.5, I agree, looks like PM10, but the new actor on the block, nanoparticles, and with the construction of tires, which just this change occurred recently along traffic corridors. The predictions of nanoparticle concentrations are both quite high. Is it the idea that this potential review would include that, because that could be an entire field in itself. And you'd hate to draw either a false positive or false negative. So maybe, just for clarity, if it said it is or is not supposed to include that, that would completely change the scope, I think, of some of the work.

COMMITTEE MEMBER GOLD: I would say the materials we received didn't really deal with that so --

COMMITTEE MEMBER KEEN: Yeah, I understand that, but that's what I -- before we walk away from it. It is that particulate matter is one that's going to be more and more in the public eye.

COMMITTEE MEMBER WHITE: There is a whole literature on that.

COMMITTEE MEMBER KEEN: And there's a big literature on experimental animals. So I think that's important just to be aware of that. My sense is that it should be -- that that would be beyond the scope. But before one just kind of blithely makes that assumption as such, just asking for clarification.

CHIEF COUNSEL MONAHAN-CUMMINGS: It depends on how you want to define it. I mean, if you think that's important, we can do -- we can include that or we can look at it separately as an additional item for you to consider. But you can define what the group is that you want us to look at in the mixture and look at the data that's available.

COMMITTEE MEMBER KEEN: Well, just to give one person's opinion and others can state their opinions. I think it's going to be a very important topic. I think it may be a little premature to address it. And the reason

that I brought this up is that I didn't want OEHHA to be suddenly caught in the process saying it's moving so quickly that we need yet two or three more studies, because, I mean, literally when -- typically, under tire construction, they almost had ignored this, and then suddenly it's there.

And so it could be a floating target over a period of the next three or four years. And I think it should -- it would stand on its own, but I just like -- I thought it was very important to get it identified one way or the other.

So my sense would be, yes, it has to be looked at, but probably the database isn't large enough yet. You can easily draw a false negative based on that.

CHIEF COUNSEL MONAHAN-CUMMINGS: Would you want to define this as PM not including the --

COMMITTEE MEMBER KEEN: Yeah, there's others who are better versed in this than I am, but that would be my instinct.

COMMITTEE MEMBER WHITE: That would be my recommendation as well.

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't know whether or not, from a scientific standpoint, you can separate those out, but that's not --

DR. ALEXEEFF: Yeah, I think the simplest thing

would be for us to bring in the data regarding PM and PM2.5. And you can make a decision on how you want to list it. But I think what you're suggesting is that we not go to the animal literature, that there might exist on nanoparticles and try to figure that out. I think that's what you are saying.

COMMITTEE MEMBER KEEN: And that's precisely what I'm suggesting.

DR. ALEXEEFF: Yeah. So we can focus on the more typical air pollution issue. And then you can decide if it's PM, PM10, PM2.5.

CHAIRPERSON BURK: May I ask a question, too, of Carol. The way that -- the two choices that are put down here are, one, do we want to begin preparation of the materials for particulate matter? And the second one is, do we want to prepare materials for particulate matter and sulfur dioxide together as components of air pollution?

So I want to make sure, what's the subtlety, because we already have sulfur dioxide in the works, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: I think Jim can answer that.

CHAIRPERSON BURK: Can you clarify that?

DR. DONALD: Sure. As I mentioned, we will be doing HIM, hazard identification materials, on sulfur

dioxide as a discrete gas.

The question would be, since many of the studies are essentially of air pollution, as opposed to -- even though in some instances they try and parse out the particulate components of air pollution that are associated with effects. The question would be, do you want us to look only at studies that address particulate matter specifically or would you want us to look at studies where particulate matter and sulfur dioxide were co-components of air pollution.

COMMITTEE MEMBER GOLD: I think the problem is that you're not always going to be able to separate them. And so I think we're going to have to ask to broaden that.

COMMITTEE MEMBER WHITE: I agree.

CHAIRPERSON BURK: All right, Dr. Hobel.

COMMITTEE MEMBER HOBEL: A quick question. You know, there's also the issue of ozone as part of air pollution. And a paper was just published that's not listed here from Australia, where they did a very careful surveillance of pregnancies. And they actually monitored fetal growth throughout pregnancy and they identified different timing points where particulate matter played a role later in pregnancy, in terms of its effect on fetal growth. Whereas, ozone had an effect earlier in pregnancy.

And it's a reference by -- the first author is Hansen, C.A. Hansen. And I can give you the reference, because it is something that you should add to the list. It was published in Environmental Health Perspectives, Volume 116, number 3, March of 2008.

