MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR./CALEPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

SACRAMENTO, CALIFORNIA

MONDAY, DECEMBER 10, 2007

10:04 A.M.

JAMES F. PETERS, CSR, RPR
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Ms. Cynthia Oshita, Proposition 65 Implementation

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

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Mr. Davis Baltz, Commonweal

Dr. Carol Burns, Dow Chemical

Dr. William Butler, Consumer Health Products Association, Council for Responsible Nutrition, Natural Products Association

Ms. Caroline Cox, Center for Environmental Health

Ms. Teresa DeAnda, Californians for Pesticide Reform

Ms. Lisa Halko, Greenberg Traurig

Dr. Steven Hentges, American Chemistry Council

Dr. Sarah Janssen, Natrual Resources Defense Council

Dr. Daland Juberg, Dow AgroSciences

Ms. Anne Katten, California Rural Legal Assistance Foundation

Ms. Gretchen Lee, Breast Cancer Fund

Ms. Domatila Lemus, El Quinto Sol

Dr. Alan Leviton, American Beverage Association

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Dr. Margaret Reeves, Pesticide Action Network North America

Dr. Jay Murray, Murray & Associates

Dr. Barbara Peterson, Exponent

Mr. Gary Roberts, Sonnenschein

Dr. Jay Schreider, California Department of Pesticide Regulation

Ms. Renee Sharp, Environmental Working Group

Dr. Robert Tardiff, The Sapphire Group

Mr. Christian Volz, McKenna, Long & Aldridge

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PROCEEDINGS

DIRECTOR DENTON: I would like to welcome all of you to the DART IC meeting. Seems that we're always doing this every December. Annual holiday event I guess is the DART IC meeting. But this is a very important meeting today.

And I'd like to start by introducing the members of the Committee. Name plates are in the front, but I do like to introduce the members of the Committee.

To my left is Dr. Dorothy Burk, who is the Chair and will be taking over the Committee in a moment. And she is an associate professor at the University of Pacific.

Next to her is Dr. Kenneth Jones, who is a professor in the Department of Pediatrics at UC Davis -- sorry -- UC San Diego. I'm sorry. UC San Diego.

Dr. La Donna White is a clinical faculty physician at the Methodist Family Practice Residency Program.

And then to her left is Dr. Linda Roberts, who's a senior toxicologist at the Chevron Research and Technology Company.

To my right is Dr. Ellen Gold, who's Chairman of the Department of Public Health Services at UC Davis -- Sciences at UC Davis.

And next to her is Dr. Hillary Klonoff-Cohen. She is a professor at the Department of Family and Preventive Medicine at UC San Diego.

And then to her immediate right is Dr. Calvin Hobel. And he is Vice-Chair of Obstetrics and Gynecology at the Cedars-Sinai Medical Center.

So welcome to all the Committee members and to all of you.

I'd like to make a few opening marks before we get into the agenda. And, that is, that all of us today are experiencing a new process and are in the process of implementing the 2004 prioritization process.

And it's 2007, and it's basically taken this amount of time to work out the epidemiology screen, which has been utilized as the first screen in our prioritization process. And we're essentially following that 2004 document.

What we're doing today is receiving the advice and consulting with the Committee on those chemicals which have passed this epidemiology screen. So I would like to remind all of us, the Committee, the audience, the staff, everyone, that today the Committee is not going to be considering listing the chemicals on the agenda. This is not a listing decision which the Committee is undertaking. Rather it's going to be making recommendations and

providing advice to OEHHA regarding which of these chemicals merit -- from the abstracts, merit taking a closer look at.

So that's the essential purpose of the meeting today.

I'd also like to mention that because these chemicals have come to this Committee does in no way mean that OEHHA is recommending that these chemicals either be taken for further consideration or not taken for further consideration. These are chemicals which passed the epidemiology screen, we provided the information, and we're soliciting the advice of the Committee on how to proceed or if to proceed on these chemicals.

Finally, I'd also like to mention that it's not usual practice for us to limit discussion especially of the participants. It's important that all of the individuals in the audience be heard. And because of the lengthy agenda, because of the importance of some of these chemicals, we have limited the discussion time to five minutes per participant. And I think Dottie or myself will be trying the keep track of that -- will be keeping track of it.

Again, we're not looking at the details of the study but just the general evidence and recommendations from the Committee on whether or not they need to be

further looked at in greater detail.

So that's basically what I wanted to say. And I think at this point, I will turn it over to Dr. Burk for the Committee.

CHAIRPERSON BURK: Good morning, everyone. Thank you all for coming, particularly the Committee members at this always busy time of year. And we are remarkably missing only one member, which is sad, but at least we've got a pretty good group here today.

And as you just heard, we're here to consider these eight prioritized chemicals and to make our recommendations about which ones should move forward in the process, that is, to be considered at a later date for listing. We're not considering today.

But before I go any further, I want to thank the staff for implementing this process. I know it's been a long time coming and it's something we asked for. So we're pleased for all the work that went into making this happen. And it is a novel thing for all of us, so we will see how it progresses.

The way I think we'd like to work this is to take each chemical in alphabetical order so there's no favoritism here. And in each case we'll have a staff presentation, followed by the quick Committee discussion, then public comments, and then further Committee

discussion and a polling as to whether we want to recommend the chemical to go forward.

I think at the end of the day, it would be wise if we would sort of review how the process went, if time permits, and see whether it met our needs.

So I think without further ado, we will start with the first chemical on the list.

Oh, okay. See, I always miss something. So before we start with the first chemical, we will have a process overview from Jim Donald. And he's ready.

(Thereupon an overhead presentation was Presented as follows.)

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION

CHIEF DONALD: Good morning. My name is Jim Donald. I'm Chief of the Reproductive and Ecological Toxicology Section.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION

CHIEF DONALD: I'm going to give just a quick overview -- It seems I've jumped ahead already -- a quick overview of the current iteration of our prioritization process. And in that iteration we have applied an epidemiologic data screen, and I'm going to describe that also. Some of what I present will be a little bit reiterative of what Joan has already said. But hopefully that will help reinforce

some of these important points.

The current iteration of our process is laid out in the document process for prioritizing chemicals for consideration under Proposition 65 by the State's qualified experts that was published in December of 2004. And this current iteration of the process was developed in consultation with members of this Committee and with members of the Carcinogen Identification Committee.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: And the purpose of the process obviously is to identify chemicals for evaluation by the Developmental and Reproductive Toxicant Identification Committee, or DART IC. And our goal is to focus the efforts of this Committee on chemicals that may pose significant hazards to Californians.

And it's important to remember that prioritization to this point is a preliminary appraisal of the evidence of hazard and it is based on abstracts of studies and not the entire study reports.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: The basis for our process is a tracking database that contains chemicals that have been identified from literature searches; suggestions from this Committee,

from other state agencies, from the scientific community, and from the general public. And these are chemicals where we have data -- we have identified at least some data that suggests the potential for the chemical to cause developmental or reproductive toxicity.

The next stage in the process is a list of candidate chemicals which consists of the chemicals from this tracking database for which we have also established there exists some data that suggests the potential for exposure in California.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: And this slide lays out in a simplified schematic the process for prioritizing chemicals. We begin with the tracking database, proceed to candidate chemicals. And at this stage we apply a screen to identify chemicals that will go forward to be proposed for Committee consideration.

We anticipate applying several screens over the next few years. And they will all be based on focused literature reviews. And in a moment I'll come back and discuss this specific screen that we applied in this iteration of the procedure.

The purpose of the meeting today is to consult with the Committee on the chemicals that have been brought

forward for review and based on the recommendations that we received from the Committee, OEHHA will select chemicals for preparation of hazard identification materials.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: And then very briefly, for the chemicals that are so identified, we will conduct what we call a data call-in to allow for submission of any data that we may have missed in our literature searches. We'll prepare comprehensive hazard identification materials containing all of the evidence, all of the relevant information on reproductive or developmental toxicity for each chemical. Those materials will be provided to the Committee and also provided for public review.

And there will be a future public meeting at which the Committee will review the chemicals and make a listing decision. And at that meeting there will be again further opportunity for public comment.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: The epidemiologic data screen that we applied in this iteration of the process was applied to 286 candidate chemicals, with a goal of narrowing that down to a manageable number to bring before the Committee.

We based the screen on online literature database searches primarily of sources such as Tox Line and Pub Med, with a goal of identifying epidemiologic studies that reported an association between exposure to the chemical and increased risk of adverse developmental or reproductive outcome. And this was the criterion that was recommended by both the committees.

The specific criterion that had to be passed through each chemical is that we had to identify two or more analytical studies that we considered to be of sufficient quality based on the information provided in the abstract.

And by analytical studies, I mean studies that were designed such as cohort studies or case control studies. Descriptive epidemiologic studies with case reports alone were not sufficient to satisfy the screen.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: For chemicals that passed the epidemiologic screen, we then conducted further literature searches to identify experimental animal studies. In the course of these searches we also in some cases identified other relevant data such as on the mechanism of action of the chemical or metabolism and pharmacokinetics and we included that information in the materials provided to the

Committee.

It's important to remember that again this a very preliminary toxicological evaluation of the overall evidence of developmental and reproductive toxicity and that it's based on abstracts of the studies.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: So based on this process to date, we have identified eight chemicals for which this preliminary evaluation indicates that developmental or reproductive toxicity may be a concern. These are Bisphenol A, bromodichloromethane, caffeine, chlorpyrifos, hexavalent chromium, DDE, methylisocyanate, and sulfur dioxide.

So for each of the proposed chemicals we compiled the abstracts of epidemiologic studies, experimental animal studies, and other relevant data that we identified during the preliminary toxicological evaluation.

To further assist the Committee in evaluating this information, we also categorized these abstracts into different categories such as those showing effects, those not showing effects, and so forth. And we recognize that there is room for perhaps differing opinions on where some of those abstracts were placed.

These materials were provided to the Committee and released to the public for what was initially a 60-day

comment period that was subsequently extended for another month -- another three weeks. And all the public comments that were received were provided to the Committee prior to today's meeting.

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REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION

CHIEF DONALD: So the purpose of the meeting today is for OEHHA to receive advice from the Committee on the chemicals that should undergo the development of comprehensive hazard identification materials and also to allow an additional opportunity for public comment.

And that concludes my presentation. I'd be happy to answer any questions you have at this point.

CHAIRPERSON BURK: Are there any questions for Dr. Donald?

No?

Okay. Then I guess now we can begin.

The first chemical on the list is Bisphenol A. Staff presentation Dr. Marlissa Campbell.

(Thereupon an overhead presentation was Presented as follows.)

DR. CAMPBELL: My name is Marlissa Campbell and I will be talking about Bisphenol A.

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DR. CAMPBELL: Polycarbonate plastic is a polymer

of Bisphenol A. And polycarbonate products include items such as eyeglass lenses, baby and water bottles, and reusable food and drink containers.

Bisphenol A is also a component of epoxy resins, which are used in products such as dental composites, paints and adhesives, and protective coatings on food and beverage containers.

Next slide.

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DR. CAMPBELL: The epidemiological data set on Bisphenol A includes two analytical studies of adequate quality, which reported increased risk for adverse developmental or reproductive outcomes. These studies measured blood levels of Bisphenol A and examined reproductive function and hormones.

A third study that reported adverse outcomes was considered to be of inadequate quality.

One study reported no increased risk of adverse developmental or reproductive outcomes. And the outcome of another study was unclear from the abstract.

And there were two related additional articles that were also identified.

Next slide.

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DR. CAMPBELL: Sixty-three animal studies of

Bisphenol A reported findings of reproductive or developmental toxicity. These studies used a variety of protocols in species to primarily examine estrogenic effects in males and females.

Thirteen meeting abstracts reported findings of reproductive or developmental toxicity.

Twenty-six studies and four meeting abstracts reported no reproductive or developmental toxicity.

Ninety-one related articles and meeting abstracts were also identified.

And 15 studies without abstracts were identified by title only.

And that concludes this presentation.

CHAIRPERSON BURK: Are there any questions of Dr. Campbell?

Any preliminary discussion? I shouldn't say preliminary. But the way it's stated here, it says Committee discussion followed by public comments and then more Committee discussion.

What we have done in preparation is to assign a lead person on each one of these chemicals to kind of get us going. But I don't know -- the first one will be Dr. Ken Jones. I don't know if you want to start discussing now or if you would like to hear the public comments and then --

COMMITTEE MEMBER JONES: Up to you, Dottie.

CHAIRPERSON BURK: You could set the tone.

COMMITTEE MEMBER JONES: Yeah. Well, I guess that I would just start off by saying that I believe that there is animal data which is of substantial concern regarding male and female reproductive function. And at present I would say that there's very little human epidemiologic data. Clearly there's this study which shows an increase in miscarriage, which looks to me like it's a pretty darn good study -- or recurrent miscarriage.

There are a few other studies which I think are important. But clearly I think the animal data is of far greater concern than is the human study -- the human studies. And when we get into this more completely, I would like, if it doesn't come up before then through public discussion, to go through in a little bit more depth the human studies, because from my perspective at any rate the human studies are of greater significance as far as our recommendation about where to go with this.

But I'd be happy to hear the public comments first.

CHAIRPERSON BURK: Okay. I think, if I can find my list now, we can start with the public comments.

Oh, I lost it already.

No, here it is.

Now, I have people that have already signed up and then I have the cards. So which ones should I use? The cards?

Okay. Well, first up then we have Davis Baltz of Commonweal.

MR. BALTZ: Dr. Denton and Chairperson Burk, members of the Committee. My name is Davis Baltz. I work for a health and environmental research institute called Commonweal. We're located in Bolinas, California.

I'm here today to urge you to vote to prepare hazard identification materials for Bisphenol A. I think that in the comments that we submitted to you during the public comment period, which you have had a chance to review, we submitted a letter signed by 32 separate organizations. They are health -- public health organizations, environment organizations. And significantly there are a number of reproductive health organizations who have joined in signing this letter. And I think it's significant that you have a -- we have a new sort of sector of the public health community who's starting to track Bisphenol A and has significant concerns about the reproductive and developmental toxicity of Bisphenol A.

You know from your literature review that there -- and as Dr. Jones has just mentioned, there is

some animal data that is of concern. And I'd like to just remind everyone that the levels that have been found in the animal studies are levels at which humans already are exposed. The biomonitoring data that we have shows that virtually everyone who's tested has Bisphenol A in their bodies. And as some of you may know, California's new biomonitoring program is just getting launched this fiscal year and, in fact, one week from today will have their first meeting. And this will shed further light on the exposure that we have here in California.

So I think that it's, from our point of view, a prudent step for the Committee to recommend that hazard identification materials are now prepared for Bisphenol A, and again we urge that you take this step today.

Thank you.

CHAIRPERSON BURK: Thank you. And next we have Gretchen Lee of the Breast Cancer Fund.

MS. LEE: Thank you very much. I'm Gretchen Lee. I'm with the Breast Cancer Fund.

The Breast Cancer Fund is the only national organization that focuses solely on breast cancer prevention by identifying and advocating for the elimination of the environmental causes of breast cancer. And I'm encouraged that the Committee has decided to take up the issue of Bisphenol A today.

We strongly urge the Committee to direct OEHHA to prepare hazard identification materials for Bisphenol A.

Every two years the Breast Cancer Fund compiles the evidence on the environmental links to breast cancer in a report called State of the Evidence. With each report the evidence linking Bisphenol A with breast cancer becomes stronger. What is most alarming is that it's the early life in in utero exposures to Bisphenol A that are setting young girls on a path for increased breast cancer later in life.

Exposure to Bisphenol A is widespread. According to a new analysis by the U.S. Centers for Disease Control, roughly 93 percent of Americans have detectable levels of BPA in their bodies. Because of the relatively short half-life of BPA, this analysis suggests that most Americans are exposed continuously to this chemical.

BPA leaches into our bodies through our everyday contact with household products containing the chemical. The following have all been shown to result in an increase of the rate of leaching of Bisphenol A:

The presence of acidic or basic food or beverages stored in cans lined with epoxy resin containing BPA or in polycarbonate plastic, the heating of polycarbonate plastic in plastic containers, and repeating washing of polycarbonate products.

Because the exposure to BPA is so widespread and because it can leach out of materials so easily, including those products that children use every day, and there is extensive scientific literature demonstrating the evidence of harm, we strongly urge you to direct OEHHA to expeditiously prepare hazard identification materials for Bisphenol A.

Thank you.

CHAIRPERSON BURK: Thank you.

Next on the list is Caroline Cox, Center for Environmental Health. Is she here?

No. Okay. We didn't get a blue card, but she -- Okay. So we will move on then to Steven Hentges. I can't pronounce that, but I hope that's close. And I will say that he is representing the American Chemistry Council, which is a group, so we will allow a longer period of time.

What do you estimate?

DR. HENTGES: Within 15 minutes.

CHAIRPERSON BURK: Okay. 15 minutes sounds good.

(Thereupon an overhead presentation was Presented as follows.)

DR. HENTGES: Okay. So, Dr. Denton, Dr. Burk, all the members of the Panel, good morning, and thank you for this opportunity to provide comments to you. We did

provide written comments, which I trust you have had the opportunity to take a look at already. And what I'll do in my presentation today is really cover some of the high points of the written comments.

And who's in control?

Okay. We'll go to the next slide.

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DR. HENTGES: We'll start with prior evaluations of Bisphenol A.

While you're here today to think about whether Bisphenol A is appropriate and necessary to review under Proposition 65, there have been a number of other evaluations of Bisphenol A that have been conducted in recent years.

And the most prominent ones are the four that I've listed on this slide from the NTP Center for the Evaluation of Risks to Human Reproduction and the European Food Safety Authority. Both of those were released this year. A couple years ago the Japanese National Institute of Advanced Science and Technology, which is Japan's largest public research institute. And then before that, a very comprehensive risk assessment was issued by the European Union. That one, although it was issued in 2003, is now in the final stages of being finalized, with that update to be available very early next year.

The only one of these that I'll talk about in any detail for a few minutes is the CERHR evaluation, the reason being that it's the most recent. The other three, there's some information and links in the public comments that you've probably been able to take a look at.

So the only thing in regard to all of these that I'll -- the other three that I'll say is that each of these evaluations focused on reproductive and developmental toxicity, and each of these evaluations consistently show that Bisphenol A is not a selective reproductive or developmental toxicant.

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DR. HENTGES: So we'll take a little closer look at the CERHR evaluation. This is very recent. The final report from the expert panel was released on November 26th. And actually it didn't become available on line until the afternoon of November 27, which was the deadline date for written comments. So because of that, we were not able to fully process it and put a lot of information in the written comments.

The panel members are listed here. This is a very comprehensive evaluation. The written report is in the range of about 400 pages in length. And so it does cover -- the panel did review a very wide range of

scientific information on Bisphenol A.

Some of that information that they found to be the most important were the multiple comprehensive reproductive and developmental studies in laboratory animals that have been conducted. Most prominent of that group are the three multi-generation studies, two in rats, one in mice. In rats, one of those studies is a three-generation study that covered a very wide dose range. Likewise, the mouse study is a two-generation study, also covering a very wide dose range.

All of those three studies were very large scale with large group sizes, in the 25 to 30 range, followed either U.S. EPA or OECD guidelines for these types of studies, and were conducted under good laboratory practices.

The panel also reviewed the NTP continuous breeding study in mice as well as the pair of developmental toxicity studies from NTP in both rats and mice.

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DR. HENTGES: Jumping to the conclusions that the panel reached, based not only just on these animal studies but also based on their review of a very large amount of other scientific information, the panel concluded for reproductive and developmental toxicity the four firm

conclusions listed here under the first four bullets:

Bisphenol A does not cause malformations or birth defects in rats or mice.

Does not alter male or female fertility after gestational exposure.

Does not permanently affect prostate weight.

All of these are at very high doses, up to the very highest doses that were tested in these studies. And at those very high doses, the animals do experience systemic or maternal toxicity.

The panel did conclude that Bisphenol A did change the age of puberty in male or female rats also at a very high dose. And that conclusion is worthy of a couple of additional comments to clarify. The first is that the effects that are driving this conclusion are delays in preputial separation in male rats and vaginal opening in female rats. Bother of these effects are linked or correlated to reduce offspring body weight, which is a result of the very high doses that were tested, doses that result in systemic or maternal toxicity.

These slight developmental delays, however, did not have any apparent functional effect, in particular no effect on the reproductive outcome for any generation in the three generation study in rats, which is the study that found those two effects.

So overall, based on the CERHR evaluation based on these toxicity conclusions, Bisphenol A does not meet the "clearly shown to cause reproductive toxicity" standard used for Proposition 65.

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DR. HENTGES: In addition to the toxicity conclusions, the CERHR panel also assigns concern conclusions, which essentially are qualitative risk conclusions. So These integrate the toxicity information with exposure information. And they're qualitative, because what the panel does is they assign these concerns on a 5-point scale starting with "serious concern" at the top, going down through "concern," "some concern," "minimal concern," and "negligible concern." The panel found no concerns for any endpoint that were rated as "serious concern" or "concern".

For all of endpoints evaluated, with one exception, the highest concern level that was assigned was either "minimal" or "negligible concern". There was only one concern that even made it to the "some concern" level, and that was for neural and behavioral effects. That concern level is also worthy of a couple of additional comments to clarify. That concern level was driven by a small number of small scale animal studies that, to use

the panel's lingo, suggest neural behavioral effects. However, the panel also noted that it was unclear if those observations should be considered as adverse effects. And, in addition, the panel also recognized that there was no definitive data available.

And in addition to these "concern" conclusions, they also identified critical data needs and they identified neural and behavioral effects as a critical data need because there is no definitive data that's available.

Next slide.

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DR. HENTGES: Just to finish up on CERHR, the evaluation process is both scientifically rigorous and procedurally sound. The panel members -- you saw those on a previous slide, probably recognize some of them -- are very highly qualified. The entire process complies with FACA guidelines to avoid any conflict of interest among the panel members. It's an open and transparent process with ample opportunity for public participation. And the final NTP report does represent the official views of NTP.

You may have heard or you may here today about a -- something that the become known as the Chapel Hill statement on Bisphenol A. That's a different review that followed a process quite different from a CERHR process.

In fact, it was quite the opposite of the CERHR procedural guidelines. It was a closed process. Conflict of interest was not controlled. And the outcome of that process is not an official NIEHS or NTP view.

Next slide, please.

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DR. HENTGES: In addition to the animal studies, the CERHR panel also took a look at the five human studies that were identified by OEHHA as part of the epidemiological screen for today's proceedings.

They did of course look at the studies in great detail. And what they concluded is that all five of those studies are of limited utility for human health evaluation. They identified quite a few technical limitations in these studies that limited their utility, including small size, confounders and effect modifiers that were not effectively managed or controlled. A couple of the bigger problems are that there are very significant different time frames for collecting the biological samples for exposure evaluation and occurrence in development of the health effects that were being examined.

In addition, it was subsequently found after these studies were published that the analytical method is unsuitable for measurement of Bisphenol A in biological

samples.