So I think looking at a combination of substances that contribute to pollution would be important.

CHAIRPERSON BURK: And how would you phrase that? So you want to broaden this to everything to do with air pollution? I mean, we've already considered carbon monoxide a long time ago and I know there are many other components.

COMMITTEE MEMBER HOBEL: Well, the four that I think people are looking at is ozone, particulate matter, sulfur dioxide and carbon monoxide. So those four things.

CHAIRPERSON BURK: So what would your --

COMMITTEE MEMBER JONES: But these still look like solvents -- the whole solvent story. The more you start adding to this -- so, I mean, if it's possible to separate these things, I would suggest separating them, rather than lump them all into one.

CHAIRPERSON BURK: I tend to agree, because I know when we get this, it's just such a massive amount of work to look at everything. And not only -- you know, basically, the sulfur dioxide came out in the screen. And

then we just said oh, it's got particulate matter with it a lot and then we added that. But I personally think maybe we should call it quits right there for the moment. Even though ozone would certainly, I'm sure, have plenty of data.

So I'm not trying to steer this one way or the other. Should I add that as a thing to vote on?

COMMITTEE MEMBER HOBEL: Well, I just mention it because it was an important part of differentiating the timing of the effect on fetal growth. I think this is sort of where oxidative stress -- and it occurs at different points in time during pregnancy, and it can be caused by different components.

And if you're going to have oxidative stress occurring at different points in time, you need to be aware of that, because the timing of these events is very, very important.

CHAIRPERSON BURK: I think so. I think maybe we'll take a vote on particulate matter. And then if you want to bring up something else, I think we can do that.

COMMITTEE MEMBER GOLD: I wonder if I might suggest that the net be set at particulate matter and ozone -- that the net be set at particulate matter and if ozone happens to fall into the net, because it co-occurs, that will enhance our information. But I think if we go

off in the direction of looking specifically for ozone, it is going to get huge.

CHAIRPERSON BURK: I think so too. So as I understand it, we're going to vote on whether OEHHA should begin preparing hazard identification materials for particulate matter and sulfur dioxide together as components of air pollution. Is that reasonable?

So all those advising yes, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Okay. And Linda is abstaining, so that's seven.

COMMITTEE MEMBER ROBERTS: Recusing.

CHAIRPERSON BURK: Recusing, sorry. One recusal.

All right. So did you want to bring up officially the ozone for some future --

COMMITTEE MEMBER HOBEL: No, I don't have any -- I just mention it, because I was aware of the literature and it's listed and it plays an important role as I mentioned. So I just want people to be aware of that. And as long as we review the paper and include it, it needs to be in our sight.

CHAIRPERSON BURK: Okay.

DIRECTOR DENTON: Can I ask for a clarification? We've already got SO2 that we're working on. So now is

the Committee advising that we also take a look at PM together with SO2 is that what -- or are you asking us to look at PM separately from SO2? I'm still kind of confused about the vote.

CHAIRPERSON BURK: Yeah, I am confused, too. And that's my fault, because we have two different things on here.

One was just particulate matter, and the other was particulate matter and sulfur dioxide together. So there's a subtle difference here, because one's already -- sulfur dioxide is already done. So are we asking for two separate considerations or were we asking them to be lumped together?

I thought what we were voting on was lumping them together.

Does that make sense to you? I don't know if that's going to interfere with what you've already started working on and you better tell us, if so.

CHIEF COUNSEL MONAHAN-CUMMINGS: The caveat was that sulfur dioxide occurs in other ways besides in air pollution, so we'd still be having a document on sulfur dioxide.

But the question was whether you want to just look at PM separately or if you want to look PM and sulfur dioxide together.

CHAIRPERSON BURK: Okay. So what we voted on was together in air pollution. Does anyone want to change their mind and just look at particulate matter separately?

COMMITTEE MEMBER GOLD: Well, if I could just clarify that though. If we have a paper on PM that doesn't mention the sulfur dioxide, it still ought to fall in the net.

CHAIRPERSON BURK: Right. So we probably should have asked for particulate matter as the topic. And then if sulfur dioxide happens to be in there, then that's fine, but we wouldn't miss the papers that were just particulate matter. So perhaps we should revote.

(Laughter.)

CHAIRPERSON BURK: Now that we're a little clearer. So the option now is, do you advise OEHHA to begin preparation of the hazard identification materials for particulate matter? All those advising yes, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Okay, the same vote seven and one recusal. I'll cross out that other one.