So these studies do not meet the Proposition 65 technical criteria for reproductive toxicity based on evidence in humans. They would be better characterized as exposure studies with descriptive cross-sectional components rather than analytic or epidemiological studies.

So in reality after examining these studies in detail Bisphenol A should have really failed the epidemiologic data screen for prioritization purposes.

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DR. HENTGES: Before I reach the conclusions at the end of this presentation, there's two other areas that I want to briefly highlight, areas that were examined quite closely by the CERHR expert panel. One of these is metabolism and pharmacokinetics, which has been very extensively characterized both in humans as well as in rodents. And this information leads to a prediction that BPA, Bisphenol A should have low toxicity such as has been confirmed in very comprehensive and robust animal studies.

In particular, Bisphenol A has very low bioavailability. It is extensively metabolized and cleared pre-systemically. It's metabolized both in the -- as Bisphenol A passes through the intestinal wall as well

as in the liver. And, in particular, it's metabolized to conjugated metabolites, primarily the glucuronide but also the sulfate, both of which have been shown to not bind to the estrogen receptor. So they do not exhibit estrogenic activity in in vitro estrogen assays.

It's also important to point out that human pharmacokinetics are different from rodents in a very important way. Humans eliminate Bisphenol A in the form of the conjugates entirely via urine. And what that means is there is no opportunity for enterohepatic recirculation. And the result of that is that Bisphenol A has a very short half-life in the body. The elimination half-life is about four hours. It's different in rodents, where Bisphenol A is predominantly excreted with bile, and it eventually comes out with feces. And what that means is that Bisphenol A has very extensive opportunity for enterohepatic recirculation and, as a result, a very much longer half-life in rodents compared to humans.

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DR. HENTGES: And the last technical area to cover that was very extensively reviewed by the CERHR panel is human exposure. There is a very good way to directly measure human exposure to Bisphenol A and, that is, to measure the presence of metabolites, the conjugates

in human urine. That's where all of it comes out.

We now have a very large data set that was very recently published, just a few months ago, by CDC in the form of their NHANES 2003-2004 data set. That data indicates that typical human exposure to Bisphenol A is in the range of about 0.05 micrograms per kilogram of body weight per day. That study included more than 2500 participants, ages 6 to 85. And, by design, the results of this study are representative of the U.S. population.

The results are also consistent with many other biomonitoring studies that have been conducted worldwide, all of which are smaller in scale. This is by far the largest scale study so far.

That low exposure is consistent with the use patterns for Bisphenol A, which were highlighted at the very beginning of this section. There are no consumer products that contain anything more than trace impurity levels of Bisphenol A. Typically less than 50 parts per million is the most you would find in any product made from polycarbonate plastic or an epoxy resin.

And so you would not expect to find very high exposure in the human population. And you don't. It's not there.

To put that in comparison, I mentioned the European Food Safety Authority review earlier this year.

The EFSA panel -- that evaluation was conducted by a panel of 21 scientists from throughout the EU -- established a TDI, a tolerable daily intake, of 50 micrograms per kilogram per day. So typical human exposure is about a thousand times below the TDI established in Europe.

And then the last slide.

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DR. HENTGES: For our conclusions, we do not believe that Bisphenol A should be considered a priority for review by DARTIC and OEHHA. It has been recently and comprehensively reviewed, and those reviews indicate that Bisphenol A does not meet the Proposition 65 standard, the "clearly shown to cause reproductive toxicity" standard.

We also believe that Bisphenol A does not meet the Proposition 65 technical criteria to recommend it as known to the state to cause reproductive toxicity. There are no suitable epidemiological studies. And the multiple animal studies consistently show that Bisphenol A is not a selective reproductive or developmental toxicant.

And then, finally, from a practical perspective, review of Bisphenol A by DARTIC and OEHHA would consume considerable time and effort and likely would duplicate the work of other highly qualified bodies that have recently reviewed Bisphenol A.

So that, just barely within the 15 minutes that I

promised. But I can answer questions if you have any, now or later.

CHAIRPERSON BURK: Are there any questions?

COMMITTEE MEMBER JONES: Yeah. You made the point that there was only one issue that raised concern.

DR. HENTGES: "Some concern", yeah.

COMMITTEE MEMBER JONES: "Some concern". Could you just go over that once more.

DR. HENTGES: Right. That goes back to the Five-point scale. Those are the qualitative risk concerns.

And one for "some concern" was from neural and behavioral effects. And that was driven -- if you dig back deeper into where did that come from, there were a small number -- it was about six small scale laboratory animal studies that, again to use their terminology -- I don't want to put words in their mouth -- but to use their terminology, suggest neuro behavioral effects. But the panel did acknowledge that it was not clear if those observations or those effects were actually adverse effects. And a big part of the problem is that there is -- they did not have any definitive data to evaluate to really be able to interpret that data. So that led to the "some concern" that also, probably more importantly, led to their first critical data need, which is for additional

research in that area.

COMMITTEE MEMBER JONES: Right. I've read quite extensively this report that came out on the 26th of November as well. And I would just like to make the point that -- you know, I think you're playing down the neural and behavioral effect to a certain extent. I mean to say they -- I agree with you, they pointed out that it was a suggestion. But they also came out in their conclusions as saying that there was some concern. And "some concern" was the middle concern that -- they had five levels and "some" was in the middle.

So it's not as though I think that this is negligible or minimal. This is "some concern" that they raised.

DR. HENTGES: Right. And, again, I think it's because of a lack of definitive data, which we would agree with. Additional research is needed in that area.

CHAIRPERSON BURK: Yes, Linda.

COMMITTEE MEMBER ROBERTS: Do you recall what the exposure periods were for those -- the neural or behavioral studies?

DR. HENTGES: I think most of those I'd have to go back and check -- study the study. But I believe most of those were gestational exposure.

COMMITTEE MEMBER ROBERTS: Okay. And you

mentioned critical data needs that they identified.

Are those underway?

DR. HENTGES: I'm sorry. Are they --

COMMITTEE MEMBER ROBERTS: Are there any critical data needs that you're aware of that are in the process of being met?

DR. HENTGES: Probably the answer is yes. They identified eight areas, and undoubtedly there's research somewhere that's ongoing that would hit some of those. But I don't have any comprehensive view of what all might be underway. Those are not -- the CERHR doesn't actually have the authority to require additional testing. So this is more of a research agenda that might be used for grant-making purposes or to suggest research that others might want to pick up on.

COMMITTEE MEMBER ROBERTS: Okay. And is the CERHR report, is that a consensus report or is it one in which that they do sort of a majority opinion and --

DR. HENTGES: I believe it would be called a consensus report, yeah.

COMMITTEE MEMBER ROBERTS: All right. Thank you.

CHAIRPERSON BURK: Okay. Thank you.

DR. HENTGES: Thank you.

CHAIRPERSON BURK: Are there any other individuals that wish to -- okay. I didn't have a blue

card, but --

MS. SHARP: Actually I was supposed to be on your list. I have a nice little e-mail --

CHAIRPERSON BURK: Okay. This is Renee Sharp?

MS. SHARP: Yeah.

CHAIRPERSON BURK: Okay.

MS. SHARP: Thank you for allowing me the time to speak.

So I'm Renee Sharp. I'm a senior analyst with the Environmental Working Group, which is an environmental research and advocacy organization based in Washington DC, with an office in Oakland. And I'm here today to urge you to recommend that OEHHA prepare hazard identification materials for BPA.

You know, just briefly, over the last decade a growing body of science has provided substantial evidence of the developmental and reproductive toxicity of BPA in lab animals at low environmentally relevant doses, and has demonstrated widespread exposures among the public.

And I think it's important to point out that -- you know, of course I'm not saying there's a cause and effect relationship, but that many of the diseases and health conditions linked to BPA in animal studies are common among the U.S. population. And this gives us great concern the BPA exposures may pose significant health

risks to the U.S. population and to pregnant women and to children, in particular.

And in our written comments to you all, we outlined, you know, many of the reasons why we think that OEHHA should prepare hazard identification materials for BPA. So I'm just going a touch on a few.

But before I do, I do think that there's another piece of the CERHR puzzle that needs to be addressed to you all. And, that is, that the review was actually plagued by significant issues around conflict of interest. For example, the House Oversight and Government Reform Committee basically leveled conflict of interest charges on the part of the subcontractor, Scientists International, that conducted the initial literature search and prepared the first draft for that panel. And that contractor was subsequently fired due to those concerns. But the document that they prepared continued to be used by the expert panel.

And it should also be noted that the panel itself lacked BPA experts, and their final draft was found to contain significant numbers of errors of omission and fact upon review by several scientists with BPA expertise.

So I just think that's an important thing to consider when looking at the findings from that review. Though I was glad to hear that you did clarify that they

did identify that there was "some concern" regarding this in utero exposures that led to near behavioral effects.

So moving on to the reasons why you should vote to have OEHHA prepare these materials for BPA. There are more than 60 studies that clearly show BPA-related developmental and reproductive toxicity, including persistent changes to breast tissue and prostate tissue that predispose cells to carcinogenesis in the offspring of exposed animals; neural behavioral changes and germ cell damage in the offspring of exposed animals; and adverse effects on both fertility and the reproductive system in the offspring of exposed animals. And as several people have mentioned, there is also extraordinary widespread exposure among the general public to this chemical. The CDC study showed that 93 percent of the more than 2500 people they tested found -- they found BPA in their urine.

And the fact that BPA has a short half-life in the body actually to me is more of an example of why you should be concerned. Because if you find it in 93 percent of the population it means that we've all been having recurrent ongoing exposures.

Also, that study found that children were found to have higher levels than adolescents, who in turn had higher levels than adults.

And BPA has also been found in breast milk, amniotic fluid, and core blood, indicating exposure to the developing fetus and neonates in addition to older children and adults.

And then, finally, I want to mention a study that EWG itself conducted last spring where we looked at BPA in canned food. And the reason why we looked at canned food is it's thought that this is probably a major source of exposure. And we found that in 56 percent of the 97 cans of name brand fruit, vegetables, and infant formula, we found detectable levels of BPA.

And of all the foods tested, chicken soup, instant formula, and ravioli had BPA levels of highest concern. And when we did our calculations, we found that just one to three servings of these foods -- or any foods with those concentrations would expose a pregnant woman or child to BPA levels that were found to cause serious adverse effects in animal tests.

And when we looked at just the infant formula results and combined this information that FDA had done -- had done in their own testing 1996 on formula, what we found was especially troubling because we found that one of every 16 infants fed ready-to-eat canned formula would be exposed to BPA doses exceeding those that altered testosterone levels, affected neuro development and caused

other permanent damage to male and female reproductive systems in animal tests. And at the highest levels that we found, 17 parts per billion, nearly two-thirds of all infants fed ready-to-eat formula would be exposed above doses that proved harmful in animal tests.

So, finally, I do want to close by reading the consensus statement released earlier this year by a group of 38 independent scientists who have done extensive research on BPA toxicity. And they published a series of four articles in the Journal of Reproductive Toxicology that outlined their conclusions drawn from more than 700 scientific articles related to BPA. And just two sentences of their consensus statement reads:

"The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a cause for great concern with regard to the potential for similar adverse effects in humans. And recent trends in human disease relate to adverse effects observed in experimental animals exposed to low doses of BPA."

So in closing, I hope that you vote to have OEHHA prepare hazard identification materials for BPA.

Thank you.

CHAIRPERSON BURK: Okay. Thank you.

Are there any further speakers on this chemical?

Okay. So seeing none, we'll begin our discussion. And I'll turn it back over to Ken.

COMMITTEE MEMBER JONES: Thank you all for your comments as well from the audience.

I just -- I'm going to be very brief. And I'm just -- I also, as I indicated, read the Center for Evaluation of Risk to Human Reproduction that was put out in November 26th. And I agree pretty much with the conclusions that were made about it.

The conflict of interest issues I knew about. But I've talked to people from the group that in fact did that study, and there's a great deal of disagreement with them about whether there was a conflict of interest. So I don't know about the conflict of interest issues as far as that CERHR evaluation is concerns.

But just to conclude, at least based on my conclusions in terms of reading, first of all, the human data, there really are no studies that have looked at birth defects as a developmental outcome in BPA. There's one study which was indicated shows an increase in miscarriages -- or recurrent miscarriages. There's one study which raises concern based on evidence of maternal blood, core blood, and placental tissue which shows levels of BPA which are similar to animal studies that were associated with reproductive organ problems. There's a

study raising concern based on concentrations of BPA in colostrum.

So there's absolutely no question, as has been indicated, that there are levels of this chemical that are of concern based upon the animal work in humans. There is insufficient data providing information whether BPA causes male or female reproductive toxicity in humans.

Now, it is indicated there's 63 animal studies. And from my perspective, there's more concern here. As far as developmental toxicity, there's obviously a lot of issues that were brought up by the CERHR evaluation that indicate that in animal studies there's not significant developmental toxicity -- or there's not substantial developmental toxicity. However, clearly rodent studies suggests that this chemical causes neuro and behavioral alterations related to disruptions in normal sex differences in rats and mice.

And you can I guess make an issue as to whether this was a moderate concern or whether this was a minimal concern. The issue is that they felt that there clearly was concern as far as this neuro and behavioral alterations.

And then as far as reproductive toxicity, I think -- that at least my reading of this shows that there's sufficient evidence that BPA does cause

reproductive toxicity, albeit perhaps minimal, in both males and females, in both rat and mouse studies.

I would just bring up a couple other things. One of which I would bring up the report that has been circulated from this international conference on fetal programming and developmental toxicity that occurred in the Faroe Islands in May of 2007. And clearly BPA was suggested in that -- from that conference to be of serious concern. And I think that without question the individuals that attended that conference and that came up with the final report from that conference are a pretty impressive group of people, and they certainly have raised concern about this chemical.

I would finally say -- and perhaps everyone here knows this -- but there is a bill that has come up before the California Legislature, Assembly Bill 558, which is called the California Toxics Use Reduction Act. It was brought up by Assembly Member Mike Feuer. And in this bill I think that BPA again was raised as concern and something which should be reduced as far as this Assembly member felt.

So I really think that it is in the best interests certainly of the chemical industry as well as the public that this committee, the DART Committee, take up this chemical and look at it with the possibility that

it is or is not a developmental and reproductive toxin.

I think it would be crazy for us not to do it.

CHAIRPERSON BURK: Thanks.

Comments from other Committee members?

Linda.

COMMITTEE MEMBER ROBERTS: Yeah, I just had a question. Ken, since you've read the report, since the estrogenicity of it has been tested quite a bit, was that not really much of a point in their report?

COMMITTEE MEMBER JONES: No, it isn't?

COMMITTEE MEMBER ROBERTS: It isn't. And that's just related to the sexual differentiation and the neural and the behavioral?

COMMITTEE MEMBER JONES: Yes.

COMMITTEE MEMBER ROBERTS: Okay.

CHAIRPERSON BURK: Any comments, questions from the other end? I keep looking this way.

Dr. Hobel.

COMMITTEE MEMBER HOBEL: I'll just make one comment. And I think this comment really applies to all the materials we're going to be talking about.

Is that we don't understand and know who the vulnerable population is. And that's why epidemiological studies are so important to try to identify who might be vulnerable to this, whether it begins during pregnancy or

maybe before pregnancy. And over the life course of changes that occur, at what point in time does it become important? And it's a timing issue. And I think that's what makes all of these subjects so complex.

And so we have to frame it in a way that we can recommend studies and approaches to provide us better data for us to make reasonable scientific conclusions. And so I think that's how I look at all of these substances.

And just keep that in mind.

CHAIRPERSON BURK: Thanks.

Any other comments?

La Donna.

COMMITTEE MEMBER WHITE: I agree with Dr. Jones with respect to the animal studies versus looking at this in a more human context.

What I'm hearing is most of the animal studies and the repeated exposure of this particular chemical. But I'm not hearing a lot about human adverse effects. And I think that it would be warranted in this case to take a closer look. Yes, I heard the animal studies. Yes, I've read the animal studies. Yes, it is metabolized in the urine. But what does that mean for the communities or potential communities who are exposed? We don't have a lot of data on that. And a closer look needs to be looked at it with respect to humans and the outcomes and the

adverse effects.

I mean the animal models -- the animal studies are great. But really what does that do for a population of people? And it needs to be looked at I think closer with respect to the communities that it affects.

CHAIRPERSON BURK: Any other discussion?

I think one thing we have to keep in mind -- and this is more philosophical than scientific. I think we should be scientific about all this, which is our job.

I'm perfectly comfortable with animal data because that's sort of my background. But of course the idea of this prioritization was to get some human Epi data as well. But the big question I have is if we recommend this go forward and have a hazard identification document prepared, and then we consider it for listing, do you think there will be enough information in there for us to make a decision, that it is clearly a cause? And that's always, you know -- and I'm not saying we shouldn't go forward, because I actually belief we should. I think it's our responsibility to look at the data independently. But I worry about again the time that it takes to do that if we think ahead of time that we'll just be sort of unable to actually ultimately list it because it won't be clear enough.

COMMITTEE MEMBER JONES: Yeah. And I feel the

same way. I don't know. But I think that either way we should be looking at this agent more carefully so that we can say whether we think it should be listed or we think based on a lack of information, which is why we would not list it, I suspect -- based on a lack of information that it shouldn't be listed.

But I think for -- I mean all -- this is a big philos -- let's put it right up front. It's a political issue right now. And this agent is being brought up by all kinds of different people at this point and all kinds of different organizations. And if it's going to be even in the Legislature at this point, I think they deserve to have this group evaluate this agent and say whether it is or is not.

CHAIRPERSON BURK: Good.

Any other comments?

COMMITTEE MEMBER KLONOFF-COHEN: Dottie?

CHAIRPERSON BURK: Hillary.

COMMITTEE MEMBER KLONOFF-COHEN: I have to say that I didn't look at this carefully other than to say that in terms of for the human data, I'm looking at the outcomes of the studies, the seven studies you've got, the ones that are worth looking at. The recurrent miscarriage would be one of the outcomes that's important. And toxicity of reproductive organs of male and female

offspring, there's a good study on that. And then two studies on the relationship between BPA and -- concentrations.

So there is some literature out there on humans, just not obviously that matches the number in the animal studies.

COMMITTEE MEMBER JONES: I have one further question maybe for --

CHAIRPERSON BURK: Go ahead.

COMMITTEE MEMBER JONES: The study that was -- I will just tell you that last March or April, I heard a talk by a woman by the name of Patricia Hunt, who's a distinguished professor at Washington State, in which she talked about damaged -- myotic disruption in aneuploidy in mice in her laboratory at Washington State University that was due to an accident in the -- they finally traced it back to an accident in the laboratory, in which there was contamination of the water supply of the mice with Bisphenol A.

Have you come across that study? I couldn't find it anywhere in the --

DR. CAMPBELL: That sounds vaguely familiar, yeah. I could look through the book and --

COMMITTEE MEMBER JONES: I couldn't find it in the book. But --

DR. CAMPBELL: Is this the one in PLoS P-l-o-s Susaharo?

COMMITTEE MEMBER JONES: It's "Currents in Biology," and she published it in "Currents in Biology" in 2003. I heard her talk about it last year at the American College of Human Genetics meetings.

DR. CAMPBELL: Tell me the name again? Hunt?

COMMITTEE MEMBER JONES: Yeah, Patricia Hunt is --

DR. CAMPBELL: Yeah. Well, she's on at least one of the papers in here. So I don't know. I mean I could dig harder for that particular one, you know, if we were going to go forward.

COMMITTEE MEMBER JONES: Does anyone from the audience know of her work?

DR. CAMPBELL: The story sounds familiar.

CHAIRPERSON BURK: Well, if someone wants to come up and enlighten us. I believe I actually read it in some of the materials that we were --

COMMITTEE MEMBER JONES: It's pretty frightening.

DR. HENTGES: Just a quick comment.

There's a study from about three years ago. And it's in -- it's "Current Biology" is the journal. But if you look at that, you should also look at two papers which have just been published on line in "Mutation Research," I

think is the journal, one from Pacchiarotti. These would not be in the OEHHA screen because they weren't available yet. But Pacchiarotti. And then I think the other one is Eichenlaub-Ritter. Both were conducted by a group of scientists in Europe, research that was funded by the European Union, specifically to follow up on that Hunt study. And what they found is that the results could not be replicated in a series of experiments that were more comprehensive than the original one.

So look at the whole set of data, not just one study at a time, is really what I would suggest.

DR. CAMPBELL: Do you want me to jump in?

If you look at the second abstract in the animal DART studies, that's the one that she is an author on that paper. And it does, you know, address that issue specifically.

That's on early --

DR. JANSSEN: I can also comment on this situation.

My name is Sarah Janssen. I'm with the Natural Resources Defense Council, and I'm a physician and a reproductive biologist.

And Pat Hunt has published several studies on aneuploidy and Bisphenol A, both in rat -- mice and then their offspring. The oocyte sites also have chromosomal

aneuploidy. And if you have problems finding those articles, I'm happy to provide them for you.

MS. SHARP: And I think there's also one other really important -- I'm so glad you brought that up actually -- one other important point to make and, that is, in one of the studies, at least one that looked at miscarriage, they actually looked at -- and they actually looked at the miscarried fetuses to see if any of them were related to aneuploidy. And in fact they found that a greater proportion than you might expect were.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION

CHIEF DONALD: I may mention also -- as I said in my presentation, we conducted focused literature searches. So we were trying to strike a balance between being broad enough to capture all the relevant information and not being so broad that we captured lots of irrelevant studies. So we recognized that there are probably a few, such as this study where aneuploidy is not commonly a reproductive or developmental endpoint, where we simply missed it.

CHAIRPERSON BURK: Good. Good comments.

Any further comments? Are we ready to take our poll?

Okay. Before we do I'm going to read a statement just to remind us of what this vote means.

The Developmental and Reproductive Toxicant Identification Committee is being asked whether any of these chemicals today presented should undergo the development of hazard identification materials and be brought back to the Committee at a future meeting for our consideration in making a listing decision. We are not making any listing decisions at this meeting.

With this in mind, I will conduct a polling of the Committee members for their advice to OEHHA concerning these chemicals.

So the question then is: Do you advise OEHHA to begin preparation of the hazard identification materials for Bisphenol A? All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2, 3, 4, 5, 6 -- 7.

Okay. All those advising no -- I'm assuming 0.

Okay. So that was 7 to 0.

Okay. Good.

All right. The next chemical on the list is bromodichloromethane. And the staff presentation will be given by Dr. Li.

(Thereupon an overhead presentation was Presented as follows.)

DR. LI: Okay. I'm Ling-Hong Li. I'm going to

present evidence available for bromodichloromethane, or BDCM.

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DR. LI: Human exposure to BDCM mainly occurs through drinking water. BDCM is a one of the major trihalomethanes that are formed as byproducts during water chlorination for disinfection.

Next slide, please.

--o0o--

DR. LI: Our literature search identified a total of eight epidemiological studies. Four of them reporting increased risk of adverse developmental or reproductive outcomes. All these four studies are analytical studies of adequate quality.