All right, moving along. Our next agenda item is update of the Section 27000 list of chemicals, which have not been adequately tested as required. And the staff presentation is by Fran Kammerer.

(Thereupon an overhead presentation was Presented as follows.)

STAFF COUNSEL KAMMERER: Good afternoon. This afternoon you've been -- all day actually -- looking at perhaps this, which is one list you're all familiar with. And some of you are familiar with another list, which is in Section 27000 of the Act. It used to be in Section 14000, but it's been changed.

The second list determines that the State publish a list of chemicals that are required to be tested under federal or State law, because they have not been adequately tested.

You have a copy in your binder of Section 27000.

COMMITTEE MEMBER HOBEL: This is Title 27?

STAFF COUNSEL KAMMERER: Yes. No Section 27000. Yes, it is Title 27. All of it is under Title 27. It's been moved from Title 22.

This list is a compilation of chemicals that already have been required to be tested by regulations such as FIFRA, which is the Federal Insecticide Rodenticide Act. However, this regulation also says that the State's qualified experts, which is you, must determine that they have not been adequately tested. It's a ministerial duty.

They've already been required by law to be

determined by other agencies that they haven't been -- or by -- actually, by other regulations, that they haven't been tested sufficiently. These regulations are under U.S. EPA, the federal EPA, and the California Department of Pesticide Regulation.

You have two copies of Section 27000 in your binder. You have the current version and you have an amended version, a revised version, that has the chemicals that have been determined not to have sufficiently been tested, the new ones, which are underlined. And you have the ones that have been crossed out that these agencies have determined that they have enough information on.

To avoid going over these chemicals individually, we created two lists.

Next slide, please.

--o0o--

STAFF COUNSEL KAMMERER: Ms. Oshita will hand you a couple of lists. We've labeled them Exhibit A and Exhibit B. And I'll be handing a copy to the court reporter now of each.

(Thereupon the above-referenced document was marked as Exhibits A and B.)

STAFF COUNSEL KAMMERER: Okay. Exhibit A is a list of chemicals that U.S. EPA suggests be added to this list. They need more testing. And it's in the slide

currently being shown now.

Exhibit B -- next slide, please.

--o0o--

STAFF COUNSEL KAMMERER: -- and the next few slides will be a continuation of this list, because it's a pretty long list. It's a list of chemicals that have been determined by U.S. EPA and the California Department of Pesticide Regulation to have been sufficiently tested.

So as I said, this is a ministerial duty that you must find that they have been adequately -- they have not been adequately tested -- through other agencies' determinations that they have not been adequately tested.

So, hopefully, I've made myself clear on this.

Are there any questions?

(Laughter.)

STAFF COUNSEL KAMMERER: Okay. Well, then, Dr. Burk, will read you the voting protocol.

CHAIRPERSON BURK: I lost it.

COMMITTEE MEMBER ROBERTS: I have one question. Do we vote on this together or do we vote on each one of these lists?

STAFF COUNSEL KAMMERER: You will vote on each one. She'll read you the protocol and then you vote.

CHAIRPERSON BURK: Yes. There are two votes coming up here. So the first one is, based upon the

information you have been provided from U.S. EPA, should the ten chemicals noted on Exhibit A be added to the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required? All those voting yes, please raise your hand?

(Hands Raised.)

CHAIRPERSON BURK: That's Exhibit A we're voting on.

Okay. Good, I think it's pretty easy, because it's a ministerial function.

(Laughter.)

CHAIRPERSON BURK: Okay. So that's eight and zero.

And then the second one is based on the information you have been provided from U.S. EPA and CDPR, should the chemicals noted on Exhibit B be removed from the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required? All those voting yes, please raise your hand?

(Hands raised.)

COMMITTEE MEMBER HOBEL: Could you give us a minute to look at them.

CHAIRPERSON BURK: Okay.

COMMITTEE MEMBER ROBERTS: Dotty, looking at the list, I think I have to recuse myself from voting on

Exhibit B.

CHAIRPERSON BURK: Okay. That's fine.

COMMITTEE MEMBER GOLD: Have we actually been provided evidence about Exhibit B that the testing has been done?

CHIEF COUNSEL MONAHAN-CUMMINGS: We provided you the letter from U.S. EPA and from CDPR that says that these are the chemicals they want added or deleted from the list. So it's basically you're relying on their determination that the testing has not yet been done or that it has been done. It doesn't mean that they haven't been tested at all. It means that they have to be tested to a certain standard that is acceptable to the U.S. EPA or DPR.