These four studies investigated the association of BDCM levels in drinking water with developmental outcomes such as birth defects, stillbirth, spontaneous abortion, reduced birth weights, et cetera.

There are four studies reporting no increased risk. In addition, there are two relevant human studies that investigated the effect of BDCM in cultured human placental trophoblasts Next slide.

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DR. LI: With regard to evidence from animal studies, our literature search identified a total of ten

studies, four studies reporting developmental or reproductive toxicity.

Among these four studies, three are developmental studies and one is a chronic study in rats. That study included endpoints for the male reproductive toxicity.

There were six studies reporting no developmental or reproductive toxicity.

There is one meeting report -- abstract reporting developmental or reproductive toxicity.

In addition, there are three relevant studies investigating the effect -- the study effect of BDCM containing mixtures in lab animals.

That concludes my presentation.

CHAIRPERSON BURK: Thank you, Dr. Li.

I assigned this chemical to Linda Roberts. And so, Linda, do you want to get things started?

COMMITTEE MEMBER ROBERTS: Sure.

I noticed that in public comments -- we received three of them -- one of them was a recommendation not to move forward with preparation of a document to consider it for listing, one was to move forward with it for a consideration for listing, and one was to move all the trihalomethanes forward as a group for consideration for listing.

So two out of three people won't be happy no

matter what.

(Laughter.)

COMMITTEE MEMBER ROBERTS: There were the epidemiology studies. Four of them had an association with adverse findings, four without. There's really no data on males.

The exposure side of the studies tended to be measurement of bromodichloromethane in water as well as total trihalomethanes and some of the other components. So it's indirect exposure measurement, but it did actually look at the material in question.

The finding -- they're both positive and negative studies looking at spontaneous abortion and pre-term birth. The related studies were looking at placental differentiation in culture. And the in vitro studies with human placentas indicated that there was an association with decreasing differentiation with the material in exposure and decreasing chorionic gonadotrophin secretion.

Developmental studies were pretty much limited to some findings for still birth and some not finding it. The same thing with intrauterine growth retardation or small for gestational age.

One study looked at birth defects and found that there was an increase in neural tube defects and a decrease in cardiovascular defects, both of which were I

believe statistically significant.

Surprisingly, the decrease in cardiovascular defects looked like a dose response. But neither of them were a particularly strong change in incidence.

The animal studies, there are four with adverse findings and four without. The interesting -- one of the -- as an animal person, so to speak, the interesting part to me is that these seem to be associated with a strain difference. Fisher 344s will have a response, Sprague-Dawley's do not.

The typical guideline type of study for reproduction and developmental toxicity have been clean. The reproduction study was done with the Sprague-Dawley rat. The developmental study was done with the Sprague-Dawley rat. And the rabbit was also negative.

The studies that have used the Fisher 344 strain have found effects. They seem to be -- the most predominant finding is that with exposure the animals either have a total litter loss or they seem to do fine.

So that kind of wraps up the information that was available to us, I think.

CHAIRPERSON BURK: Okay. We have two names submitted to make public comments. The first one is Sarah Janssen from NRDC.

DR. JANSSEN: Good morning, members of the

Committee. My name is Sarah Janssen. I'm a physician with Natural Resources Defense Council. And I'm here first to congratulate you for taking on these eight chemicals for priority review. We're quite pleased that finally your expertise is being used, and we encourage you to consider all of them.

But with exception for bromodichloromethane, we feel it's a special case because it tends to co-occur in the environment with other chlorinated and brominated halomethanes. In particular, chlorodibromomethane, bromoform, and chloroform.

And in the epidemiological studies these four chemicals tend to occur as a group, and it's hard to separate out one from the other. In some cases the statistical association was stronger with one of the THMs over another. In other cases it was hard to separate them out.

So due to the fact that these chemicals tend to co-occur, it's likely that you're going to have a hard time figuring out a single THM in isolation without also reviewing at the same time the scientific evidence around the other chemicals.

So we encourage you instead to prepare the document on trihalomethanes as a group. That way you're not wasting your time looking at these other chemicals at

the same time and then having maybe later on to come back and evaluate them. It gives you a little more flexibility in your scientific evidence and use of your time.

And that's really all I have to say about these, unless you have any questions for me.

CHAIRPERSON BURK: Thank you.

The next speaker is Dr. Robert Tardiff, Sapphire Group.

(Thereupon an overhead presentation was Presented as follows.)

DR. TARDIFF: Thank you very much, members of the Committee, Dr. Denton and Dr. Burk.

I represent the Chlorine Industry. The comments that we submitted and the information that I'm about to summarize for you this morning was information that I'd been working on for many decades now. But I do represent the Chlorine Industry through the American Chemistry Council.

If I could have the next slide, please.

--o0o--

DR. TARDIFF: I want to make a point before talking about the data themselves. The reason that we're dealing with bromodichloromethane is because it is a byproduct of the use of chlorine to destroy infectious organisms that we know produce serious illness in the

population; illness not only to the general population, but also to women of childbearing age and to women who are pregnant and also to their offspring. So this is a pretty serious issue.

And in looking at the evidence at this point, I've tried to summarize here for you the evidence specifically for bromodichloromethane since that's the topic of your main interest.

What we have at this point is based on an examination of all of the literature that's been published so far over the past several decades. We have nine studies that have looked at eight reproductive and developmental measures in epidemiology studies where BDCM was looked at specifically.

There are another 25 studies that have looked at chlorination byproducts in one way or another. And that issue is discussed in our comments.

But in all of those 25, you can't really differentiate between bromodichloromethane and/or any of the other 200-plus substances that are in there. So there's no way to use that evidence as a means for deciding what that might mean for the conclusion that you're looking for with regard to bromodichloromethane and whether or not to proceed with a hazard identification measure.

For six of those eight measures that will look at the epidemiologic -- I'm sorry. For the eight measures that were looked at, six of them have no statistically significant association. Many of those were only looked at in one study. But, nonetheless, we know that for six of them that's the case.

With regard to spontaneous abortion, the so-called seventh one, if you will, we have a false positive study which for a couple of years didn't appear to be false positive until Dr. Savitz and his team, sponsored by the Environmental Protection Agency -- the Federal Environmental Protection Agency, conducted what is one of the most extensive and robust studies of this particular outcome with regard to not only the major chlorination byproducts but bromodichloromethane specifically. And their exposure assessment was so extensive that it basically demonstrated not only that there was no association, but there was such a close correlation with the exact dosimetry of these women that one could make the judgment that indeed the first study was no doubt a false positive one.

And they even went so far as to recommend, much to my surprise, that the degree of information that they had now with regard to this compound and with regard to other -- some of the trihalomethanes didn't require any

further epidemiologic investigation. They didn't say, no, don't do any more research, period. But with regard to that, that was the case.

Finally, neural tube defect was a source of considerable concern for a while. And what we have is we basically have two studies. One is a case control and the other is a cohort study. The one was positive and the one was negative. So we have an equivocal set of information here. We can't tell whether one is necessarily better than the other. The case control was really fairly strong, even though there were a few individuals that were looked at. But, indeed, the cohort study had many more subjects associated with it.

So at this point we really can't tell.

The toxicology information is I think a bit more clear-cut. We've got state-of-the-art investigations that we've done on reproductive toxicity -- two generation reproductive toxicity in rodents, as well as a developmental toxicity study, which were done with the latest and greatest designs, increasing number of animals that were included in there. And what we have with those is an indication that there is maternal toxicity at the highest doses. And that maternal toxicity led to some fetal toxicity, but it didn't lead to any kind of impairment of fertility. Nor did it lead to any degree of

structural malformations.

And because the fetal toxicity was associated with a secondary phenomenon, namely maternal toxicity, it's felt that that's not really suitable for judging the hazardous properties of this material.

Now, in our business in toxicology and in risk analysis, one of the things we look for is what's the margin of exposure between a no-observed adverse effect level in a laboratory animal and what people are exposed to on a daily basis. And we certainly have good information about human exposures. And basically what we find is the margin of exposure is no less than 5,000, and can be up as high as 70,000, which would suggest that there probably is no reason for concern for this particular set of adverse consequences.

Now, there were three other studies that I wanted to mention. And they were studies of what we call hypothesis generation. Some of them were in vitro studies. And all of them were unusual inasmuch as people were looking for ways in which to find out whether or not at very high doses, doses that are physiologically unrealistic -- you can't reach these concentrations in an in vivo setting in humans -- but it's interesting to determine whether or not there may be certain hormonal influences that might be altered as a result of these

unusual events.

Those studies are not the kind of studies that the World Health Organization, the Environmental Protection Agency, or even California has said you could possibly use to define human hazards, much less human risks.

Could I have the next slide, please.

--o0o--

DR. TARDIFF: Basically the conclusion from all of this is that there isn't any evidence to clearly show that bromodichloromethane is a reproductive toxicant in either animals or laboratory -- excuse me -- in humans or laboratory animals; that basically there isn't any basis for reaching that determination. And that conclusion -- that set of conclusions is consistent with what the World Health Organization has said over the past several years, as has the U.S. Environmental Protection Agency.

I might also mention -- and I know it's not part of your charge. But there clearly is an indication under Proposition 65 that drinking water and the constituents of drinking water, which are not added to the drinking water per se, are actually exempt from Prop 65.

And then, finally, I think the public health issue. If there's an unfair warning that is issued to women of childbearing age, women who are pregnant, that

might impede their ability to consume drinking water when the entire OB/GYN community says how important it is to consume water prior and during and even after pregnancy, I think it would really be a great misfortunate if we were to mislead them into suggesting, with virtually no foundation, that this might be a hazard. And for that reason I think that the Committee should vote to simply not proceed any further with the hazard identification.

And with that, I would conclude my comments. And if you have questions, I'd be happy to try to answer them.

You can turn the slides off if you want.

CHAIRPERSON BURK: Any questions?

Actually I missed one thing. What did you say about exemptions for drinking water?

DR. TARDIFF: Oh, for drinking water there's are -- why don't you throw up the next to the last slide, I think it is. I've got the citations out of Prop 65 that basically says that drinking water is exempt. And I don't remember the numbers. I apologize. I'm sure Joan would -- Dr. Denton would know them.

CHAIRPERSON BURK: Well, maybe Carol could --

DR. TARDIFF: There we go.

It's Section 12502 250249.11. It talks about the exemptions for drinking water.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think

it's important to note here, as you'll also hear from some other commenters, about warnings and things like that, that the issue of providing warnings or who is subject to the warning or discharge requirements under the act is really -- it's a very premature question, when all we're doing today is deciding whether or not to proceed with preparation of materials. We're not listing. We're not -- you know, and even at the point of listing, it's not really something that this Committee needs to concern itself with. There's regulations. There's statutory provisions that can guide people on whether or not they need to provide a warning and whether or not they can discharge.

So I don't really think that that's a relevant issue before the Committee today.

CHAIRPERSON BURK: Yes, thanks. I do agree. We're here to discuss the science, not the other issues.

So are there -- do you have anything else you want to say, Linda? And then we'll open it for other comments.

COMMITTEE MEMBER ROBERTS: Well, maybe just one point of clarification from my colleagues. When there is a maternal no-effect level in an animal study that's lower than what you see for a development on no-effect level and the developmental effects look like they could be

secondary to reductions in body weight gain, reductions in water consumption and what have you, I think that's what I put down as negative. There was nothing that was jumping out as being a developmental toxicant. The total litter loss on the Fisher 344 is clearly not related to reduction in body weight. It's not that kind of severe toxicity. It's a strain difference there. Just to clarify what I mentioned earlier.

CHAIRPERSON BURK: But do you place any significance on the strain difference?

COMMITTEE MEMBER ROBERTS: I called -- well, much of the work with the Fisher 344 has been done in the laboratory of Michael Narotsky in North Carolina. And I phoned him on Friday to ask him what he thought which one might be more similar. And he declined to make a suggestion about that. But he found it very interesting, and he was interested in looking further in additional research in the future at probably the total trihalomethanes or at least the mixture of them as opposed to specifically bromodichloromethane.

DR. TARDIFF: If I may make the comment, one of the difficulties that we have with this database is the fact that we have very limited metabolism information and very limited kinetics. We don't have a full-based PBPK model, for example; and we actually in our organization

generate those, maternal fetal and PBPK model. They give us a chance to really know what to extrapolate to humans and what not to.

And in addition to the negative information that exists there, the absence of information really I think doesn't make it persuasive on my part to think that this should really move forward in any tangible way.

Thank you for your attention.

CHAIRPERSON BURK: Okay. Thank you.

So do you -- first I'll say, does anybody have any comments on this one?

MS. SHARP: Can I make a comment?

CHAIRPERSON BURK: Yes. Well, okay.

MS. SHARP: It's really quickly. I'm Renee Sharp, EWG again.

I think there's clearly significant, you know, both Epi evidence and animal tox evidence to warrant a closer look at this chemical. And either this chemical alone and/or in conjunction with other THMs.

But I think the other thing that is really important to note is that again, like Bisphenol A, the exposure to this chemical is enormous. Right? Millions of Californians are being exposed to this chemical. It's not like some obscure lab chemical or, you know, whatever. So I just think that's an important thing to consider.

You know, if you're sort of leaning, like, well, maybe, maybe not, you know; this is a case where it's, like, okay, well, you know, erring on the side of caution would be an especially important thing to do here.

Thank you.

CHAIRPERSON BURK: So, Linda, do you want to give -- I don't know -- Do you want to give us your feelings on this?

COMMITTEE MEMBER ROBERTS: Sure.

CHAIRPERSON BURK: Basically I guess what I'm getting at for my own mind, the idea of looking at the total trihalomethanes makes a bit of sense to me. Because I just don't think, knowing how we work, that this amount of data is likely to make things clear enough for our standards. But that's not saying that we shouldn't go forward with it. I just think that maybe -- would it be stronger if we looked at it as a group?

COMMITTEE MEMBER ROBERTS: Well, I think we don't know because that wasn't the way it was presented to us for today.

In looking at this, I tried to look at whether or not we would have sufficient information to make a decision if it was pulled forward. And on the basis of looking at the abstracts that were put together from the developmental endpoint, I think it would be doubtful that

there would be a pressing -- that there would be sufficient evidence to convince us that something would be listed if it was brought forward.

And the same for the male reproductive endpoint, because there's virtually nothing there. There was the one animal study that had a reversible finding and nothing that was functional in the repro study that was done with it.

It would come down to the female. And as -- I don't know if it was mentioned in the comments or if it was mentioned in the staff report. But I guess trihalomethanes are regulated as a group as opposed to, you know, per individual material.

So I think what I would personally like to see is a prioritization screen put together for the trihalomethanes as a group for us to make a determination on that. Because what we were asked to do was make a decision about bromodichloromethane. And I think it does not persuade me to go forward with it as bromodichloromethane. But I might feel differently about looking at a similar data set for the total trihalomethanes.

So that would be my recommendation, not to proceed with listing. Not to say that we're not going to list it, but to request instead that we move to the

trihalomethanes as a group.

CHAIRPERSON BURK: And let me just clarify too. Your recommendation would be not to move forward on bromodichloromethane but to recommend a screen for the total trihalomethanes -- not a hazard identification document --

COMMITTEE MEMBER ROBERTS: Correct.

CHAIRPERSON BURK: -- right, a screen, because we haven't seen the abstracts that would fall out.

COMMITTEE MEMBER ROBERTS: Which I suspect are going to -- it would look very much like what we have right now, but it would be focused on the total trihalomethanes as opposed to the focusing on the Bromodichloro.

CHAIRPERSON BURK: Yeah, because many of the abstracts we read are looking at multiple products.

Any comments down on this end?

Anything about the epidemiology?

COMMITTEE MEMBER HOBEL: One quick comment.

Recently there's been a lot on NPR about using toilet bowl water recycling, and especially in Orange County, and some of that being put back into the drinking water as compared to golf courses.

Is there any data available on this substance in that type of water product, and whether that's been tested

or not?

DIRECTOR DENTON: Ling-Hong, do you know anything about Dr. Hobel's question?

DR. LI: Sorry. Could you repeat your question again, Dr. Hobel. What's your question again? Could you clarify your question?

COMMITTEE MEMBER HOBEL: Yes. Orange County is now recycling sewer water. And through a very careful process as reported on NPR, that it's okay water and it's being recirculated into a certain segment of the population as compared to what it used to be used for golf courses -- watering golf courses. And I just wondered whether or not this substance has been tested in that type of product.

DR. LI: We did a literature search for NPR tox data. We did not look for an extensive exposure data. Sorry. No, I don't have any knowledge.

CHAIRPERSON BURK: Okay.

COMMITTEE MEMBER KLONOFF-COHEN: I just want to talk about the four studies that found something.

Just looking at them one by one. The first one by Dodds had a very large sample, 49,842. And they determined that the BDCM exposure of 20 micrograms per liter or more was associated with an increased risk of neural tube defects, with a relative risk of 2.5.

The next study was by Wright, et al. And it was a retrospective study. They examined 196,000 infants to examine the effects of third trimester exposure on various indices. And they observed reductions in mean birth weight 12 to 18 grams for maternal DHM exposures greater than 90th percentile compared to the 50th percentile.

The third study was by King, was a retrospective cohort. And they talked about the strongest association was observed for a BDCM exposure where the risk doubled for those exposed to a level of greater than 20 micrograms again per liter compared to those exposed to a level of less than 5 with a relative risk of 2.

And the last study was by Waller -- this was a prospective study. And they examined the exposure on THM and spontaneous abortion of 5,144 pregnant women in a prepaid health plan. And they found that women who drank greater than five glasses per day of cold tab water containing greater than 75 micrograms per liter of TTHM had an adjusted odds ratio of 1.9.

So those are the four significant studies.

CHAIRPERSON BURK: What's your feeling on the Savitz study though, the one that -- since we just heard that that was such a great study.

COMMITTEE MEMBER KLONOFF-COHEN: It's an awkward question since he was my dissertation advisor.

(Laughter.)

CHAIRPERSON BURK: Won't put you on the spot then.

COMMITTEE MEMBER KLONOFF-COHEN: I have to say I'd find it hard to believe that Dave would say not to do other studies to confirm his findings. He's just not that type of scientist.

So to be honest, I've looked at the abstract. I haven't actually seen the entire study for him.

CHAIRPERSON BURK: No. And as a matter of fact I mean I think the only fair thing in our whole deliberations today are that we've only seen abstracts. We're not really able to evaluate the quality of the studies without seeing the entire study.

So what's your thought? Would this be -- would the four positive, would that be enough for you to consider it?

COMMITTEE MEMBER KLONOFF-COHEN: Well, I think when I look at it, obviously the sizes of the samples are quite large for epidemiologic studies, very large actually. And so certainly -- obviously just looking at abstracts it's hard to say. But there are four statistically significant studies that seem like from the abstracts that they may methodologically be sound. However, that's really difficult to tell from an abstract.

So I'm just saying that perhaps it's worth a look from the epidemiologic point of view.

CHAIRPERSON BURK: And do you have any feeling one way or the other about looking at the individual or the total group?

COMMITTEE MEMBER KLONOFF-COHEN: Can we do both?

CHAIRPERSON BURK: Well, I mean I guess -- I guess that's possible.

I mean we're going to be taking a poll as to whether we should proceed with this one in particular. And then I suppose we could follow up with, you know, requests for a screen for the group.

COMMITTEE MEMBER KLONOFF-COHEN: I'm just looking. Just give me a couple seconds to look and see in terms of their results.

CHAIRPERSON BURK: Yes, Linda.

COMMITTEE MEMBER ROBERTS: I can pass down all the papers except the Waller. I'm not the Epi person, but I can -- you know, so I should not be the final say on this sort of thing. But I can pass them down if you'd like to take a look at them.

COMMITTEE MEMBER JONES: Linda, was there a prospective study that was negative for neural tube defects? Because this second paper -- I thought this gentleman indicated that there were two studies, one which

showed an increase and one that showed a decrease of neural tube defects.

The only one that I can see is the one by Dodds that shows the increase for neural tube defects, which seems retrospective.

COMMITTEE MEMBER ROBERTS: Yeah, that was the only one that I had for specifically birth defects.

Can you address that, please?

Could you come forward, please.

DIRECTOR DENTON: Bob, you need to come forward.

DR. TARDIFF: The first author's name is spelled K-l-o-t-z and the second author is P-y-r-c-h. And they published in 1998. I don't have the full citation with me at the moment. But it is in our comments.

DR. KAUFMAN: I believe that's an unpublished paper. I'm sorry. It's not published in the open literature. It was a study done by ATSDR. There's a subsequent publication that came much later from them that hasn't been included because it wasn't at the time of our screen.

COMMITTEE MEMBER JONES: And is that a prospective or a retrospective study?

DR. TARDIFF: That was a retrospective study.

DR. LI: Could I add a little bit on that study?

We looked at the abstract of that study. Dr.

Farla Kaufman did the Epi search. We did look at the abstract. And the BDCM was not initially in the abstract. And if you read that abstract, it's about THM and its association. And some were -- you know, reduce the -- alter the endpoints, some didn't. So that's why that abstract is not in the pile in the document that was sent to you.

CHAIRPERSON BURK: All right. Well, that explains that, because you're looking for that specific one.

DR. LI: Correct.

CHAIRPERSON BURK: So if you were to screen for the total group, that paper would have shown up?

DR. LI: It should.

COMMITTEE MEMBER KLONOFF-COHEN: Dottie?

So all four studies -- yeah, I just looked. All four studies found an association somewhere, talking about the results between BDCM and birth abnormalities.

CHAIRPERSON BURK: Pardon me?

COMMITTEE MEMBER KLONOFF-COHEN: All four studies described BDCM --

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER KLONOFF-COHEN: -- and those different endpoints.

CHAIRPERSON BURK: Yes. No, I'm clear on that.

COMMITTEE MEMBER ROBERTS: To address Ken's question just a little bit.

Dodds, King both used the same database. Those are retrospective.

Wright used birth certificates. So that's retrospective.

Savitz, it appears to be prospective in terms of soliciting pregnant women and exposures at the same time. It's also a smaller group size.

CHAIRPERSON BURK: Okay. Is there any further discussion?

Ellen.

COMMITTEE MEMBER GOLD: I concur with my epidemiologist colleague here on the right. But based on the epidemiologic evidence, I think I would actually advocate going forward with the investigation as to whether we should list.

I guess where I'm a little more unclear, and I'd appreciate more input from my colleagues, is with regard to the trihalomethanes as a group. And some of it came up in this. But we haven't actually asked for a search of that. And I'm wondering if maybe that's what we ought to do in addition.

CHAIRPERSON BURK: Yes, I think that's sort of been suggested, that we -- we make a decision on the one.

COMMITTEE MEMBER GOLD: Right.

CHAIRPERSON BURK: And then we could always make a request that the next screen that's done, look specifically at that, and give us those abstracts.

I don't know if that's legit. But I mean we can always ask, right?

DIRECTOR DENTON: Oh, it's certainly legitimate. In fact, one of the items at the end of this is other chemicals proposed for Committee consideration and suggestions, as well as I think Jim will be describing. As far as the next screen, we probably will do another epidemiology screen anyway and could certainly consider THMs if the Committee so desires.