Just for the Committee's knowledge, I just wanted to let you know that we are going to initiate a process of changing this regulation, so you all don't have to do this and you can just delegate the task to us, because there really isn't a reason for you to spend your time doing it. But right now the law and the regulations say you need to.

CHAIRPERSON BURK: Okay. He's had enough time. He's comfortable.

(Laughter.)

CHAIRPERSON BURK: Okay, so this is Exhibit B. I read that part. So all those voting yes, please raise

your hand.

(Hands raised.)

CHAIRPERSON BURK: And I see seven and one recusal.

All right, so that's that.

STAFF COUNSEL KAMMERER: Thank you.

CHAIRPERSON BURK: Next on the agenda, staff updates --

COMMITTEE MEMBER HOBEL: I have a question. May I ask a question?

CHAIRPERSON BURK: Please.

COMMITTEE MEMBER HOBEL: On the 27000 list, some of them have an asterisk on them and what does that mean?

CHIEF COUNSEL MONAHAN-CUMMINGS: Hold on. Let me get the regs.

COMMITTEE MEMBER HOBEL: Like acid blue, acid yellow. And then methanol is listed, castor oil. Why are they --

CHIEF COUNSEL MONAHAN-CUMMINGS: In the actual regulation some of the chemicals who have an asterisk next to them and there's -- it references to -- claims -- claiming that review of this data should not be required.

So basically it's saying that someone is claiming that they shouldn't have to review the data -- I mean, that they shouldn't have to present the data. So it's not

really germane to the question you just decided about whether or not they should remain on the list or not. It's just additional information for someone who might be referencing this.

COMMITTEE MEMBER HOBEL: Okay.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm not sure what value this list has, to be honest.

CHAIRPERSON BURK: Are we ready for staff updates?

This will be Cynthia Oshita.

MS. OSHITA: We're almost done here.

Okay. Good afternoon. Since the Committee last met in December of 2007, OEHHA has administratively added ten chemicals to the Prop 65 list. Three of the chemicals were listed as known to cause reproductive toxicity. And they include hexafluoroacetone, nitrous oxide and vinyl cyclohexene.

And seven chemicals were added as known to the State to cause cancer, which include dibromoacetic acid, benthiavalicarb-isopropyl, mepanipyrim, pirimicarb, resmethrin, gallium arsenide and oryzalin.

And a summary sheet of these latest additions to the Prop 65 list are in your -- and their effective meeting dates are in your meeting materials behind the staff updates tab.

In addition to these listings, there are a couple of chemicals that are under consideration for administrative listing. And they include methanol, as a chemical known to the State to cause reproductive toxicity. And the other chemical is 4-methylimidazole, as a chemical known to the State to cause cancer.

Also, included in your binders, is a summary of the safe harbor levels that have been adopted this past year. That includes a Maximum Allowable Dose Level for di-n-butyl phthalate, which was effective July 23rd, 2008. And a no-significant-risk-level, which was established for nitromethane effective April 28th, 2008. And for C.I. Direct Blue 218, which was effective September 7th, 2008.

DIRECTOR DENTON: Cindy, excuse me. In the binders it says it was effective for the di-n-butyl phthalate July 28th.

MS. OSHITA: Oh. I believe it's supposed to be the 23rd and it's the nitromethane that's April 28th.

There was also a rule-making package adopting the MADL for di-n-hexyl phthalate. And it's been submitted to the Office of Administrative Law and we await the Office's decision within the next month.

Earlier this year in March, OEHHA also issued a Notice of Proposed Rule-Making announcing a proposed NSRL for ethylbenzene. Written comments were received, which

we are and will respond to as part of the rule-making process.

Thank you.

CHAIRPERSON BURK: Thank you. And then we have Carol Monahan-Cummings.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. I'll make this quick, because I know you want to get out of here. But I just wanted to update you on two cases that are pending currently in the California courts.

One I believe I mentioned to you last time is a case where Exxon-Mobil Corporation has sued OEHHA and our Director for listing a chemical known as DIDP, diisodecyl phthalate. I don't know if I pronounced that correctly. But in any event, we've administratively listed that under the authoritative bodies mechanism. And they challenged that decision as beyond our authority.

In December of last year, the trial court upheld our authority to list the chemical and Exxon has appealed it. The case is fully briefed. And a hearing on the appeal is set for December the 9th -- I'm sorry, December the 11th in Los Angeles. So the next time you meet, we'll have an update on that.