CHAIRPERSON BURK: I got it. I have to find my sheet.

Now, I don't have to read the entire thing again. We know we're just recommending preparation of hazard identification documents.

So the question to the Committee is: Do you advise OEHHA to begin preparation of the hazard identification materials for bromodichloromethane?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: Okay. I count three.

Four?

Oh, okay. Four. Okay.

And all those advising no, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: Okay. So that's three.

4 to 3.

I think -- I don't know if there's a rule on this. Does it take five for it be -- it's only a recommendation, so you can decide what you're going to do with it.

CHIEF COUNSEL MONAHAN-CUMMINGS: The rule when you're making a listing decision is it has to be at least five. But when you're giving advice, you know, a simple majority is fine.

CHAIRPERSON BURK: Okay. We're getting ready for a big chemical, so the suggestion has been just to take a five-minute break. And then we'll start in with caffeine.

(Thereupon a recess was taken.)

CHAIRPERSON BURK: We're ready to get started again.

And I've been asked to remind the Committee members, as always, that when you speak, please speak directly into the microphone so that you can be heard.

All right. The next chemical up for consideration is caffeine.

And the staff presentation will be by Dr. Farla Kaufman.

(Thereupon an overhead presentation was Presented as follows.)

DR. KAUFMAN: Thank you.

As mentioned, my name is Farla Kaufman. And I will present the extent of the evidence available for prioritization of caffeine.

Next slide.

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DR. KAUFMAN: Caffeine is a psychoactive compound naturally occurring in or added to numerous products such as coffees, teas, chocolate, soft drinks, and over-the-counter pharmaceuticals.

Consumption is widespread in California as well as in most parts of the U.S. and the rest of the world.

Next slide please.

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DR. KAUFMAN: Due to the abundance of literature, the epidemiologic data considered for this prioritization process only includes studies published in the past ten years. If caffeine progresses to the next stage, then all of the published data will be included in the preparation of hazard identification materials.

The epidemiologic data included 32 studies

reporting increased risk of adverse developmental or reproductive outcomes. Most of these studies looked at caffeine intake as an exposure measure. While the majority of studies reported adverse outcomes such as spontaneous abortions, decreased fetal growth and birth weight. Other outcomes included shortened gestational age, decreased fecundability, and fetal death.

Thirty of the 32 studies were analytical studies considered to be of adequate quality. One meeting abstract also reported increased risk of adverse developmental or reproductive outcomes. Eighteen studies reported no increased risk. There were two studies with unclear findings and three related studies.

Next slide, please.

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DR. KAUFMAN: The animal data included 52 studies reporting developmental or reproductive toxicity. The reproductive studies reported effects on fertility and other endpoints in males and females. The developmental studies included a wide range of effects such as neural tube defects, decreased brain weight, ocular abnormalities, intrauterine growth retardation, skeletal and dental abnormalities, as well as altered behavioral development.

There were five studies reporting no

developmental or reproductive toxicity. Twelve other studies had unclear outcomes. And there were 63 related articles and meeting abstracts.

That concludes the presentation for caffeine.

CHAIRPERSON BURK: Thank you.

I have asked Hillary Klonoff-Cohen to be the lead person on caffeine. So I will turn it over to her.

COMMITTEE MEMBER KLONOFF-COHEN: After reviewing the articles face significance I found that 30 studies actually found a significant association of caffeine with a reproductive or developmental outcome. The most common outcomes with significant associations were spontaneous abortion or miscarriage, where there were 11 out of 18 studies.

I'm going to start with the miscarriages. And there were actually two cohort studies, nine case-control studies, and one nested case control study. And I'm just going to go through some of the studies and give some of the pertinent results.

Starting with Karypidis, with a population-based case control study. And he had 507 cases and 908 controls. And basically he was looking at CYP1B1 Val Val. And the adjusted odds ratio was 100 -- excuse me -- odds which was 2.63, looking at 100 to 299 milligrams per day.

As well, greater than 500 milligrams per day he

found an odds ratio of 3.61.

And he adjusted for age, smoking, alcohol, parity, miscarriages in the past, and pregnancy symptoms.

The next study by Khoury looked at women with type 1 diabetes and prenatal smoking, caffeine consumption. He found an association with spontaneous abortion. There were 191 pregnant women. And it was a significantly increased risk for spontaneous abortion with an odds ratio of 4.5.

Giannelli, which she wasn't in the table but was described in the abstract, found that if you consumed caffeine during pregnancy there was an odds ratio of 1.94 that was statistically significant if they consumed 301 to 500 milligrams per day and an odds ratio of 2.18 if they consumed greater than 500 milligrams per day.

There was a little less of an effect for pre-pregnancy.

The next study by Rasch also found an odds ratio of 2.21 for greater than 375 milligrams per day.

Signorello in 2001 used 101 spontaneous abortion with normal karyotype and 953 controls. There were pregnant women at 12 -- looked at 6 to 12 weeks gestational age -- weeks. Sorry. And he found with the high CYP1A2 activity the odds ratio was 2.42, as well an odds ratio of 3.17 for greater than or equal to 300

milligrams per day of caffeine for women with high CYP1A2.

The next study by Wen looked at a population based -- they're primarily middle class white women and found in a significant association between spontaneous abortion and caffeine after nausea started during the first trimester, with a risk ratio of 5.4.

Then the next study by -- I believe it's pronounced Cnattingius -- found a significant increase in spontaneous abortion in non-smokers consuming greater than or equal to 500 milligrams per day. Klebanoff actually looked at serum paraxanthine concentrations. And he found an odds ratio of 1.9 for spontaneous abortions for greater than 1845 nanograms per mill of serum paraxanthine.

Then there was Parazzini, which was a case controlled study in Italy. And he looked at duration and found that greater than ten years duration of drinking during pregnancy he found an effect. And as well he also looked at quantity at two to three cups and greater than four cups and found an effect.

And last of all, there was a meta-analysis which of course pools basically all the good and the bad in studies. So we have to look at that with a lot of scrutiny. And they found a moderate to heavy caffeine consumption during pregnancy on spontaneous abortion was small but statistically significant, with 1.36.

So that was the first endpoint I wanted to talk about.

The next end point I'll talk about very quickly is small for gestational age and low birth weight. And that was a study by Vik in 2003. And he found that high caffeine intake increased pregnancy risk. And he used food records -- three-day food records and looked at the second and third trimesters.

And moms who had small for gestational age infants had higher caffeine intake in the third trimester. And the odds ratios were anywhere between 1.9 to 2.3 to 2.7. The 1.9 was not statistically significant. But the 2.3 was for 205 to 309 milligrams per day and the 2.7 was for greater than 310 milligrams per day.

Bracken's study didn't use odds ratios. But he basically found that the mean birth weight basically reduced by 28 grams per 100 milligrams of caffeine.

As well, Klebanoff also didn't use any odds ratios. And he was looking at serum paraxanthine concentrations. And he found that woman who gave birth to small for gestational infants did have a difference of 754 nanograms per mill compared to normal growth infants of 653.

Eskenazi's study was a retrospective population-based study on 7,855 live births. And found

for preterm deliveries, those who consumed both decaffeinated and caffeine had an adjusted odds ratio of 2.3.

And then there was also the meta-analysis by Fernandes that found an effect, but actually didn't adjust for maternal age smoking or ethanol use. And they found an effect of 1.51.

And the Santos study who found significant decrease in mean birth weight.

So I think I could go on and on in terms of that.

And then I'm going to just talk for a few seconds about another endpoint, and that is the fetal death. And there were three studies worth mentioning. And they were Matijasevich, who found a significant increased risk of greater than 300 milligrams per day of caffeine resulted in an increased odds ratio of 2.33 for fetal death.

Another study by Bech, who found that coffee consumption during pregnancy was associated with late fetal death. And he used hazard ratios, and they were statistically significant.

And, let's see. Wisborg, who found that coffee consumption during pregnancy increased the risk of still birth. And he found an odds ratio of 3.0 for still births when consuming greater than eight cups per day during pregnancy.

And then there was, last of all, an IBF study that found not achieving a live birth was associated with usual caffeine consumption. They had odds ratios of 3.1 and 3.9. And consuming caffeine on the week of the visit odds ratios were 2.9 and 3.8.

So looking at the various study designs and sample sizes and the exposure assessments and looking at the timing of -- and the quantity and the frequency and the duration of the caffeine and the definition of the outcome and the actual size or magnitude of the odds ratios and relative risks, and if they adjusted for potential confounders as well as the strengths and limitations and of course the sources of caffeine, and looking across studies -- and of course it's hard when you're looking at abstracts, although I did try to get most of the papers -- I believe that we should definitely take a further look because there are certainly a body of strong studies.

CHAIRPERSON BURK: Thank you. Very nice. You didn't mention your own name there in that one.

Anyway, any comments before we go to the public comments?

Linda.

COMMITTEE MEMBER ROBERTS: One question. But I noticed that, at least when I was going through the

abstracts, it appeared that often caffeine was on the basis of coffee, tea or cola consumption. The one study that looked at decaf versus caffeinated seemed to have an increased risk with consumption of decaffeinated coffee. And I wondered if that one argued towards coffee potentially being harmful when it's in larger amounts as opposed to specifically caffeine

COMMITTEE MEMBER KLONOFF-COHEN: Are you trying to say that we should just look at the studies that were consuming coffee or -- I'm not sure what you're saying.

COMMITTEE MEMBER ROBERTS: No, I'm just trying to ask if -- it appeared, and maybe I'm wrong -- I mean these are the animal -- I mean the human studies. I don't think animal has any questions about it. But it appeared that these were surrogate measures on the basis mostly of coffee. And we're assuming that it's the caffeine in the coffee. But coffee contains other materials. I'm not familiar with the data. I don't know if any of those other materials have been examined for any other reproductive or developmental endpoints. I'm not even familiar with all the constituents in coffee.

So I'm posing the question as to whether or not there were other exposure considerations that could be influencing the information that's in the database.

COMMITTEE MEMBER KLONOFF-COHEN: The majority of

the studies actually -- they talk about caffeine, but they do actually focus on coffee. I can say that our study actually focused on coffee and tea and chocolate and medications and soft drinks, and found effects. And there are other studies in there that do.

The study that was on decaffeinated and caffeinated coffee actually is a very nice study that actually does support looking further at coffee -- caffeine rather.

CHAIRPERSON BURK: All right. We have quite a number of public comments. So hopefully we'll limit each one to five minutes or less.

The first up is Gary M. Roberts representing Sonnenschein

(Thereupon an overhead presentation was Presented as follows.)

MR. ROBERTS: Members of the Committee, thank you very much. My name is Gary Roberts. I am with Sonnenschein. I'm representing the American Beverage Association today. And I want to identify for you the top three points that we have.

Next slide please.

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MR. ROBERTS: And I also want to speak on behalf of two scientists who could not be here today, but whose

comments I think are very important.

The first thing that is important for you to hear from us is that we do not believe that caffeine has been clearly shown to cause reproductive toxicity, and that Doctors Leviton and Murray will be addressing that in greater detail.

The second point that is very important for you to consider today and for you to respond to is, if caffeine is listed, OEHHA has told you in the September 7 notice that it provided to you and that it provided to the public that there would be no warnings on coffee but there would be warnings on products containing manufactured caffeine such as soft drinks.

That is an issue that is appropriate to address today. OEHHA said it was appropriate to address today by mentioning it in its notice. And the whole purpose of this meeting and the purpose of your input is to advance public health. There's a lot of information that we want to provide to you about how it would not advance public health to move forward with an evaluation of caffeine.

The first is that, as Dr. Petersen will tell you in more detail, coffee exposure accounts for approximately three times more exposure than exposure from soft drinks.

The second thing is that when we analyzed through consumer research the effect of a Proposition 65 warning

on cola in the absence of any communication on coffee, confusion and misperception not surprisingly resulted. Dr. MacInnis will provide the details of that to you.

So we believe that moving forward with caffeine would be a step back for public health.

One of the scientists who could not be here today is someone who may be familiar to some of you, former FDA Commissioner Dr. Schwetz, who also is a specialist in the area of reproductive and developmental toxicology.

Dr. Schwetz in his letter to you, which he asked us to reiterate today, included in his comments, "The best of intentions of regulators sometimes cause the public to draw conclusions that are not in their best interests. This could happen in at least two ways with caffeine.

"The first relates to listing caffeine for further review under Prop 65 when the large data set does not really warrant such a review, raising a level of concern among the public that is not necessary or advisable."

And I footnote that there is -- it is obviously a consideration that there will be a public impact of even a decision to move forward here that the Committee should consider.

The second issue that Dr. Schwetz noted, and I quote, "The second issue about a further review of

caffeine-related risks is the problem that a distinction could possibly be made between the risk of caffeine from natural sources versus the risk of caffeine from other sources. To suggest a higher risk from lower sources of exposure through inconsistent placement of warnings is contrary to good public health practice."

So that's the comments from Dr. Schwetz.

The third point that we want to be sure that you hear today is the point that to provide a Proposition 65 warning on soft drinks or other products that contain caffeine that are not exempt, as OEHHA has stated coffee would be, would communicate to women that moderate amounts of caffeine is not safe. And the consistent message from health care providers is that moderate amounts of caffeine is safe.

And one of the things that we would like to share with you, which we did in our comments, is the groups that have expressed, including quite recently, the opinion that moderate consumption of caffeine is safe:

The American College of Obstetricians and Gynecologists; the March of Dimes in a review -- in a statement in 2007; ACOG, 2005; the Mayo Clinic; our federal government, other organizations, including Health Canada in a 2003 review.

So before -- this is an important consideration

for you to have in mind.

The second scientist, a practicing OB/GYN who could not be here today because she's seeing 35 patients, in the course of her practice of delivering 400 babies a year, Dr. Laurie Green, who is also the former President of the California Academy of Medicine, wanted us to communicate to you again, to reiterate, that "placing caffeine on the Prop 65 list would undermine the advice of moderation I give my patients. It would create harmful stress among a number of women in California and would confuse, rather than enlighten, because of the inconsistent treatment of natural and added caffeine. Accordingly I recommend that you assign caffeine a low priority for further Prop 65 review."

"If caffeine were to be included on the Prop 65 list as a reproductive toxicant, the harm and health risk associated with the very real fear that many pregnant women will develop far outweigh any theoretical benefit of providing additional cautions concerning caffeine consumption."

Thank you for your time. Thank you for your efforts to advance public health. Please consider the ultimate impact on public health of your decision to move forward.

I'd be happy to answer any questions.

CHAIRPERSON BURK: Questions?

Hillary.

COMMITTEE MEMBER KLONOFF-COHEN: Could I respond?

CHAIRPERSON BURK: (Nods head.)

COMMITTEE MEMBER KLONOFF-COHEN: Well, thank you so much for your comments, first of all.

When you addressed about not advancing public health and public health not moving forward by reviewing caffeine, I have to say that to me advancing public health is to evaluate fully whether or not a substance is safe for the public. And to actually discuss whether or not it should go for further review to me seems like that would be advancing public health.

A lot of the comments are based very much on politics and not very much on the data. Certainly, we very much want to avoid stress and confusion and not worry about fear in the public if we don't need to. But we also need to look at the data and what they actually are showing. And so I'd like to hear some discussion in terms of that rather than the ramifications of scaring the public. I think we're certainly not anywhere near that. We're just discussing right now whether or not we should bring caffeine up for further review.

MR. ROBERTS: May I offer a brief perspective on that?

This is a committee that has one tool, and that tool is Proposition 65. This is not a committee of global jurisdiction of general safety reviews. Please, before you move forward on examining further science related to the one tool you have, have in mind how that tool is going to work. The comments that we have provided are not comments of politics. The comments that we have provided are the comments of how this tool will work. Today is your opportunity to consider how the end game under one scenario would play out. And if it doesn't make sense to pursue that end game, this is the time today. You will not be asked again, does this make sense to move forward? That is the question that is before you today.

Thank you.

CHAIRPERSON BURK: Thank you.

The next speaker is Dr. Alan Leviton, American Beverage Association.

DR. LEVITON: Thank you very much. I appreciate the opportunity to speak to you.

Although I represent the American Beverage Association today, you should know that I do have a day job as Director of the Neuro-epidemiology Unit at Children's Hospital of Boston and Professor of Neurology at Harvard Medical School. I'm the principal investigator of a multi-center study of the antecedents and correlates

of brain damage in very preterm babies.

My major credentials, however, are listed on the handout. You will see three publications in which I have reviewed the literature dealing with the relationship between caffeine and coffee consumption and the risk of pregnancy and fetal disorders.

The first one is dated 1988, and the last one in 2002 is almost 40 pages long. I am familiar with this literature. I have reviewed it extensively.

In the limited time that I have, let me deal with the four outcomes I think that we need to address.

The first is birth defects or malformations. And I think that has been summarized very well by Marilyn Brown. In a publication in 2006 her conclusion was there is no evidence to support a teratogenic effect of caffeine in humans.

The next item on the list is spontaneous abortion. And as Dr. Klonoff-Cohen has mentioned, that's a big issue. I will come back to that.

The risk of prematurity does not seem to be risk increased at all in caffeine and coffee consumers.

And the risk associated with reduced birth weight is minimal and often can be explained by residual confounding.

If you turn the page, there's an illustration of

my presentation for residual confounding. In light of the limited amount of time available, I ask that you skip that and go to the next page, the one that has a figure on it.

This figure is from a 2000 publication by Cnattingius and colleagues. And let me walk you through it, because I think it's to the heart of the matter.

On the X axis is the week of gestation. On the Y axis is caffeine intake on a daily basis. The solid black line in the graph itself refers to the women who miscarried. The dashed line refers to the women who carried to term. Let me go through the details.

The first item is that the mean consumption in this sample is 350 milligrams per day. That's large by everybody's estimation. These data are from Sweden where the consumption of coffee is higher than in most other countries.

I want you to notice that the consumption does not change for the first four weeks of pregnancy, at which time the consumption declines in both groups. It declines modestly in the women who miscarry, but it declines dramatically in the women who carry to term.

The question is: What is the biology going on here? And the interpretation by those who were knowledgeable about it, obstetrical endocrinologists and others, is that at about four weeks, five weeks perhaps,

women experience a pregnancy signal. They feel pregnant. If they've been pregnant before, they know the feeling.

For many of these women the first symptom is sensitivity to odors. This is the time when they avoid perfume, look for fragrance-free cosmetics and soaps, and they avoid the smell of brewed coffee. So what happens? They decrease their coffee consumption.

And the interpretation here is that the women who are destined to miscarry have less of a pregnancy signal. And, indeed, if you look on the right, the Y axis there is a measure of nausea severity. And that measure is much higher for the dashed line, for the women who carry to term. They had a stronger pregnancy signal than the women who miscarried.

The issue here is that a healthy pregnancy is associated with solid implantation of the ovum in the endometrium, with the placenta functioning well as a hormone factory. And the pregnancy signal is really minor toxicity of hormones, estrogens, human chorionic gonadotrophin. And that explains it. In this situation caffeine and coffee consumption does not cause the abortion, but is an indicator of the pregnancy signal. So that the women who are destined to miscarry were the ones who are destined to have a later fetal death even, have a poorer placental implantation, and have lower pregnancy

signal.

If we go down to the bottom of the page, our data from the U.S., from Cincinnati, to be specific, Tina Lawson shows the line that is highest on the left with the triangles is coffee consumption. And in her sample begins even at three or four weeks. And if you look to the right, the other table there, you see that most of the caffeine consumption that decreases is associated with coffee and not with soft drinks or tea.

For me, this kind of view of the relationship between spontaneous abortion and caffeine or coffee consumption indicates quite clearly that I don't think there is a substantial relationship. It cannot be said that it is clearly shown. I think that applies to spontaneous abortion. I think it applies to the other pregnancy and fetal disorders.

Thank you very much.

CHAIRPERSON BURK: Thank you.

Next.

Did you want to make a comment?

No?

We can discuss this all after. So we'll just continue with the public comments.

Next is Barbara Petersen, Exponent.

(Thereupon an overhead presentation was

Presented as follows.)

DR. PETERSEN: Barbara Petersen from Exponent, representing the American Beverage Association today.

I believe there are slides coming as the projector warms up.

I've been conducting risk assessments for the past 20 years or so, and in particular looking at consumer exposures and the impact of regulatory decisions or the potential impact of regulatory decisions on consumers' exposures.

I've also done a wide variety of exposure assessments under the rules of Proposition 65. And we'll be talking a little bit about that today.

And in particular in the case of the warnings for caffeine, I submitted the details of the research I've done as part of my written comments. Today I'm just going to focus on the highlights. And I do welcome any questions that you might have.

My most important overall conclusion is that coffee and tea have much more caffeine per serving than manufactured beverages, including soft drinks, and that they're also consumed with a greater frequency.

I'll show you some specific results using different assumptions and different databases. In all of those I've followed the procedures that are outlined and

applied to Proposition 65. And not to steal my own thunder, but since Gary already has, consuming coffee and tea beverages that would be not -- would not be subject to the warning results in three times the amount of caffeine that you would get from manufactured sources of caffeine, regardless of which data set I use for doing that.

And if I can have the next slide.

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DR. PETERSEN: Specifically I looked at soft drinks. And I concluded the energy drinks, which I know are of special interest. And then I also did an energy drink alone. I looked at coffee and tea together. And I also looked at coffee alone.

If I can have the next slide.

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DR. PETERSEN: In the first set of analyses, I used two data sets. These are both publicly available and done by the National Center for Health Statistics. NHANES 2003 and 2004 is a survey of two days per person, and it's a record. It's quantitative information. And I used that to estimate the grams of caffeine per eating occasion.

But under Prop 65 we also want to look at the frequencies so that we can get a usual intake. Again, in all these analyses we're looking at consumers only, not averaging over the whole population.

And in order to do that, we used an older NHANES study, the NHANES III, which estimates frequency of consumption. The categories for frequency are relatively broad and do not exclude the decaffeinated coffee, so these are what I would term to be a worst-case upper exposure estimate for the soft drinks. But they do distinguish for coffee and tea between caffeinated and decaffeinated. So we've limited the analysis to caffeine only.

I think -- I won't read through these numbers. But you can see for soft drinks the estimates are around 46 or 47 milligrams per eating occasion; for energy drinks, which do have a higher caffeine level, about 85; but still lower than the mean for coffee and tea, which is 128; or coffee alone, which is 154. It seems a little bit paradoxical that you'd take away a beverage and the number goes up.

But, remember, we're limiting it to consumers, so it's a little bit different population. And tea has lower levels of both the quantity and the caffeine.

Next slide.

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DR. PETERSEN: Taking that data and combining it to look at a usual intake. So we're essentially multiplying the distribution of frequency times the

distribution of grams -- or milligrams of caffeine per eating occasion.

The usual intake -- and I'll just focus for now on the geometric mean on the right -- for soft drinks is about 26 milligrams per day. And I think that's helpful in light of some of the previous discussions you've been talking about to anchor those decisions and what typical consumers are consuming on a daily basis.