The other case I'm not sure if I mentioned to you, because it was pretty new at that time, is called Sierra Club versus Schwarzenegger. A coalition of

environmental labor groups that have sued the Governor, the Agency, Dr. Denton and all of the members of the CIC Committee, your sister panel, for failure to list enough chemicals under Prop 65 under the various methods of listing, including the Labor Code mechanism, the Authoritative Body mechanism and the CIC process. They didn't sue you. And they haven't sued over the listing of DART chemicals by you. Although, DART chemicals are covered, you know, under Authoritative Body and Labor Code provisions.

That case is in the trial court in Alameda County and is currently in a fairly early stage. We have a motion pending on December the 9th -- that's why I got confused between the two. They're both in the same week -- regarding whether the Court will order us to list 92 chemicals that have -- that the plaintiffs believe have been identified under the Labor Code as required to be listed in Prop 65. The rest of the case has not been set yet for trial. We're in the discovery phase on that.

Does anybody have any questions on that?

Thank you.

CHAIRPERSON BURK: Thank you. And then finally, summary of the Committee actions and closing remarks by Dr. Denton.

DIRECTOR DENTON: Before I do that, I'd like to

have a clarification on what it is that the Committee is recommending us to do about ozone. I didn't quite get clarity on that. And I know that we may go back and scratch our heads exactly what -- if we come across an article, then we include it in the materials? I'm just not quite sure what it is that you'd like to see on that front.

COMMITTEE MEMBER HOBEL: Well, I just wanted it to be on the radar screen, because it's listed in this particular paper and it's listed in other papers as part of air pollution. And so it's just something that we should be aware of. I only mentioned it for information purposes, because it's going to come up when we start reviewing other papers.

DIRECTOR DENTON: So no real active product that you want to see at this point in time?

COMMITTEE MEMBER HOBEL: No.

DIRECTOR DENTON: Okay. So with that, I'll summarize the decisions of the Committee today.

The Committee decided to list chromium (hexavalent compounds) but not to list chlorpyrifos. They are recommending OEHHA not to prepare hazard identification materials on THMs, but to continue with BDCM and to include chloroform.

They also would like to see hazard identification

materials on particulate matter and particulate matter and sulfur dioxide together in air pollution.

I think that's -- Dotty, you're looking a little quizzical. Is that -- that's maybe a more quicker summary than --

CHAIRPERSON BURK: No, no. I just wanted to make sure. That's what we -- okay.

I'm still about the particulate matter. I think we reversed ourselves on this.

DIRECTOR DENTON: Jim is questioning it, so maybe we ought to take a moment here.

DR. DONALD: Yeah, clarify that.

CHAIRPERSON BURK: We took a second vote on particulate matter. A separate set of materials.

DIRECTOR DENTON: Hazard identification materials on particulate matter and particulate matter and sulfur dioxide?

CHAIRPERSON BURK: No.

COMMITTEE MEMBER WHITE: Just the particulate matter.

CHAIRPERSON BURK: We already have sulfur dioxide in the works. And now we want a separate one on particular matter.

DIRECTOR DENTON: Only.

CHAIRPERSON BURK: Only, but that encompasses

everything about particulate matter and it may overlap in some places.

DIRECTOR DENTON: I misunderstood.

CHAIRPERSON BURK: But we want to cast a broader net than --

DIRECTOR DENTON: See if everybody is awake and still here.

DR. DONALD: We know that in looking at particulate matter, they will include some papers that also address sulfur dioxide in the analysis.

DIRECTOR DENTON: So let me back up. On the particulate matter item, the Committee is recommending us to develop hazard identification materials on particulate matter.

Now, moving on. Of course, I'd like to thank the participants at the meeting today. I'd like to really thank my staff who have spent many, many, many hours, weekends, vacation days working on the documents, which were presented to the Committee today. And so I would like to acknowledge their very hard work. Public service is under assault these days, but we really have just such a superb group of individuals and scientists. And I really do want to acknowledge that so strongly and their support of this Committee.

And, also I would like to thank --

(Applause.)

DIRECTOR DENTON: I would like to thank the Committee for their diligence, for their commitment, for their serious consideration of the matters which come before you. It's always very humbling to be part of this. And so I'd like to thank you all for attending it, for sticking it out and, as always, wishing you, as I always do, a Happy Holidays.

(Laughter.)

DIRECTOR DENTON: With that, I guess the meeting is adjourned.

COMMITTEE MEMBER KEEN: Before we adjourn, I would just like to second, by the members of the panel, that I think that these were not just great reports, but I think this is one of the earliest that we got the reports. We actually had adequate time to review them in detail. And that's not meant as a chastisement for earlier, but to really say that was very much appreciated.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 4:25 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 1st day of December, 2008.

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