Energy drinks, about 40; coffee and tea, 85; and coffee alone, 95. And even when we combined all those drinks, together, we're getting to about 100 milligrams per day.

If I can have the next slide.

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DR. PETERSEN: We also were able to access some more recent frequency data and some more finely tuned to the soft drink categories we're looking at. It's called the eSIP data. It's a very large consumer panel. The E stand for electronic. About 35,000 individuals per year are surveyed.

The data are more specific to the categories of interest to us. For example, in the soft drinks, excluding the decaffeinated beverages. And so the absolute numbers are lower. For soft drinks it's about 20 milligrams per day. And coffee is 75.9.

If I can have the last slide.

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DR. PETERSEN: Again, coming back. So that regardless of the numbers we use, the coffee from the naturally occurring sources represents about three times the caffeine intake per day of the manufactured beverage. And if a warning were placed on soft drinks, it would be likely that people would switch to a different beverage, which is not warning, assuming that it would be a lower intake; and that would be coffee and tea, which seems counter completely to a sensible public policy.

Thank you.

CHAIRPERSON BURK: Okay. Thank you.

DR. PETERSEN: Are there any questions?

CHAIRPERSON BURK: Any questions?

COMMITTEE MEMBER KLONOFF-COHEN: I just wanted to comment just for a second.

There is something put out by the Nutrition Action Health Letter, which is actually the largest health letter in North America. And FDA just gave them their highest honor. And in September 2007 the Center for Science in the Public Interest put out different amounts in terms of for caffeine. And so I'm not sure how these jibe with yours. I just want to state them.

So in terms of an 8-ounce cup of coffee, they

quoted 133 milligrams. A coffee choice that many people go to -- I won't give the brand -- but they serve 16-ounce cups of coffee. There's 320 milligrams in a cup.

In terms of a particular company that puts out lemon peach tea, it ranges anywhere between 42 to tea brewed, which is 53. High tea lattes are 100 milligrams.

And certainly soft drinks such as Mountain Dew, Coke, Pepsi, things like that, range anywhere between 54 and 69, depending on what the particular brands are.

And then there are other things, such as chocolate, which wasn't mentioned, where they can range anywhere from Hershey's dark chocolate is 31; Häagen Daz ice cream is 58; all the way to certain over-the-counter meds such as No Doze tablet, 200 milligrams; Excedrin Extra Strength is 130 milligrams.

So I'm not sure how those numbers jibe with what you're presented.

DR. PETERSEN: I'd have to look at them category by category. For our caffeine concentrations in the analysis, caffeine is included in the USDA nutrient database that is used in conjunction with the NHANES surveys, and they do have data for each of the categories of product. Whether it's soft drink or coffee, espresso, each one has a different level of caffeine and those are values we used.

CHAIRPERSON BURK: Okay. Any further questions?

All right. Thank you.

The next speaker is Dr. Debbie MacInnis from the University of Southern California, on behalf of the American Beverage Association.

And we found we have a timer up here. So we're actually going to stick to it this time.

(Thereupon an overhead presentation was Presented as follows.)

DR. MacINNIS: Well, thank you for inviting me to present my comments here. My name is Debbie MacInnis. I'm a faculty member at the University of Southern California in the Marshall School of Business.

There's been discussion around the table this morning about the fact that cola has -- cola will be required a warning label whereas coffee will not, and that this could potentially cause unintended consequences of consumer misperception and confusion.

I was asked by the American Beverage Association to design a study to determine whether those outcomes would indeed be realized.

Next slide please.

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DR. MacINNIS: The study I conducted was an experiment that involved 309 pregnant women from the State

of California. They were throughout -- women who lived throughout the State of California who were pre-screened for consumption of both cola and coffee over the past two years.

They were randomly assigned to one of two conditions in a between-subjects design experiment.

Next slide.

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DR. MacINNIS: Consumers in the control condition represented the condition where there was no warning label present on cola. They were exposed to a representative package of a cola soft drink as well as a representative package of a coffee product. They were asked to read these packages and respond to a self-administered questionnaire.

Respondents in the experimental condition were given the exact same information with the exact same questionnaire. Next slide, please.

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DR. MacINNIS: But they were given the Proposition 65 warning label at the bottom of the cola product. You can see it at the bottom of the left-hand side.

The placement of the warning label, its wording, and the content is exactly identical to what would be true

were a warning label to be required.

Before moving on to the conclusions, I should note that there were no significant differences between the experimental and control conditions on any potentially confounding factors like education, ethnicity, income, that could be associated with misperception or confusion. Suggesting the random assignment to conditions was successful.

Next slide.

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DR. MacINNIS: We did see evidence of misperception. Consumers who were exposed to the Proposition 65 warning label on cola were significantly more likely to believe that the caffeine in cola is stronger than the caffeine in coffee, different from the caffeine in coffee, and more of a safety concern than the caffeine in coffee.

In addition, we found evidence of confusion. Significantly more consumers were confused about which is safer, cola or an equivalent amount of coffee, when they were, versus were not, exposed to the Proposition 65 warning label.

Next slide.

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DR. MacINNIS: We asked respondents in the

experimental condition: Why is there a caffeine warning label on cola but not on coffee? As you can see the modal response to consumers -- by consumers was one of confusion. 32 percent indicated that they were confused about why the warning label was present on cola but not on coffee. The next two most frequent categories of responses indicate misperception. About 19 percent inferred that the reason why there's a warning label on one product and not on the other is that cola has more caffeine. An additional 15 percent inferred that the presence of the warning label meant that cola's ingredients are less safe.

And an interesting observation is that only 1 percent of the sample inferred the real reason for the warning label, which is that it would be required by law.

Next slide, please.

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DR. MacINNIS: The results of course should be interpreted in the context of the limitations of this study. This was an experiment. 309 respondents is certainly large enough to demonstrate significant differences between the two conditions. But this was not a survey of the California population.

In addition, although we made every effort to represent respondents who were representative of the

population of the state in terms of demographics and other variables, we were slightly under-represented in terms of consumers that were at the extreme ends of the education continuum and extremely high income consumers as well as Asian consumers, and had a slight over-representation of African American consumers.

The bottom line of these results though do suggest that if a warning label were to be presented on cola and not to be presented on coffee, we would find evidence of confusion and misperception.

Thank you. And I'm happy to answer any questions you might have.

CHAIRPERSON BURK: Thank you.

Linda, question?

COMMITTEE MEMBER ROBERTS: Yes. On our screen I could not read what the warning statement was. Could you just let us know.

DR. MacINNIS: Sure. The warning label reads, if I can recall it from memory, "Warning: This product contains caffeine, a chemical known to the State of California to cause birth defects or other reproductive harm."

CHAIRPERSON BURK: Good. Thanks. Yeah, I couldn't read that either, and I wondered. Maybe my eyes are too old.

Okay. Any other questions?

All right. Thank you.

Next speaker is Dr. Jay Murray, Murray and Associates, again on behalf of the American Beverage Association.

(Thereupon an overhead presentation was Presented as follows.)

DR. MURRAY: Thank you. My name is Jay Murray, and you've seen me before.

First, thank you for listening to our presentations this morning and for reviewing the written comments we submitted.

This one is different. Usually when you're considering a chemical, you're considering a chemical for listing, and you don't get into the policy issues like the ones that are raised today. But in this case, you can and should consider those issues.

Now, Dr. Leviton earlier reviewed the epidemiology studies. And I'm going to touch very briefly on the animal studies.

Next slide please.

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DR. MURRAY: The animal studies do not support a high priority. One thing that we've learned over the years is that the route of administration is critical for

caffeine. When you give caffeine to laboratory animals in drinking water, the results are not the same as the results that you get when you give it as a large bolus dose by oral gavage or give it intraperitoneally, which was the way caffeine was given in the early animal studies.

And the animals evidence shows that caffeine is not a reproductive hazard except when it is given at high maternally toxic dose levels, which are not relevant to human exposure to caffeine in beverages.

The National Toxicology Program conducted a continuous breeding study of caffeine, both in mice and rats. And their conclusion is caffeine is not a selective reproductive toxicant.

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DR. MURRAY: So when you consider the epidemiology, the confounders in the epidemiology, the bias issues, and the animals studies, caffeine will not meet the listing standard of "clearly shown to cause reproductive toxicity."

Recent reviews all conclude that caffeine is safe at moderate levels of exposure. And at higher levels of exposure the data are inconclusive and conflicting.

And if the data are inconclusive and conflicting,

caffeine will fall short of meeting the "clearly shown to cause" standard.

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DR. MURRAY: Now, the question you may be asking yourselves is: Why if caffeine is not clearly shown to cause reproductive toxicity wouldn't the American Beverage Association want to see you go forward, put it on your agenda and draw exactly that conclusion?

There's a very good reason. Because of the very -- because the very consideration of caffeine for listing at a DART Committee meeting will create a lot of media attention. You saw the cameras here today. Those cameras weren't here for the other seven compounds. They were here for caffeine. And that media attention will cause confusion, anxiety, and lead to a lot of misinformation about caffeine.

And if there is any doubt in your minds -- I don't know how many of you had a chance to read the newspaper this morning before you came here. You all think you're at a meeting where you're discussing the prioritization of eight chemicals. Let me read you the headline for the story. This is Sacramento Bee this morning.

"State may eye safety of caffeine in drinks." It's not till you get to paragraph number 18 that any

substance other than caffeine is mentioned. Now, if you're a pregnant woman, wakes up, has your cup of coffee this morning, because you're trying to consume caffeine in moderation, and that's the headline you read, what do you think that person is going to think?

So you really have to think about the consequences of going forward with this one.

Next slide.

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DR. MURRAY: Actually I missed one. Let's go back.

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DR. MURRAY: Warnings on soft drinks would not advance public health. You've heard this message already from some of the others. And, you know, many of you know I served on your Committee for several years because, like you, it was important to me that my work advance public health and that I do the right thing. And what deeply concerns me here is that moving forward with caffeine, given the "naturally occurring" exemption of the law, is going to create confusion, misperception, anxiety, and it has the potential to do a lot more harm than any theoretical good that could come out of this.

You saw professor MacInnis's study. And in all the years that I've known Prop 65 it's the first time I've

seen anything like this. You saw the responses. That's the take-home message that would result if you put caffeine on the Prop 65 list. So if you go forward, the message that's going to be heard is "I'm confused, I think cola just have more caffeine than coffee, I think cola must be less safe than caffeine." It undermines the caffeine in moderation message.

Last slide.

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DR. MURRAY: So, in conclusion, if you're worried about any of the first three bullets on this slide, today is the day when you have to do something about this.

If caffeine were listed, the inconsistent mix of warnings on some products and not other products would undermine public health and confuse the public.

The warnings would be at odds with the advice that physicians give their patients, which is consume caffeine in moderation. My goodness, you start putting warnings on soft drinks, and it doesn't sound like caffeine in moderation is the message anymore. You don't put warnings on coffee, how is that consistent with caffeine in moderation?

Caffeine does not meet the "clearly shown" standard.

So this is your opportunity. If you proceed with

caffeine and caffeine moves forward, the question at your next meeting will be: Is caffeine clearly shown to cause reproductive toxicity? Dose won't matter. How many times have we heard this. The consequences of listing and having inconsistent warnings on products won't matter. You will have to stick to the science.

Today you have an opportunity to consider the public policy implications of this as well as the science in making your decision.

So this is your only chance to say it doesn't make sense to proceed. You should recommend that caffeine be assigned a low priority and that no hazard identification document should be prepared.

Thank you.

CHAIRPERSON BURK: Thank you.

DR. MURRAY: I'd be happy to answer any questions you might have.

CHAIRPERSON BURK: Are there any questions for Dr. Murray?

Okay. Thanks.

DR. MURRAY: Thank you.

Next speaker is William Butler, Ph.D, representing CHPA, NPA, and CRN.

DR. BUTLER: That's the Consumer Health Products Association, the Natural Products Association, and

Committee for Nutrition.

I'm going to speak to the epidemiologic studies on coffee and adverse reproductive outcome and how they relate to assessment of caffeine.

I will start off by calling to your attention that, unlike the other substances, there were so many epidemiologic studies of coffee and caffeine, that they couldn't even all be listed here. So this is not an issue which is not getting attention from the scientific community. And if indeed it was a real resolved issue or resolvable issue, you would question why are there still so many studies being conducted.

And I start off with -- in my written comments to you I listed around 20 recent review articles with their quotable quotes and the citations. They're almost all unanimous, that we haven't come to a conclusion, that we can't come to one, that it's equivocal, that it's inconsistent, that it's contradictory.

I know there were some specific epidemiologic studies cited here at the beginning. But when you look at the whole body of literature, that's not what you find. And if the purpose of this meeting is to anticipate what would occur with a health hazard evaluation, then I think the best place to look is the last 20 reviews that have taken place. And these have been by quite respected

bodies which I think you'll recognize: The American College of Obstetricians and Gynecologists; FDA; March of Dimes; NIH; National Toxicology Program; Health Canada; European Commission; The Food Standard Agency, which seems relevant, for the UK, all within the last couple years.

And they all are similar in saying, "Well, it doesn't look like there's a problem. But it's inconsistent. We can't come to conclusion." There are some inconsistencies that weren't brought out. Some studies showed very high association. But when you look at the studies, you look at the details, it doesn't all come together. It doesn't tell a good story, a consistent story.

There's also one item which I'll call to your attention, which was brought up, is: Are these studies of coffee or caffeine? And typically, even though they say they're a study of -- excuse me. Typically they're studies of coffee, "How many cups of coffee did you consume?" And even though they might measure coffee as precisely as 182.7 milligrams per day, it really boils down to a self-report of how many cups. So it's not very precise.

If you then go further and say, "Well let's look at other dietary sources of coffee," then the literature gets much, much, much thinner. And often times it's not

reported. There's a study by Bech, which is in the list from the OEHHA, listed as a positive study, a 2005 observational cohort. When you look at the details, it says, "Well, we looked at the association of caffeine and we found it" -- "with caffeine from coffee we found an association." But there's two sentences that say -- embedded in the text, no tables, no analysis -- that "when we looked at the association of caffeine from soft drinks, we didn't find it. It wasn't there. It's only with coffee. And when we looked for the association of adverse reproductive outcome for caffeine from tea, it wasn't there. It was only with coffee."

Now, lots of times studies -- epidemiologic studies don't report that detail or it's not conspicuous. But when you look at the epidemiol -- the reviews of the epidemiologic studies, the 20 that I've cited there, they get into those details. And the conclusions that have been reached -- I'm just repeating myself -- is the results are contradictory, inconsistent, equivocal.

There was also mention of meta-analysis. And I'll call your attention to the quote -- I don't think it's the same one that came here. It was from Santos, 1998. It says, quote, "The high heterogeneity of the available literature on the effects of caffeine on low birth weight, intrauterine growth retardation, and preterm

delivery prevents estimation of reliable pooled estimates through meta-analysis."

That's sort of getting at the same thing that the results are equivocal. Yes, there might be some high relative risks. But that's -- but the body of the literature doesn't support that.

There's also the question of controlling for confounding. And I'm quoting now from Fernandes, 1998. Quote, "Control for confounders such as maternal age, smoking, and ethanol was not possible because of the heterogeneity of reporting from the individual studies."

So if the purpose here of this meeting is to have a priority of what it is that we anticipate we might find, then I think the literature is fairly specific in saying we're not going to find a specific result right now. There's lots of studies still being done. There's progress still being made. But right now it doesn't seem -- the literature does not support putting a high priority on caffeine.

CHAIRPERSON BURK: Thank you.

Any questions for Dr. Butler?

COMMITTEE MEMBER KLONOFF-COHEN: I just wanted to state that when you were talking about Fernandes and Santos, as you aptly pointed out, they're meta-analyses. And meta-analyses, as you well know, are taking all the

studies with all the limitations that they have and all of the differences in study designs and sources, et cetera, et cetera, and putting them all together. So you view meta-analyses results very skeptically.

DR. BUTLER: But the quote I gave on the meta-analysis of the quantitative pooling was consistent with about the 20 other studies -- the 20 other reviews which were not specifically meta-analysis. They weren't quantitative. They weren't driving to get a single number and a confidence interval. It was incorporating all of the epidemiologic information into an attempt at a causal conclusion.

CHAIRPERSON BURK: Thank you.

And I think our last speaker on caffeine is Lisa Halko. Same initials as the previous speaker.

MS. HALKO: Good morning. And thank you for hearing our comments this morning. I'm Lisa Halko from Greenberg Traurig and I also represent the Council for Responsible Nutrition, the Natural Products Association, and the Consumer Healthcare Product Association.

As Dr. Denton said at the beginning of this meeting, the question that OEHHA is answering now and the question on which OEHHA is asking your advice is whether these chemicals -- and here the question is caffeine -- whether it merits a closer look.

Staff worked for two years to develop a perfectly beautiful prioritization process that helps to answer that question. The prioritization process focuses on exposure potential and on epidemiological data. And usually you would expect that the most important chemical to look at, the chemical that should have the highest priority for a full review, will be those with a high exposure potential, will be those for which there is ample epidemiological data.

But in this case that is not true. In this case, the exception proves the rule. I should say the exemption proves the rule, because, as you've heard discussed, caffeine is present for most people in coffee. The source of that epidemiological data that pushed this chemical up on the prioritization list, the source of the exposure that pushed this chemical up will never have a Proposition 65 warning, no matter what your closer look eventually decides.

Now, this is an opportunity for this Committee to consider factors other than exposure, factors other than epidemiological data. Dr. Jones characterized those as political questions and Dr. Burk I think you mentioned philosophical questions. But for caffeine the question is a public health question.

The reason that the exemption exists is because

both OEHHA and FDA have acknowledged that when you start to put warnings on foods, you end up with unintended public health consequences, unintended and undesired public health consequences.

The reason that we have the naturally occurring exemption is so that thousands of foods that have been eaten over thousands of years don't have warnings that will obscure the most important public health message that there is about diet, and that is moderation.

The warning messages drown out that message. It drowns out that message particularly for pregnant women. I've been an anxious pregnant woman, and so I have some personal experience of that. It is difficult to process information when you are as risk averse as that population needs to be.

So for that reason, OEHHA has exempted naturally occurring chemicals in foods from Proposition 65 warnings. For that reason FDA so carefully limits warnings on foods and drugs that it reaches to the point of preempting state laws sometimes including Proposition 65. Those are public health realities, not just legal realities, not just political realities, but the public health motivations for those exemptions.

So let's think about -- suppose you take this beautiful prioritization process that staff worked so hard

on and go ahead and factor in the public health questions, say to yourself, "Well, okay. For good public health reasons, no matter what we decide, the source of all of the epidemiological data, coffee, will never bear the warning, the source of two-thirds of the exposure will never bear the warning, the prioritization process itself will tell you then that without coffee there is no epidemiological significant data to consider." Without coffee there is no -- excuse me -- there's not the same kind of significant exposure. So the exception proves the rule. The prioritization process itself informs you that, given this exemption, caffeine should have a low priority. It does not merit a further look. And I would ask you to make that finding and that advice to OEHHA.

Thank you very much.

CHAIRPERSON BURK: Thank you.

Renee, just very briefly.

How's our stenographer doing?

MS. SHARP: I wasn't planning on making a comment on this chemical. But after hearing basically an hour mostly from the American Beverage Association, I felt really compelled to provide a comment for the public-health-oriented people here. And, that is, the only confusion that might be created by this panel recommending to OEHHA that they go ahead and create a

hazard identification document for caffeine -- the only confusion that might be created is if you decided not to do that. Because if you had 32 Epi studies suggesting that caffeine might be causing reproductive or developmental harm, including fertility effects, how you could not recommend that would be just baffling.

Thank you.

CHAIRPERSON BURK: Okay. Thank you.

So are we ready to discuss this further?

I think I know how you feel, Hillary. But let's ask for other comments.

Dr. Hobel, Calvin.

COMMITTEE MEMBER HOBEL: Yes. I have been a person who's been practicing maternal-fetal medicine for over 30 years, and I've been aware of this literature for a long time about caffeine. And I've reviewed these papers very carefully. And I think the focus has been on coffee and -- but in clinical medicine there's only one situation where caffeine products have been a problem. And that's in patients admitted with a fetal arrhythmia, an intrauterine arrhythmia of the fetal heart rate. And there is an association with that causing the arrhythmia to occur. But it's really in the vulnerable fetus who has an abnormal conduction system that is at risk for problems later on.

And that's the only time we really talk to patients about limiting their primarily coffee intake. But we also mention chocolate and sodas. But that's the only clinical situation where I've found it to be important.

And as I review the literature, I find it very difficult to be able to focus on caffeine as being a major issue, because there are so many confounding other variables that seem to make a difference. For example, smoking. Smoking seems to be very powerful. And it's hard to disentangle people who use these additional substances for very good reasons. Smoking and coffee drinking tend to go together.

And even when you look at preterm -- or abortion or preterm birth or developmental issues with a child, it's very difficult to disentangle the effect of caffeine.

The focus seems to be primarily on smoking.

So I find it very difficult to consider myself that caffeine should be listed as an issue, for those reasons.

COMMITTEE MEMBER KLONOFF-COHEN: Can I answer that?

It's true, it's like many of the epidemiologic studies, there are multiple confounders that are taken into account and many of the studies do and a lot of the

studies don't.

But since you brought up smoking -- I should have actually mentioned this. But several of the articles actually found a significance in nonsmokers but not in smokers. And those studies were George, Torfs, Cnattingius, Jensen, Stanton, and Gray. And it's been hypothesized that a higher metabolism as a result of smoking causes individuals to digest caffeine faster and, therefore, have a lower risk.

And so all of those studies actually found an effect then, therefore, with the nonsmokers and caffeine.

COMMITTEE MEMBER HOBEL: Okay. I think that's a very good comment. But I think that when I look at some of the other studies, when caffeine does seem to be important, it seems to be excessive use of caffeine. And that's very clear in several of the papers. Yet, the March of Dimes, the America College of Obstetrics and Gynecology clearly makes it a point to tell patients that they have to be careful with the amount of coffee or caffeine intake.

So from my point of view -- I'm on the Scientific Advisory Committee for the March of Dimes -- I'm very comfortable with their recommendation.

And I also belong to ACOG, and I'm comfortable with their recommendation.

So I think things are in order in terms of the messages to patients about excessive use of caffeine.

COMMITTEE MEMBER KLONOFF-COHEN: I don't want to argue with either of those organizations, because I greatly respect them, frankly. But I did actually -- when I went through the studies, that's why I kept mentioning, you know, 300 milligrams, 300 milligrams, 325 milligrams, to show in fact what the actual exposure amount was, so that it didn't reflect that they were drinking over the moderation, as you put it.

CHAIRPERSON BURK: Who else?

Ken.

COMMITTEE MEMBER JONES: So, Hillary, the epidemiologic studies you're saying included -- that show an effect included moderate coffee exposure?

COMMITTEE MEMBER KLONOFF-COHEN: Yes. That's what I was focusing on, yes.

COMMITTEE MEMBER JONES: Thank you.

COMMITTEE MEMBER HOBEL: That's why I made the comment about excessive use of caffeine.

CHAIRPERSON BURK: Other comments?

No?

COMMITTEE MEMBER ROBERTS: I have a question for Dr. Petersen with relationship to the slide you presented on the total exposures from different sources.

DR. PETERSEN: Yes.

COMMITTEE MEMBER ROBERTS: What would be the proximate --

DR. PETERSEN: Can we put that back up.

Go ahead.

COMMITTEE MEMBER ROBERTS: I was just wondering what would be the approximate percent of caffeine consumed from non-natural sources on a daily basis out of the total amount of caffeine consumed?

DR. PETERSEN: I think if we look at the "Total" slide, what -- that ends up being a more complicated question than you would think, because there are different consumers that you're talking about. So you have people who get their caffeine from coffee and you have the people who get caffeine from soft drinks.

For people who get it from both categories, it was just a small increase. I believe if we -- there's a total on the -- keep going. I think it's on the -- right here on this slide.

So you can see that from people who consumed soft drinks were around 25; people consuming coffee, 94. If you looked at people -- so essentially you'd looked at everyone who consumed any beverage with caffeine, it went up to 108. So from 94 to 100 -- roughly 10 percent increase by looking at both sources at the same time. So

it's kind of an either or for most people.

COMMITTEE MEMBER ROBERTS: Okay. So if I understand this, if there was a person who drank both, then -- and if, you know, for some reason caffeine was eliminated from all soft drinks, that would be about a 25 percent reduction in a person's daily amount? And if it was a person who only had caffeine from soft drinks, they're currently only at approximately 25 milligrams per day?

DR. PETERSEN: That's correct. On mean over a usual intake, that's correct.

COMMITTEE MEMBER ROBERTS: Okay. Thank you.

COMMITTEE MEMBER WHITE: Okay. I think I'm probably going to be the one to create the most controversy here today, but that's okay. I tend to do that.

As a clinician -- and I have to agree with our obstetrician in a very big way -- I too have had the opportunity to take care of patients -- prenatal patients. I've also had an opportunity to take care of patients, particularly mothers, who consumed large amounts of Dr. Pepper, for example, which has a high caffeine level. I've seen those mothers. I've seen maternal tachycardia, I've seen fetal tachycardia as well. But that's really the only time I've actually seen caffeine be a problem. I

don't have as much experience, but I do have some experience.

Having taken care of people in a population where soda and coffee, particularly soda, is ingested quite a bit, I can honestly tell you that from a public health standpoint, if caffeine were to get the big label, particularly in the communities I have served in, it would be mass hysteria. I have seen mothers actually decrease their intake of caffeine, whether it's sodas, coffee, whatever it is -- the moment they discover that they're pregnant, they self-decrease it. And this is in a population that drinks a heavy amount of soda. And I mean particularly your low income and also in the African American community as well.

So from my own personal experience as a clinician, even in reviewing the data, I too would make caffeine a low priority I think at this point.

When a doctor showed the paper, the Sacramento Bee, the headline, I could just imagine my patients coming into me screaming, "What is this? What am I going to do now? I can't just stop drinking coffee. Or "I took a cup of coffee this morning. I'm 16 weeks pregnant. What do I do?"

And trying to decrease that hysteria in a population of women who are pregnant -- and for you all

who have been pregnant, you know that when those hormones are raging, nothing makes sense.

(Laughter.)

COMMITTEE MEMBER WHITE: So looking at it from the standpoint just of the public health and the clinical aspects of it, but not negating the data -- I think the data is there -- I personally would make it a very low priority. I really would. I think it can do more damage public-health-wise than anything else than it could do with respect to the data.

COMMITTEE MEMBER JONES: I would just point out that that happened with alcohol and all kinds of other things as well, that there was hysteria when we first discovered that alcohol was a human teratogen. But I really don't think that that's a reason not to proceed with looking at this if in fact it's real.

I have a question for Dr. Leviton.

DR. LEVITON: Yes.

COMMITTEE MEMBER JONES: Thank you, sir.

And I'm sure I just don't understand this.

On the second -- I guess it's the third page of your handout, you show two figures, one at the top and -- actually two at the bottom. But the one I'd like you to look at is the one at the top and the one at the bottom on the left.

And I think what you were pointing out here was that nausea and vomiting that occurs sometime around the fourth week of gestation in many, many pregnancies is in fact protective against spontaneous abortion. And it's probably due to an estrogen effect or some other kind of hormonal effect on pregnancy.

DR. LEVITON: I'm not saying it's protective, but it's an indicator that everything else is going well.

COMMITTEE MEMBER JONES: Well, I think it is protective, in fact. And, in fact, you're showing that the -- I think you are showing that the consumption of caffeine decreases about this same time. And I think that you're saying that that relates to the smell of coffee. Is that what you said?

DR. LEVITON: That's one interpretation.

COMMITTEE MEMBER JONES: Okay. And then you go down to the bottom left. And what it looks like to me is that not only with the smell of coffee, which is the triangular line, but also with tea and soft drinks --

DR. LEVITON: Yes.

COMMITTEE MEMBER JONES: -- it also drops off, and with milk it goes up.

DR. LEVITON: Yes.

COMMITTEE MEMBER JONES: So it's really -- from what I can see on the bottom left, that it's not the smell

of coffee, because soft drinks and tea drop as well. Am I confused?

DR. LEVITON: I wouldn't say you're confused. We just differ in our interpretation.

COMMITTEE MEMBER JONES: Well, what would be your interpretation?

DR. LEVITON: Let me walk you through this. Okay?

What you see is the coffee decreases dramatically --

COMMITTEE MEMBER JONES: Yes.

DR. LEVITON: -- much more --

COMMITTEE MEMBER JONES: Bottom left now or top?

DR. LEVITON: The bottom. Take the bottom.

COMMITTEE MEMBER JONES: Okay.

DR. LEVITON: Compare that to the tea and the soft drink.

COMMITTEE MEMBER JONES: Right.

DR. LEVITON: Drops much more dramatically.

COMMITTEE MEMBER JONES: Is there statistical significance in the extent --

DR. LEVITON: -- I don't have a P value.

COMMITTEE MEMBER JONES: -- to which they drop?

Excuse me?

DR. LEVITON: Just look at the figure.

COMMITTEE MEMBER JONES: Well, I am looking at the figure.

(Laughter.)

DR. LEVITON: I don't have P values. I don't think that was the test of the study.

So what I'm trying to say is if you look at it and you get a gestalt. We don't have P values.

COMMITTEE MEMBER JONES: Okay.

DR. LEVITON: In the absence of P values, what you see is a more prominent decline in the coffee consumption, you see some modest decline in tea and soft drink.

The issue here and the interpretation of the investigators is by about the fifth week or so, sixth week, the women are beginning to recognize that they really are pregnant and they're beginning to change their behaviors voluntarily. So that's why the milk goes up, that they're becoming -- they're becoming in their own mind more responsible. And they're decreasing their caffeine consumption. This is done by many women.

And so I think trying to separate what is, if not involuntary, the first indication of the pregnancy, then followed by the willful desire to reduce their caffeine consumption.

This was a middle -- higher middle class

population. And I think they were doing what they thought was best for their fetus.

COMMITTEE MEMBER JONES: Okay. Thank you.

COMMITTEE MEMBER ROBERTS: Dr. Leviton, looking at the bottom right graph, I'm assuming -- it looks like soft drinks and tea come -- they both come out clearly on the black and white reprint, a photocopy -- is soft drink the bar on the right or the bar on the middle in each of these?

DR. LEVITON: I believe it's the one in the middle.

COMMITTEE MEMBER ROBERTS: Okay. It looks like then, whether -- and as it says, it's daily caffeine consumption. So if you're looking at the dark bars for coffee consumption, as you get out to week 7 through 14 coffee consumption has pretty much stabilized to what looks like around 20 milligrams per day.

DR. LEVITON: Yes.

COMMITTEE MEMBER ROBERTS: This is a fairly large group of individuals from whom the coffee consumption was estimated?

DR. LEVITON: I don't have the sample size, but it was a good size. Several hundred clearly.

COMMITTEE MEMBER ROBERTS: Okay. The reason I'm wondering, then how do we get to the people who have the

300-plus milligrams of coffee consumption, I mean in these --

DR. LEVITON: I think there are very few of those in the United States. And I think that almost -- what I think the top figure shows you is that most women will decrease their coffee consumption whether they plan to -- they just decrease it.

COMMITTEE MEMBER ROBERTS: For women that do not lose pregnancy, are there any other social, demographic, biological factors associated with maintaining high levels of coffee or caffeine consumption during pregnancy?

DR. LEVITON: Other than smoking, I don't know.

COMMITTEE MEMBER ROBERTS: Thank you.

CHAIRPERSON BURK: Are there any other comments?

COMMITTEE MEMBER ROBERTS: I guess I'd like to pose one question to Dr. Jones, because you have the Teratogen Information System. And I'm just wondering what sort of information you give to women who call in that are concerned about caffeine.

COMMITTEE MEMBER JONES: Well, we make a distinction between moderate caffeine consumption and heavy caffeine consumption. And we tell them as most people who drink moderate amounts of coffee that there is probably -- that there's no evidence of concern; and that with greater than that, there certainly has been evidence

of concern.

CHAIRPERSON BURK: Okay. Last chance.

Ellen.

COMMITTEE MEMBER GOLD: Can I ask Dr. MacInnis two questions?

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER JONES: I might add, Linda, that we may be wrong based upon what Hillary has just told us today.

COMMITTEE MEMBER GOLD: I was interested in two things.

One, was your trial published?

DR. MacINNIS: No, this has not been published.

COMMITTEE MEMBER GOLD: And, secondly, have you done any work to see if these results are any different than what you would expect for labeling of any other compound from Prop 65?

DR. MacINNIS: There's very little research that I'm aware of that can draw on that question, so I can't answer with any definitive information.

COMMITTEE MEMBER GOLD: Thank you.

CHAIRPERSON BURK: That is an interesting question, because there's a whole another world about risk communication and all that.

But I think we need to sort of make our

recommendation based on the role that we play and consider that the implementation is done by others. And I understand, you know, that we can't help but think about public health, and that's why we're all on this Committee. I don't know -- Carol, did you want to say anything else about implementation?

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I could just reiterate what I said before, that there are regulations in place. There's provisions in the statute that all deal with when a warning might be required for a particular exposure. And there is a regulation about naturally occurring chemicals in foods. We aren't at a point now where we would be able to say what the level would be that would require a warning, because, for one thing, the chemical isn't listed. And that's not something that we look at until after the chemical's listed.

So it is to me a premature question about whether or not -- what an effect might be for a warning that we don't even know when it's going to apply to what kinds of exposures. But if any of the other members have questions about that, I'd be happy to try and respond.

MR. ROBERTS: Lawyer to lawyer.

If the issue is premature today, when is it mature?

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. What I'd like to say is that there are forums for this kind of issue to be resolved. Whether or not a warning is required, for example, we have regulations avail -- where someone can come and ask us, "Is a warning required for my product or the exposure that I'm causing?" for example.

So this particular forum here is scientists and medical people talking about the scientific evidence for this particular chemical and whether or not it's sufficient for us to proceed to the next step in the process.

MR. ROBERTS: One of the things about Prop 65 is the thousand-fold factor for warnings. It doesn't offer the precision that ACOG and others have in delineating between safe exposures and exposures where there are no questions.

The reason Dr. MacInnis has not published is because her work was directly responsive to the September 7 notice. We're not aware of any other chemical where there is this vast imbalance between a high exposure source that's natural and a low exposure source that's manufactured.

CHAIRPERSON BURK: All right. One last chance before I ask the question.

All right. Do you advise OEHHA to begin

preparation of the hazard identification materials for caffeine?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: So I count 4.

All those advising no, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2 -- 3.

Okay. So that is our advice.

And we're all hungry now.

(Laughter.)

CHAIRPERSON BURK: So how long shall we take?

Okay. So no more than 30 minutes?

Well, how about 2 o'clock? That's 35.

Okay. We'll begin again at 2 o'clock.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON BURK: All right. Good afternoon. I think we're ready to get started again.

And the next chemical to be considered is Chlorpyrifos and the staff presentation will be given by Dr. Poorni Iyer.

(Thereupon an overhead presentation was Presented as follows.)

DR. IYER: Good afternoon. My name is Poorni Iyer, and today I'm going to be presenting the extent of the evidence available for prioritization of chlorpyrifos.

--o0o--

DR. IYER: Chlorpyrifos is a broad spectrum organophosphate pesticide used in a variety of crops, on golf courses, as a nonstructural wood treatment, and as an adult mosquitocide.

The retail sale of chlorpyrifos for residential use was discontinued in the U.S. prior to 2002.

--o0o--

DR. IYER: In preparing for today's meeting it was discovered that the file containing the materials on chlorpyrifos that was sent to the Committee had been incorrectly saved in our server, leading to duplication of several of the abstracts. We apologize for these errors in the materials, but want to confirm that chlorpyrifos

still clearly passes the epidemiologic's data screen.

The slides that I'm about to show you now give the correct numbers of the abstracts in each category.

--o0o--

DR. IYER: So presenting the extent of the epidemiologic data for chlorpyrifos.

There were eight epidemiologic studies of environmental exposure. The majority of these was from chlorpyrifos used indoors for pest control.

The reports of increased risk of adverse developmental or reproductive outcomes include effects on cognitive and motor development, fetal growth and semen quality.

Five of these studies were analytical studies of adequate quality.

There were four meeting abstracts reporting increased risk of adverse developmental or reproductive outcomes. And one epidemiologic study reported no increased risk of adverse developmental or reproductive outcomes.

Next slide.

--o0o--

DR. IYER: The animal data included studies submitted for regulatory purposes as well as studies in the peer-reviewed literature with developmental endpoints

such as resorption, fetal weight, and long-term effects on the brain and behavior in laboratory rodents.

Of these, 21 animal studies reported developmental or reproductive toxicity, 3 animal studies that did not report developmental or reproductive toxicity.

And in the category of related studies the material sent to the Committee states 43 studies, but 6 of these report a developmental and reproductive toxicity and were also inadvertently included in this related studies category. Hence, there are 37 related articles.

And that concludes my presentation for chlorpyrifos.

CHAIRPERSON BURK: Okay. Thank you.

And I will take the lead on this one and say a few words. And then we have quite a number of people that wish to speak.

So I just want to reiterate, I did notice the duplications and all that. So when I did my own count, essentially for the human studies there are a series of them using pretty much the same population of people. So that's the Columbia University mothers and newborns studies that were looking at inner-city minority population. And able to measure cord plasma chlorpyrifos levels. And in different studies reported low birth

weight and length. And the others were the neural and developmental effects using an index.

So those I think -- again I'm only looking at the abstracts. So I'm sure they're open to criticism. But I'm just saying I think that data is there.

The Meeker studies -- there are two studies on semen quality that I can't really evaluate very well, and don't seem to fit much with other things. But they're there as well.

One of the studies that showed a small reduction in head circumference was actually looking at the metabolizing enzyme levels in different women, which I thought was very interesting from an mechanistic point of view.

One thing I should say about chlorpyrifos is that it's an anti-cholinesterase. That's it way of acting.

So some of these things are actually perhaps explainable mechanistically. Other things, I don't know.

Then there were a couple of case reports. And, again, very little information was given in the abstracts, so I can't say a whole lot about the case reports. But -- and maybe someone here is familiar with those. One of them reported four children with a pattern of birth defects that they were trying to say was caused by that, but I don't know.

Again, I was trying to play sort of by the rules, so I didn't go out and try to get a whole lot of extra information. I was just looking at what we were presented to see if I thought it was sufficient to recommend.

The one negative epidemiological study, Eskenazi, again was a population with pesticide exposures in the Salinas Valley. And they found no adverse relationship with fetal growth in the pesticide exposure. So there's -- you know, there are -- definitely it meets the screen, but it's not super clear from that, I would say.

The animal studies, there are quite a bit, there's quite a number on developmental and repro tox. So I think we could look at that.

The studies for pesticide registration, there were three, over the years '71, '83, '87, of course were the standard two and three generation studies, and they were all essentially negative.

But there were other ones that did show developmental toxicity primarily along with maternal toxicity. But there were a few that looked like they were not linked.

So the most interesting studies to me, and then I'll let other people speak, were the animal models of the behavioral and neural development endpoints. And there's one lab which had, boy, eight studies in there where they

have a model of getting neurological and behavioral effects at doses not otherwise toxic to the fetuses. So I found that very fascinating. I don't know how it will be used in our decision, but it is there.

So I will come back to my conclusions in a bit.

But let's start with the public comments. And we have, again, quite a number. So we will please ask you to stick to the five minutes.

The first person is Margaret Reeves, Pesticide Action Network.

DR. REEVES: Good afternoon, and thank you for this opportunity to address the Committee. My name is Margaret Reeves. I'm a senior scientist at the Pesticide Action Network. It's an environmental health organization focusing on pesticide issues.

We did submit comments. And I'll start by saying we strongly support a prioritization of chlorpyrifos, preparation of chlorpyrifos materials. We appreciate OEHHA's review of the literature and find it fairly compelling in terms of developmental and reproductive toxicity, especially developmental toxicity. And I have two main points I want to make.

The first is that we encourage the Committee to take serious consideration of exposure; and that is, given the level and form of use of chlorpyrifos, that result in

regular common exposures. Nearly 2 million pounds of chlorpyrifos are used in California, and with the greatest concentration in the Central Valley counties.

It's routine application by spray tractor to tree crops and it's relatively high volatility result in substantial drift and drift-related exposures among workers and bystanders. So both workers and people who live in agricultural communities near sites of application.

It's also important to note that virtually all of the tested exposures used by regulatory agencies to derive reference doses, whether they're looking at cholinergic effects, as were mentioned, or non-cholinergic effects, fail to include inhalation exposure. So drift is very, very important. Drift exposures is important. Yet most of the studies fail to include drift exposure. And that's largely the focus of our comments that you've received.

In our comments we show strong evidence of repeated widespread exposure to chlorpyrifos among residents of agricultural communities. This, together with its documented developmental toxicity, create a real urgency that OEHHA move as quickly as possible to prepare the materials necessary to make a decision for a Prop 65 listing; and that these materials should specifically address inhalation exposure or clearly identify the

serious data gap. And I think these are one of the examples where there is a serious data gap, despite the fact that I think the data out there are compelling regarding developmental toxicity.

And we're also here today -- we are fortunate to be able to hear from some individuals who can talk about exposure in their communities. And so I don't know exactly the order in which we'll hear people speak. But I think that's an element that we don't always get to hear. And I think it's really important that people, that the Committee, that all of us are able to hear from folks in the field and what it really means in their communities.

So I thank you very much. And will all -- I can speak for my colleagues, trying to keep our comments short.

Thank you.

CHAIRPERSON BURK: Thank you.

The next person I have on the list is Teresa DeAnda.

MS. DeANDA: Good afternoon. My name is Teresa DeAnda and I come from Earlimart, California, in the Central Valley. And they use a lot of pesticides there. I'm trying to focus on chlorpyrifos, because that's what the subject is today.

I just -- I really recommend that it be put on

the Prop 65 list. I get a lot of calls from people who are exposed. And one person in particular from Tivy Valley where there's orange groves all around said that it's just foggy there with chlorpyrifos that the farmer's spraying. And it's day in -- it's just -- sometimes he sprays in the night, sometimes he sprays in the day, because he's got groves all around. And it seems to just stay in that little area right there.

And then I've been doing work with Lindsay, where they had the drift catchers and the biomonitoring, where they found amounts of chlorpyrifos in the drift catcher and also in the bodies of these women and men that participated in the biomonitoring. So it's not staying in the fields.

A couple years ago when I heard that they had banned Dursban from homes, I was really glad. I said, "All right, they're not going to use it anymore." And then I found out, no, they're still going to use it in agriculture. So I said, "What's the difference between using it in homes and using it on agriculture?"; where we live across the street, our schools are across the street from these field where it's applied. And so I just really hope that it can be put on Prop 65 list.

Thank you.

CHAIRPERSON BURK: Thank you.

Next, Irma Arrollo.

MS. ARROLLO: Good afternoon. My name is Irma Arrollo. I came from a small town, Lindsay, of Tulare County.

So my small town it's around for orange trees. And my home is in middle of the orchards. So in these -- this orchard, several times is apply pesticide. These pesticide is -- this chemical is chlorpyrifos. And now we know what effects come from this chlorpyrifos.

In this chlorpyrifos, I can smell. I can taste and I can smell many times, many days of the year.

So recently we're making a study in our bodies, in the air. And we discover what is contaminated is our air. What the chlorpyrifos is on our bodies during the time with the application. So we are very scared.

And now we want this chlorpyrifos, you need to include in the Proposition 65. Because we don't -- this is unacceptable. We live with this in our communities. Because you need to -- you need to make the picture when our communities -- our small communities we live with this every day.

So we need to recognize and you need to -- you need to be concerned about this, because every day we have our families, our children will very health problems.

So, again, we ask for your concern about this

chlorpyrifos and you need to add on Proposition 65.

CHAIRPERSON BURK: Thank you. I appreciate all of that.

The next person I have is Davis Baltz, Commonweal.

No?

He had to leave? Okay.

How about Anne Katten, CRLA.

MS. KATTEN: Hi. Good afternoon. I'm Anne Katten from the farmwork advocacy organization, California Rural Legal Assistance Foundation. I'm an industrial hygienist by training.

And I've come today to urge the Committee to proceed with the development of hazard identification materials for chlorpyrifos, because of the very excellent review that OEHHA did of the body of evidence and also because of the very high degree of exposure in many rural areas to farmworkers and rural residents, as you've already heard somewhat about.

Use of chlorpyrifos in California, unlike many other organophosphate insecticides, it has not been decreasing in recent years. It's been about 2 million pounds over the last six years or so. And each year there are documented poisonings of farmworkers from exposure to drift or early reentry. Just this past summer, there were

two separate incidents in July in Tulare alone, affecting about 100 workers.

It's typically applied by aircraft to cotton and alfalfa and some vegetables, and by air blast sprayers to nut and citrus crops. And an air blast sprayer is a ground tractor sprayer with a fan in the back that shoots the pesticide up into the trees. And this probably isn't too surprising: Both those methods do all too often result in drift off-site and exposure to people, as Irma mentioned.

The monitoring -- air monitoring conducted by Pesticide Action Network and also monitoring conducted by the Air Resources Board has found exposures -- ambient exposures at levels of concern, especially for children.

And then we also have to keep in mind that farmworkers are, you know, the applicators and also field workers reentering fields are directly exposed to residues, particularly I think weeding cotton and weeding vegetable crops that have previously been treated. And the reentry intervals right now, they're set to prevent acute illness rather than any reproductive or developmental effects.

Thank you.

CHAIRPERSON BURK: Thank you.

The next one -- I'm not sure -- Domatila Lemus.

Oh, I guess I should have gone in a different order.

MS. LEMUS (through Dr. Reeves): Good afternoon. My name is Domatila Lemus. And I'm --

MS. KATTEN: I have to get her to speak in shorter amounts.

So she's grateful to be here this afternoon and to tell you what her experience is regarding chlorpyrifos use.

MS. LEMUS (through Dr. Reeves): When one sees agricultural communities or just sees what the layout is like, you see that there are a lot of farms with olives, citrus, and grapes. Applications are very common and we always see it when they're applying the pesticides.

And one minute we're fine, the next minute we're sick. A lot of headache is one of the symptoms.

Kids with a lot of problems with cough and asthma, a lot of kids at the school, for example, the one that we have right near our house, it's surrounded by orange groves. And they are often spraying and the kids have to go outside -- I mean they are outside to play and coming to and from school. And they're always breathing those pesticides.

And, please, whatever you all can do to help us with this problem. And remember that these pesticides are

affecting our kids and that's our future.

Thank you.

CHAIRPERSON BURK: Thank you. I appreciate what that takes to come and speak in public.

Okay. Next we have Christian Volz from McKenna, Long & Aldridge.

(Thereupon an overhead presentation was Presented as follows.)

MR. VOLZ: Good afternoon, Dr. Denton, Chairperson Burk, and members of the Committee. On behalf of Dow AgroSciences, thank you for the opportunity to address you this afternoon on the reasons why Dow believes that chlorpyrifos should not be selected for priority development of hazard identification materials.

We've submitted detailed written comments, which I know that Chairperson Burk at least has read, and I hope you'll all take a chance to read. We won't belabor them in detail today. We'll just give the high points.

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MR. VOLZ: There'll be three speakers. I'm going to give an overview of the three principal reasons why we think the compound should not be selected for priority development and a discussion about the prioritization process itself.

I'll be followed by Dr. Carol Burns, who will address the epidemiology issues. And then she in turn will be followed by Dr. Juberg, who will address the animal toxicity studies.

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MR. VOLZ: As an overview, the three principal reasons why the compound should not be prioritized for development of hazard materials are:

First, several -- well, chlorpyrifos, as you know, is a major commercial pesticide product. It's been around for more than four decades. And as a result, it's been evaluated and reevaluated continually for all of its human health effects, including specifically potential DART effects. Those studies -- or those evaluations are ongoing and will continue to be ongoing.

Several agencies have recently examined the compound and have concluded specifically on the basis of exhaustive reviews of the data that the data do not support a finding that it is a developmental or reproductive toxin.

As a matter of priority -- or as a matter of resource allocation, it is extremely unlikely that this Committee would reach a different conclusion reviewing the same data. And, therefore, it should be a low priority to

make that exercise.

The second point, which Dr. Burns will discuss, is that, contrary to the OEHHA survey and contrary to Chairperson Burk's initial sort of overview, which is an accurate overview of the abstracts, when you actually take a hard look at the epidemiology studies themselves and not just the abstracts, you will see, and Dr. Burns will explain, that they do not in fact support a conclusion that the compound has developmental or reproductive toxic effects. There is not even one, much less two or more, epidemiologic studies of adequate quality that support a conclusion that the compound is a DART.

Third, and finally, and again contrary to the abstracts and the way OEHHA has characterized the results of the abstracts, the actual animal toxicology studies in the OEHHA survey that meet Proposition 65's demanding criteria, which is to say studies of adequate scientific quality under generally accepted principles, they do not show DART effects. The studies on the other hand that do purport to show DART effects are studies that don't meet those criteria and that use extreme and unusual routes of exposure and doses, which make their results essentially irrelevant as a risk assessment measure.

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MR. VOLZ: Just to expand a little bit more on -- well, okay. The OEHHA prioritization process specifically provides, and I quote, "It is unlikely that chemicals will be proposed for CIC or DARTIC review that have recently been reviewed by an authoritative body and found to have insufficient evidence of carcinogenicity or reproductive toxicity, respectively."

Because the compound is such an important commercial pesticide, it has been very extensively and very recently reviewed by a number of expert agencies, including one agency recognized as an authoritative body for Proposition 65 purposes. That's U.S. EPA, and specifically the U.S. EPA Office of Pesticide Programs.

It has concluded very exhaustive reviews of all the existing toxicology data on the chemical in 2002 and updated in 2006. And as reported in detail in our written comments -- and I won't again -- we'll get into a little more detail later, but not much -- those reviews failed to find sufficient evidence to designate or to describe the chemical as a developmental or reproductive toxin.

Similarly, three other agencies which certainly qualify as expert, namely, the European Commission on Classification and Labeling, in 2002; the Australian National Pesticide Registration Authority, in 2000; and California's own Department of Pesticide Regulation, in

2001 have completed searching evaluations of the compound specifically including its potential to produce reproductive or developmental toxicity.

All of them found that no such designation was justified by the available scientific data.

And at the end of the day, I mean the same conclusion is what would be reached by the DART Committee. You'd be looking at the same data that these agencies did. And, you know, we're confident that if you were to be put through that exercise, you would come to that same conclusion. And as a result, the decision that you should make logically today is that it should not be a priority of this Committee to attempt to second guess the conclusions that have been reached by these other agencies looking at all of the data and not just the data in the OEHHA survey.

Any questions before I turn it over to Dr. Burns?

Thank you.

(Thereupon an overhead presentation was Presented as follows.)

DR. BURNS: Good afternoon. My name is Carol Burns, and I am a Ph.D epidemiologist educated at the University of Michigan, and I serve as an epidemiologist for the Dow Chemical Company.

The purpose of my talking to you today is to just

cover the Epi studies and my view on those studies.

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DR. BURNS: I think it's important to step back a little bit and consider that sometimes a lack of a negative study doesn't mean there's a lack of evidence. If you look at the history of epidemiology, which is really an observational science, publications in the field were starting in 1920. Research on birth defects, as exemplified by the founding of March of Dimes, started before World War II.

Chlorpyrifos itself became registered in 1965. By 1982 epidemiology associations were having annual meetings, discussing issues of the day and priorities for research.

Between the time that chlorpyrifos was registered -- I did pub med search from 1966 to 2002 on birth weight and epidemiology. And there are nearly 9,000 publications. So it's not for lack of looking that not until 2003 do we see the very first published study on decreased birth weight and chlorpyrifos.

So let's look at the studies that are considered today for the OEHHA review.

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DR. BURNS: What I did was to put the three major studies. I took the icons from each prospective study to review for you. And if you think about them, they all have a very similar design. They're all mothers and children studies, studies of infants. They all collected either blood or urine to evaluate exposure. And they're all done by highly respected institutions.

The one on the top right is the Columbia mothers and newborns study. And there are three publications. But as was mentioned before, they really are all on a similar number of mothers and their infants. Sort of if you consider they -- small, bigger, and biggest by the time they were publishing these studies.

The study on the bottom by Berkowitz from Mt. Sinai also had a similar design, collecting data from the mothers and evaluating birth weight and so forth in the children.

Now, in the abstract though, however, this should be considered a negative study, because none of the birth endpoints were related to the urinary endpoints with exposure.

And, in addition, there was a finding of the paraoxonase enzyme, but that was irrespective of TCP exposure. It was elevated in both -- it was associated with head circumference in both groups. So really that is

considered a negative study.

And the third study is the one here in California on the Salinas Valley mothers. They're all rural mothers, perhaps similar exposures to what we've heard about. And this study is larger than the Columbia mothers and newborns study, and they show no effects on reproductive outcomes.

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DR. BURNS: In your packet we reviewed the critical weaknesses of the Columbia mothers and newborns study. And just really briefly, first of all, we feel that this should be considered a single study. And there are many confounders in this population that we don't have time to go into.

Exposure may also have been misclassified. And in general the plausibility of the cause-and-effect relationships are pretty weak.

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DR. BURNS: Now you see these three icons again. And the point of these studies is that not only are they looking at the infants, but they're following those newborns through their childhood to look for other effects.

And, again, the study on the right, the Columbia mothers and newborns study, published in 2006, was actually negative. The children had no neural development effects at 12 months of age and had no neural development effects at 24 months of age.

And interestingly, not listed in the packet is the Ciamaga study, which had very similar endpoints, very similar study design, and showed no neural development effects whatsoever.

The Mt. Sinai study has yet to publish on the children as they've aged through their study.

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DR. BURNS: So in summary, the epidemiology studies that I viewed do not support the conclusion that chlorpyrifos is a developmental and reproductive toxicant.

Those conclude my slides. Do you have any questions?

CHAIRPERSON BURK: No. Just one, I guess, where you said that in your previous slide a follow-up, there were no differences. Was that in here? Because I didn't actually -- okay, I see what you're saying.

DR. BURNS: There's no results.

CHAIRPERSON BURK: They examined cognitive and motor development 12, 24, and 36 months. Okay, I see what

you're saying.

Do you have -- this is a general question that I was just curious about. They in some of their studies found that after the ban on chlorpyrifos, the residential use, that they didn't see the same results after that. So obviously that's not a study finding. It's just an observation. But do you know why it was banned residentially? Does anyone -- do you know, Poorni?

DR. IYER: When U.S. EPA came out with their numbers and their risk assessment on 2002, if you actually go through the entire -- that was around the time just after FDA was passed protecting infants and children, and they had a number of uncertainty factors added on to. And they made the decision -- I guess they did not categor -- you know, classify it because the U.S. EPA's not in the business of classifying them as DART.

But they made the decision to ban it for residential indoor use.

CHAIRPERSON BURK: Okay. But you're saying it wasn't for DART endpoints or it was?

DR. IYER: No, they don't state that.

CHAIRPERSON BURK: They don't state it. Okay.

DR. IYER: But infants and children, there was concern. In fact I think -- I don't have the sheet of paper with me right here. But in their -- there are

statements that you can get out of their documents which actually talk about that concern.

CHAIRPERSON BURK: Sorry. I probably should have asked that during our discussion. I didn't want to interrupt the speakers.

Did you want to say something?

DIRECTOR DENTON: Jay Schreider is here, and I know he wanted to make a statement about the -- something that was said previously. So maybe you could address the same question.

DR. SCHREIDER: Sure, I'll try and address both of them.

I'm Jay Schreider. I'm a toxicologist with the Department of Pesticide Regulation.

I think one of the primary movers for the banning of the residential or the home use I think related to the cholinesterase inhibition and the effects that was -- the residues they were finding in the home with the kids. They addressed some of these other issues, but I think that was probably one of the primary movers.

The other thing I wanted to correct is in fact that DPR has looked at chlorpyrifos. At the current time we've got it in risk assessments, so it's probably -- or it is in this a little bit of an overstatement to indicate that we'd reached conclusions about the reproductive

toxicity. The risk characterization is going on at this point. That's one of the considerations. And I'm not saying it should or shouldn't be considered for listing. But it's currently under review by us and both DPR and, in fact, Office of Pesticide Programs have expressed an interest in if it is decided to develop a hazard identification document to work with OEHHA directly in developing that document.

CHAIRPERSON BURK: Thank you.

This should be Dr. Juberg.

DR. JUBERG: It's actually Daland Juberg, yes.

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(Thereupon an overhead presentation was Presented as follows.)

DR. JUBERG: My name is Daland Juberg. I'm a toxicologist with Dow AgroSciencies. And I appreciate the opportunity to speak before OEHHA and the DART Committee today, particularly just focusing on one particular aspect and, that is, data quality.

You have our submitted comments, which I appreciate the Committee's understanding and recognition of.

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DR. JUBERG: And when I say data quality, I think

it's very imperative at this early stage to consider the importance of study design. In the prioritization process OEHHA noted that factors considered in weighing evidence from animal studies include routes of administration and dose response, amongst others. The Society of Toxicology, the mainstream society for professional toxicologists in the world notes the following two key factors related to study design:

The relevance of experiments using doses that are many multiples of conceivable human exposure and unrealistic routes of exposure is, at most, quite dubious. Use of routes of exposure and high level -- high dose levels set primarily for purposes of experimental convenience should be avoided.

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DR. JUBERG: I give you those quotes as we look at the OEHHA survey because, with respect, I believe that the 21 studies cited as evidence of DART have been mischaracterized. And let me just substantiate that with a few bullets.

Most had major deficiencies in study design.

Two in fact included co-exposure to other chemicals: One, xylene; one, chlorpyrifos methyl. Those are not germane to an evaluation of chlorpyrifos.

Six had no information included on route of exposure.

And I fully recognize that these are just at the abstract stage. But I'm a believer in data quality at all stages.

Six had no information on route of exposure, as mentioned.

Four had no information on dosing regimen. And, in fact, I took the time to go beyond the abstracts. And fully more than half use routes of exposure not relevant to evaluation of developmental or reproductive toxicity. They use subcutaneous exposure and intraperitoneal exposure, neither of which are used in standard developmental or reproductive toxicology testing.

Of the 21, only 5 used an appropriate design. And let me speak to those 5.

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DR. JUBERG: These were design studies that did use appropriate routes, all oral gavage, which is a standard methodology for evaluation of developmental toxicity. One included dietary exposure, which is the standard when evaluating reproductive toxicity.

These five studies and the italic conclusions are not my conclusions. These are author conclusions.

The first, an oral gavage developmental study, no evidence of teratogenicity.

Farag, '03. Fetotoxicity and teratogenicity only at maternally toxic doses.

Breslin, which included both a developmental study and a reproductive toxicology study concluded that chlorpyrifos was not embryolethal, embryo or fetotoxic, or teratogenic, and did not adversely affect fertility or the function or structure of the reproductive organs.

Ruben in '87 concluded that a chlorpyrifos is not teratogenic and is not fetotoxic in the absence of maternal toxicity.

And, finally, an early study reported that there was equivocal developmental effects that were not replicated in later studies at higher doses.

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DR. JUBERG: My summary and what I would submit to you today is that the animal toxicology studies included in the OEHHA survey do not support the conclusion that chlorpyrifos is a DART. Most studies cited used inappropriate routes of administration and/or have confounding issues such as the use of DMSO as a vehicle. DMSO has neurotoxic properties of its own. That was the body of work that Dr. Burk spoke to when there are eight

or nine studies that used that. That's a major confounder that we have to weigh.

Appropriately designed studies do not indicate that chlorpyrifos is a developmental or reproductive toxicant.

And this is a conclusion that has been alluded to earlier by Mr. Volz: That regulatory authorities and expert panels worldwide have looked at this exhaustively, extensively and do not consider chlorpyrifos to be a DART.

My last concluding statement then.

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DR. JUBERG: Neither the epidemiological nor the animal data support prioritization of chlorpyrifos for consideration as a DART.

Thank you. And I'd be happy to take any questions of the panel.

CHAIRPERSON BURK: I guess I don't see any questions.

This is a somewhat difficult one for me. You know, again I'm limiting myself to the abstracts. But I am aware of, you know, some of these criticisms of the studies. And certainly if we were to go ahead and recommend this and look at it, we would look closely at the study designs, routes of exposures, and all that.

So the question I think I'm asking myself is: Is

there a sufficient data here for us to consider? And not saying what the decision would be. But, you know, somehow I feel that it is our responsibility to independently take a look at the data.

So I'm not pushing one thing or the other on the group. And I'd be curious to hear from anybody else as to their opinion.

COMMITTEE MEMBER JONES: I must say I'm intrigued by this study by Sherman of the -- I'm intrigued by the study by Sherman, which clearly is not an epidemiologic study, in which they -- or he or she documents four children with what is described, without reading the paper, as a pattern of malformation. And that's --

CHAIRPERSON BURK: I know. And I almost looked it up. But I was trying to sort of play by the rules. And so, you know, I just put it in the list as another intriguing thing that I thought would be interesting to look at.

The other thing that is very intriguing to me, but I don't know that we'd be able to tease it out, are the neural and behavioral effects, because it's something that -- you know, I don't know that it shows up in the standard multi-generation studies that we look at for developmental tox. But here you do have an Epi study with it and then you have a bunch of animal studies that look

at it sort of with a plausible mechanism.

COMMITTEE MEMBER JONES: Are you talking -- the Epi study, you're talking about the Rauh study published in Pediatrics?

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER JONES: Yeah, it looks pretty darn good, doesn't it?

CHAIRPERSON BURK: It does. And with the, you know, animal back-up it's -- at least to me it seems like it's worth taking a look at.

Again, I don't want to waste, you know, people's time doing something that many other authorities have looked at. But I kind of feel it's our responsibility to independently look at these things. So that's just my opinion.

Are there any other comments?

Yes. Please come forward.

DR. BURNS: Sorry. If I may address the panel again.

I think in talking to the Sherman study, there's also another case report study. And it was my understanding that case reports were not studies of adequate quality. There's lots to be said about case reports and their value to physicians and alert physicians coming forward. But they may just be something you see

that's coincidence and it's not analytical research, despite how interesting it may or may not be.

And I think the important thing to keep in mind with the Rauh study, however interesting it may be as well, there's another study, designed the same, larger, that didn't support those conclusions. I think it's important to look at them together.

COMMITTEE MEMBER JONES: I must say I would take exception to the fact that four children, all exposed to the same drug, all of whom have a pattern of malformation, all exposed to this insecticide, that that's not analytical. Maybe from the standpoint of an epidemiologist it's not. But from the standpoint of a dysmorphologist it is. Very, very, very important.

COMMITTEE MEMBER KLONOFF-COHEN: I also want to just ask quickly before you left. Sorry.

The Rauh study -- you're dismissing the Rauh study because there's a larger study that -- I'm sorry, I don't know which study you're referring to. But are you dismissing the Rauh study for any inherent weakness of the study itself or just because there's another study out there that's got divergent findings?

DR. BURNS: Well, no. In the interests of time I didn't think it was appropriate to go through what we had written as the weaknesses. But you had mentioned in

earlier discussions this morning that a bigger study should be given more weight than a smaller study. And so I thought it was important to comment that --

COMMITTEE MEMBER KLONOFF-COHEN: Oh, no. I didn't say a bigger study was given more weight. I just said that one of the strengths of the studies that I was reviewing was that it had a larger sample size with striking findings. They adjusted for a lot of methodologic strengths, including sample size.

DR. BURNS: I didn't mean to mischaracterize you. I'm sorry.

COMMITTEE MEMBER KLONOFF-COHEN: So I guess -- I'm just looking at the Rauh study just because Dottie had said something. And actually I thought it was -- it looks like it's a well done study. So I was just wondering what you were taking --

DR. BURNS: Well, I think it's interesting in the study itself that the average IQ of the women in the study is 80. And at one year of age half of the children already have neural developmental delays. And so then to characterize it -- there is no relationship with the maternal blood chlorpyrifos levels at 12 months, there's no association at 24 months, but that biologically that becomes plausible at 36 months, when they already had problems compared to standards. I'm just saying that

there are other studies that show differences.

DR. MATTSON: Just a very quick comment about Sherman's report on the --

CHAIRPERSON BURK: Would you identify yourself again.

DR. MATTSON: Yes. Excuse me. I'm sorry.

Joel Mattson. I am an ex-employee of Dow AgroSciences, now a consultant to them. A toxicologist for a really long time.

CDC has reviewed those cases and has concluded that there is no basis for concluding that they're related to chlorpyrifos exposure. And so that's published and can be gotten to you.

COMMITTEE MEMBER JONES: And what are they related to?

DR. MATTSON: I don't know that CDC can determine. All they did was review Dr. Sherman's presentation and materials and said there was no basis on that, and felt sufficiently motivated that they published a -- I don't know if it was a letter to -- it was a number of years ago, you'll notice. And I'm remembering back. But she wrote that. CDC reviewed it because it's a significant allegation. And CDC found no scientific basis for the allegation.

COMMITTEE MEMBER JONES: Okay. Is our -- can you

find that for us, CDC's report? And maybe you could --

DR. MATTSON: We can provide it to you.

DR. REEVES: If I may. Margaret Reeves again, Pesticide Action Network.

I wanted to draw your attention to one piece in our comments that -- this is in reference to the listing of authorities who consider -- who have presumably decided, including U.S. EPA, to register chlorpyrifos and therefore recognizing that it's not a developmental toxicant.

I want to draw your attention to the comment -- the letter written to Steven Johnson in May of '06 from EPA staff scientists, specifically in opposition to that decision from EPA, specifically based on their considerations of the literature over many, many years that it is in fact developmental toxicant. And it's their concern for that that led them to write this letter in opposition to the EPA decision to go ahead and register chlorpyrifos. So you can check that out from the comments.

Thank you.

CHAIRPERSON BURK: Okay.

MS. ARROLLO: Yes, I want to add my comment. And apparently I don't understand on many technical parts. But I just I want to say something.

So you need to put a consideration that really to our lives because we are exposed to this chlorpyrifos in our communities. And I know for many years make this kind of studies. So I think we have the right to know what is happening with this study, saying we need to know what these chemical affects our lives.

And we need to know science on something and what that kind of chemical is. Because all the time we talking about the short -- the effects for short times and long terms. So now we live the long-term affects our health. So now it's time we need to know what is happening with this chlorpyrifos. So you need to put in consideration our lives in our communities.

Thank you.

CHAIRPERSON BURK: Okay. Comments?

COMMITTEE MEMBER WHITE: I'll make a pretty quick comment.

We do know many things here, but we know three things for sure: We have abstracts, we have literature that's been refuted, and we have a community of people who are living in a chemical fog.

Because of those three things, I would make the recommendation that we take a closer look as a body, that we look deeper into the literature. We can look at the abstracts or read the abstracts and draw a pretty

significant conclusion, maybe even on either side. And being told that the literature really isn't conclusive enough is not good enough for me, when we have a group of people here who live in the middle of that chemical fog. We need to take a closer look at the literature just to see if it's even worth it to present it for eventual listing. We're not here for that. But I think it would be worth it to take a look at the literature as an independent body and see where we can go from there.

CHAIRPERSON BURK: Any other comments from the Committee?

Are we ready to take our poll?

Okay. Do you advise OEHHA to begin preparation of the hazard identification materials for chlorpyrifos?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2, 3, 4, 5, 6 -- 7.

Okay. So it's unanimous.

Thank you.

Let me get back to my schedule. Oh, I have too many papers here and I'm confused.

No, I know. I was just seeing. It's three o'clock. We still have -- that's all right. We're going to just keep going.

The next one is chromium hexavalent. And the

staff presentation will be given by Dr. Mari Golub.

(Thereupon an overhead presentation was Presented as follows.)

DR. GOLUB: Thank you, Dr. Burk. I'm Mari Golub and I'm presenting the extent of the evidence available for prioritization of hexavalent chromium, or Chromium 6.

Chromium 6 is used as a colorant agent in dyes, paints, and inks. It's used as an anti-corrosive agent surface coatings and in electroplating baths. Occupational exposures occur in some kinds of welding and in chromium sulfate manufacture.

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DR. GOLUB: There are five epidemiologic studies reporting increased risk of adverse developmental or reproductive outcomes. They involve occupational exposure of men in Denmark, China, and India, and use endpoints such as sperm parameters, hormones, and partners spontaneous abortion. All five are analytical studies of adequate quality.

And there are eight studies reporting no increased risk of adverse developmental or reproductive outcomes.

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DR. GOLUB: There are 20 animal studies reporting developmental or reproductive toxicity. Many of these use

sperm and testes endpoints in species such as rats, mice and monkeys. There are also studies of developmental toxicity and of other reproductive toxicity.

There are three animal -- abstracts of unpublished animal studies reporting developmental toxicity and one study that did not report developmental or reproductive toxicity in animals.

And that concludes my presentation on hexavalent chromium.

CHAIRPERSON BURK: All right. That's straight and to the point.

COMMITTEE MEMBER JONES: As always.

CHAIRPERSON BURK: Yes. Thank you.

And this is the one that I was assigning to Carl Keen. But since he's not here, I'll just put in my two cents, which pretty much echoes what we just heard.

And I will say right upfront that there's no one signed up to speak one way or the other.

Oh, there will be one?

Oh, I didn't -- I guess maybe there was, but it didn't get printed out on any -- well, anyway, I'll let you talk.

I'll just say a few things. As you heard, there are a number of Epi studies. They are focused on -- I learned a lot from reading these -- stainless steel

welders and their semen quality. So it's occupational exposure.

These are backed up with quite a large number of animal studies, a number of which are on male parameters. That seems to be the biggy here.

The positive findings are on sperm morphology, concentration, motility, counts, FSH levels. And this is across several countries. And there was also one interesting one on possible male mediated spontaneous abortion in stainless steel welders and not in the other welders, with some suggestion of mutations being possible.

There were also negative Epi studies, some done by the same investigators but in, you know, slightly different populations. And I do think there are -- for example, one was done in male mediated spontaneous abortions in the wives of welders that were undergoing in vitro fertilization, you know. So slight differences on the theme.

And also probably lower exposures in some of these. I have a feeling that exposure levels are playing a role here.

Anyway, so I guess my conclusion, there seem to be enough studies to look at at least male effects for positive. And there are also positive developmental tox assessments in rats and in mice. Although I'm not quite

sure about the study designs on those and whether there was maternal toxicity and so forth. They're not the traditional type of studies that we like to look at.

So without having much idea about the quality of some of these studies and not hearing many comments to mull over either, I would say that there are sufficient number of studies of humans backed up with numerous animal studies, particularly focused on male reproductive toxicity, and it would be enough to warrant consideration for us to, you know, go forward with a hazard identification document preparation.

Would you like to come up and make your comment now?

MS. SHARP: Hello again. I'm Renee Sharp with the Environmental Working Group. And I think that it's pretty clear that there's enough occupational-related studies to warrant a closer look.

But I also want to make the panel aware of some of the broader context. And that is -- I mean granted there are exemptions for drinking water chemicals. But hexavalent chromium is a chemical that's found in drinking water widely around California.

And it's also sort of interesting to think about the national context, because right now the EPA has a federal standard for total chromium. And that was based

on certain assumptions about the proportion of hexavalent chromium to Chromium 3. And when OEHHA started looking into hexavalent chromium for a public health goal, and subsequently the drinking water providers around the state started actually testing for hexavalent chromium, they actually realized that a portion of hexavalent chromium to Chromium 3 was a lot higher than they expected. It's probably true around the country. And it's probably true that the EPA's standard is probably really too high.

And I realize that this is not the panel's, you know, job to sort of -- this is not the reason why they would go ahead with a prioritization of this chemical. But I'm just saying that it would be really helpful if OEHHA were to look at the data and devolve the hazard -- sorry, I speak too fast -- hazard identification document, because it would be also -- it would be helpful to inform the EPA and those of us in the, you know, public health advocacy community, you know, who are concerned about this chemical in drinking water.

So thanks.

MS. COX: Could I make a quick comment?

CHAIRPERSON BURK: Yes, certainly. Come forward.

MS. COX: My name is Carolyn Cox and I'm with the Center for Environmental Health in Oakland.

And I just wanted to speak about hexavalent

chromium because it seemed like it hadn't gotten a whole lot of public comment.

And one of the things I did to prepare for this meeting was just look at brand new research that's just been published in the last few months, with the idea that if there's new research being published about one of these chemicals, that's strong support for the idea that OEHHA should go ahead with a more extensive study of whatever the chemical is.

So with Chromium 6 there's an interesting new paper where the European community looked at effects on embryonic stem cells and found that Chromium 6 is toxic to those stem cells. And it doesn't directly show developmental and reproductive toxicity, but it certainly indicates that it has that kind of potential. I thought it was worth considering.

Thanks.

CHAIRPERSON BURK: Another public comment?

Yes.

DR. TARDIFF: Thank you. Again, I'm Bob Tardiff with the Sapphire Group. And in this particular set of comments I don't represent any organization but my own.

I find it a bit disturbing that given all of the information that we have about hexavalent chromium ingested, that we would be pressing ahead to try to show

that it's a reproductive and developmental toxicant. It just doesn't make sense, because what we do know is that this compound when ingested gets converted to trivalent chromium, which barely gets absorbed. And if it does, it doesn't have any toxic potential whatsoever. It gets mixed up with the normal background of hexa -- or trivalent chromium that we obtain in the diet.

That information is readily available. It wasn't alluded to by the earlier presenters in this regard. It should completely dismiss any particular consideration of that. If you want to talk about hexavalent chromium inhaled, which is really an occupational issue, that's a separate matter. But I think we're talking about an environmental exposure; and as one of the commenters mentioned, concern about drinking water. There's just enough empirical evidence that you shouldn't have any concern about that and you shouldn't be trying to put this in a high priority as a result.

Thank you very much.

MS. SHARP: Sorry, I had to respond. I only used, you know one minute of my five minutes anyway.

Well, with regards to, you know, whether you should be concerned about, you know, drinking water and it being converted to trivalent chromium, that's absolutely true; it is converted, at least most of it. But, you

know, as we know, it's -- the point that it is converted doesn't mean it's not toxic, right, because it can be around in the body and then it can be doing damage and then it can be converted. So that was point number one.

Then point number two is that there was a recent study done by -- I want to say National Resource Council, but that's not actually it. But it was a federal study that essentially looked at rats that ingested hexavalent chromium through drinking water, and they found that essentially it was carcinogenic in at least a couple of different ways.

So given that was a very strong finding, I have a hard time believing that the fact that it's converted to trivalent chromium is -- you know, just make it not an issue.

DIRECTOR DENTON: Just from OEHHA's perspective, we have been in the process of revising and looking at a PHG for hexavalent chromium. And I think it's quite evident, at least from what we've seen, is that the debate is not over as far as carcinogenicity conversion and so forth. So there's still information continuing to come out about that and will continue for some time.

CHAIRPERSON BURK: Are there any other comments from the Committee?

COMMITTEE MEMBER HOBEL: I'd like to make a

comment.

I think that is really interesting subject. And there are several papers that --

THE REPORTER: Can he speak into the mike.

COMMITTEE MEMBER HOBEL: Sorry.

I find this paper -- or this subject very interesting, and there's several papers that I think are really relevant. First of all, I think that in terms of inhaled toxicant, this is -- there's one paper here that suggests it's related to spontaneous abortion. And in the animal studies, it suggests that this could be a male factor that leads to increased risk of abortion by affecting spermatogenesis. And this issue that just came up recently about stem cells is also I think very interesting.

And, number three, this is one of the few where it's been mentioned in animal studies and in human studies that the effect is through oxidation, and antioxidants may eliminate the effect of this. So this is one area where there is a potential solution to the problem of those who have inhaled exposure.

So I think this is very important and needs to be addressed.

CHAIRPERSON BURK: Thanks.

Okay. So are we ready for the next poll? I'm

getting faster now.

All right. Do you advise OEHHA to begin preparation of the hazard identification materials for chromium hexavalent?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2, 3, 4, 5 -- 6.

And Linda is recusing herself.

COMMITTEE MEMBER ROBERTS: (Nods head.)

CHAIRPERSON BURK: Okay. Put down six and one recused.

All right. Next on the list is DDE. And this will be presented by Farla Kaufman again.

(Thereupon an overhead presentation was Presented as follows.)

DR. KAUFMAN: Thank you. As Dr. Burk said, my name is Farla Kaufman and I'm presenting the extent of the evidence available for the prioritization of dichlorodiphenyl-dichloroethylene, otherwise known as DDE.

DDE is the initial and predominant environmental breakdown product of dichlorodiphenyl-trichloroethane, rather known as DDT. DDT was banned in the U.S. in 1972. It's still used in other countries, mostly for controlling malaria.

DDE, like DDT, is a persistent organochlorine

pollutant. DDE is also a biological metabolite of DDT. Most exposure to DDE in this country comes from the diet.

--o0o--

DR. KAUFMAN: The epidemiologic data includes 38 studies reporting increased risk of adverse developmental or reproductive outcomes. These include a wide range of studies from many different countries. Most of the studies measured biological levels of DDE, with only a few of these being occupational studies.

The wide range of outcomes included preterm birth, neuro developmental delays, altered hormone levels, changes in menstrual cycles and serum quality, and asthma.

Two meeting abstracts were also reporting increased risk.

Thirty-three studies reported no increased risk of adverse outcomes.

Two meeting abstracts reported no increased risk.

There were four studies that were unclear, six studies that were deemed related, and one study without an abstract.

--o0o--

DR. KAUFMAN: The animal data shows four studies reporting developmental or reproductive toxicity. These included effects on the development of the male reproductive tract and sperm production.

There were 11 studies reporting no developmental or reproductive toxicity. And 22 related articles were found.

--o0o--

DR. KAUFMAN: And that concludes the presentation for DDE.

CHAIRPERSON BURK: Okay. Thanks.

I've asked Dr. La Donna White to lead the discussion on DDE.

COMMITTEE MEMBER WHITE: Okay. With respect to DDE, I -- it was quite interesting, primarily because most of the studies done were conducted with significant exposure of the chemical. Since it's not -- since DDT really isn't used here anymore in this country, and particularly, as we know, in California, and it's metabolite, DDE, the studies that supported a DART conclusion were all over the map. So I was significantly confused after reading all of the studies.

A lot of the studies that supported a DART conclusion had to do with male reproductive studies. They had to do with sperm motility, et cetera. Some studies even made the correlation with spontaneous abortion with respect to the impaired sperm, et cetera.

So as it pertains to DDE in the diet, I did not see -- and I've read through the studies -- I did not see

a significant correlation with respect to development and reproductive health as it pertains to DDE in the diet in this country.

There were several studies, when I read the studies on no correlation between development and reproduction, seemed to be stronger in their conclusions, with less attention paid to "maybe," "could have," "might suggest." So I thought the studies on DDE with respect to their not being a correlation were actually stronger.

If you look at the animal studies, the animal studies quite interestingly enough supported the male reproductive studies in humans.

So the question becomes for me: Is there enough conclusive evidence in these abstracts that we read to warrant even considering this particular chemical?

And in reading through other countries -- about other countries with respect to a cognitive development, with respect to higher concentrations and sperm motility, with respect to asthma, I think any organophosphate that any child is exposed to can be a problem with respect to asthma. One study looked at the prenatal exposure and asthma, but that was at a higher level of exposure with respect to asthma.

But the studies that refuted a lot of these positive studies were just -- they just seemed to be more

compelling to me as well.

So for us to consider listing DDE, period, or even considering it, period, just seems like -- I would rather see other chemicals that we've already discussed placed in the forefront, because there's -- these studies are just too confusing with respect to this being a DART chemical to even recommend for listing.

But that was from me. I was confused after reading all of the studies. Because at first I thought, okay, why don't we go ahead and consider this. But then when I went further in to some of the other abstracts, I thought, wait a minute, this is way too confusing. There's too many assumptions made in the abstracts. Maybe in looking more at the studies, it may be more conclusive. But it was -- they were just all over the map with suggesting possibilities and not concrete evidence for this particular chemical to be placed higher on the list.

And those are my thoughts. I've read them. I've highlighted them in every color imaginable.

(Laughter.)

CHAIRPERSON BURK: Were there any public comments on DDE?

Okay. I didn't receive any.

So I guess we'll open it up to the others on the Committee for comments.

COMMITTEE MEMBER HOBEL: Yes, I found this somewhat confusing initially also. But I think this is a good example of the whole issue of timing and this issue of fetal programming. Because I think when you begin to put all the pieces together, it's a complex puzzle, but there's endocrine disruption; it affects a person preconceptually; it affects the fetus in utero, which then programs the fetus to have, and as a child to have, and as an adolescent to have menstrual cycle dysfunction. It's associated with preterm birth. It's associated with increased risk for abortion.

So it seems to have an effect throughout the life course of events. And because of that, I think more time and effort should be spent in trying to sort all this out and find out exactly when and at what time is this really important both in males and females.

COMMITTEE MEMBER WHITE: There was actually one study that drew my attention. I actually -- the abstract caught my attention. And that is the transplacental and lactational transfer of DDE in Sprague-Dawley rats. And what the authors looked at, which was quite interesting, was the concentration of DDE in adipose tissue. And I thought that was quite interesting, because any particular chemical that is lipophilic that can actually be mobilized from fat storage sites, et cetera, to create an effect

such as that of the fetus would be quite interesting to take a look at. I think that particular study caught my attention primarily because of the fact that if this particular chemical is mobilized from fatty tissue in both the fetus and in the fetal tissue and in the maternal -- they also looked at maternal tissues as well -- that would be quite interesting, because it could have more far-reaching effects throughout the life of the fetus. And I think that would be quite interesting there.

But it needs more time. I would agree. We need more time and more attention to sort out the confusion.

COMMITTEE MEMBER KLONOFF-COHEN: I'm just looking through this really quickly. It looks like there's six studies that talk about impaired seminal parameters in men, sperm motility - numbers 1, 11, 14, 32, 60, and 78.

CHAIRPERSON BURK: Yes, I noticed that too. I mean there are patterns in here. It's not totally --

COMMITTEE MEMBER KLONOFF-COHEN: Right.

CHAIRPERSON BURK: And also the --

COMMITTEE MEMBER KLONOFF-COHEN: Three studies on decrements in estrogen and progesterone. Yeah, there are groups of studies where they find significant findings. So maybe to group it by associated problems might be a way to go.

CHAIRPERSON BURK: Yeah.

Any other comments?

Any more comments, Linda?

Oh, you're up more on endocrine disrupting chemicals, aren't you?

It's something we haven't dealt with much before, so it would be a novelty, I mean particularly looking at things like, you know, age at menopause and age at menarche and things like that -- irregular cycles. A lot of hormonal type of effects.

All right. Well, are we ready for the poll on this one?

Could I ask something first before that? Which is just kind of a general question.

If we were to consider this and list it, how would it possibly be warned against?

I know that's not our job, but --

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think -- what I understood was that the exposures are coming through food. So what you'd have to look at is whether or not there's an exposure that's high enough in some food source. And if that was the case, then -- it doesn't matter how it got there so much as -- you know, when you're looking at warnings, you'd have to look at whether an exposure, you know, is high enough to trigger a warning requirement.

So the fact that it's not used here and things like that, it doesn't make a lot of difference in that regard. You're looking at the exposure.

CHAIRPERSON BURK: Okay.

COMMITTEE MEMBER WHITE: So then I guess the question would be: What would be the food sources? What would be the likelihood of the exposure? And I didn't garner that from anything I read. So --

CHIEF COUNSEL MONAHAN-CUMMINGS: Once again, it kind of goes back to the discussions we were having before, is that it ends up being something that's considered much further down the road, you know. I think that we have kind of some initial ideas about where the exposures might be coming from, but at this point we wouldn't be able to say.

CHAIRPERSON BURK: All right. Well, I'll read the question again.

Do you advise OEHHA to begin preparation of the hazard identification materials for DDE?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2, 3, 4, 5, 6 -- 7.

All right. Some of those hands were a little slow in coming up, but --

(Laughter.)

CHAIRPERSON BURK: All right. So making progress.

The next chemical is Methylisocyanate.

And again the staff presentation will be by Dr. Poorni Iyer.

(Thereupon an overhead presentation was Presented as follows.)

DR. IYER: Good afternoon. And, again, my name is Poorni Iyer. And I'm going to be presenting the extent of the evidence available for the prioritization of methylisocyanate, or to refer as MIC.

Methylisocyanate is used in the production of pesticides and plastics. And in the material provided at the Committee it was mentioned that MIC was used in polyurethane foam. But it was brought to our attention that that is not the case, and so we removed that from the exposure.

Exposure is generally via occupational sources or through environmental release.

--o0o--

DR. IYER: There were seven epidemiologic studies of methylisocyanate reporting increased risk of adverse developmental or reproductive outcomes. And these were all related to the environmental release of MIC some 23 years ago in Bhopal, India. The adverse outcomes included

higher pregnancy loss and neonatal and/or infant mortality. Of these studies, two were analytical studies of adequate quality.

There were no epidemiologic studies reporting no increased risk of adverse developmental or reproductive outcomes.

And also including in the material are two related articles.

--o0o--

DR. IYER: Moving on to the animal data.

The animal studies were also spurred by the Bhopal incident and the abstracts of these studies presented effects such as anomalies, implantation loss, fetal loss, and disturbed estrous cycles.

There were six animal studies of methylisocyanate reporting developmental or reproductive toxicity. And one animal study that did not report developmental or reproductive toxicity.

And that concludes the presentation for methylisocyanate.

CHAIRPERSON BURK: I have asked Dr. Ellen Gold to lead the discussion on methylisocyanate.

COMMITTEE MEMBER GOLD: First, let me compliment Dr. Iyer. I think she covered it pretty well.

Basically all of the human studies are based on

the incident in Bhopal. And it's a little bit hard to tell if they're the same people or different people.

And I also stuck to the rules. I just looked at the abstracts. So I'd like to see more before I make any judgments.

But I think by and large they're showing consistent results with regard to fetal loss. And there are some other outcomes of interest as well.

And I think at this point that's about all I'd want to say. I mean I think the animal studies are supportive as well largely.

CHAIRPERSON BURK: Again, I don't have any cards. Was there anyone that wishes to speak on this one from the public?

No?

All right. Are there any other comments from the Committee?

COMMITTEE MEMBER JONES: So in terms of exposure in California, where --

COMMITTEE MEMBER GOLD: Are you asking me?

COMMITTEE MEMBER JONES: Yeah.

COMMITTEE MEMBER GOLD: I didn't see anything in the abstracts. These are all pretty much restricted to the incident in India.

COMMITTEE MEMBER JONES: Do we know anything

about that?

DR. IYER: Well, other than, you know, it's one of the intermediate products for MIC -- for metam sodium, which is a pesticide. And it's during -- that can break down to MIC. But I'm not too sure exactly as far as -- we have to look more into the exposure aspects how it would actually affect Californians.

COMMITTEE MEMBER GOLD: Just in response to that, I think there were some things in the public comments that dealt with the likelihood of it being an intermediate product in some of the processes in California. Possibility for exposure there was all.

DR. IYER: Actually metam sodium breaks down to MITC, not MIC. And that's always a confusion.

CHAIRPERSON BURK: So that wasn't the -- okay. That wasn't it.

Do you know in -- I mean I don't know that much about the Bhopal incident. Were they making that there or was that again -- with the accident, was that just a byproduct of something else?

COMMITTEE MEMBER GOLD: Yeah, they were making pesticides there. And this was a byproduct of the process.

DR. IYER: Yeah. And it was stored in a huge tank.

CHAIRPERSON BURK: Okay. Let's have something from the public.

DR. SCHREIDER: Maybe a little bit of clarification. Again, Jay Schreider, Department of Pesticide Regulation.

When metam sodium breaks down to produce MITC, which is really the active ingredient for the fumigation, there is a small pathway. There is some MIC produced. The majority of it is MITC, but there is some amount of MIC produced and a few other similar chemicals.

CHAIRPERSON BURK: Is there anything else anyone wants to add? This one is kind of different maybe since we don't know -- there's not as many studies. Do you think there are enough, if we looked at them closely -- my fear is that if they're all a high dose that seems to be clearly associated with spontaneous abortions, that we won't be able to -- we'll be able to say I guess that it caused --

COMMITTEE MEMBER GOLD: Well, actually there's some discussion of that even in the abstracts, so that they looked at people that were at different distances and protection and so forth. And so I think with further inspection you could learn a bit more about dose response and that sort of thing, hopefully.

CHAIRPERSON BURK: Okay. Well, it doesn't seem

like it would be too difficult to get the literature together at least.

All right. If there are no further comments, we'll poll this one.

So, do you advise OEHHA to begin preparation of the hazard identification materials for methylisocyanate?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: Is yours up, Hillary?

COMMITTEE MEMBER KLONOFF-COHEN: No.

CHAIRPERSON BURK: Okay. She's still thinking?

All right. 1, 2, 3, 4 -- I see 5.

Okay. All those advising no, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: I see one. Okay.

And one undecided, huh? Okay.

COMMITTEE MEMBER KLONOFF-COHEN: I think the reason I'm undecided is because when I looked at the abstracts -- when I was looking at the abstracts, it looked like fetal loss -- abstract 2, 3, and 4 were talking about fetal loss. But I guess there was just such positive results, it was just really hard to tell. But I guess we're talking right now about whether to have further discussion. So with three studies looking at that

endpoint, I guess I would vote yes.

CHAIRPERSON BURK: Okay. So you're going to vote yes?

All right. I will add that and make that 6 and 1.

All right. The last chemical on the list today is sulfur dioxide.

And I can't remember who's doing the staff report because I lost my page.

All right. There it is. Dr. Francisco Moran Messen.

Thank you.

(Thereupon an overhead presentation was Presented as follows.)

DR. MESSEN: Thank you. Good afternoon. My name is Francisco Moran Messen and I'm going to be presenting the evidence available for prioritization of sulfur dioxide.

Sulfur dioxide is an intermediate in the production of sulfuric acid. It has been used as a fumigant, a preservative in the wine and dried fruit industry, a bleach and a steeping agent for grain in food processing; catalyst or extraction solvent; flotation depressant for sulfide ores; intermediate for bleach production; and a reducing agent.

Sulfur dioxide in ambient air comes from activities such as the burning of coal and oil at powerplants or from copper smelting.

--o0o--

DR. MESSEN: In reviewing the epidemiologic data, we found 18 epidemiologic studies reporting increased risk of adverse developmental or reproductive outcomes, 7 of which were analytical studies of adequate quality. These studies were air pollution type of studies with endpoints of preterm delivery and low birth weight.

One meeting abstract reporting an increased risk of adverse developmental and reproductive outcomes was also determined.

They found as well one epidemiologic study reporting no increased risk of adverse developmental or reproductive outcomes.

One related article in the epidemiologic data was also found.

--o0o--

DR. MESSEN: In reviewing the animal data, six animal studies reporting developmental or reproductive toxicity were found with endpoints in reproductive effects including biochemical parameters, like the glutathione oxidation-deoxidation system, on balance in males; disturbances in the estrous cycles; and lower fertility.

In the developmental outcomes effects including low birth weight and altered social/agonistic behavior.

Two studies that did not report developmental or reproductive toxicity were also found, as well as four related articles.

That concludes the presentation of sulfur dioxide.

CHAIRPERSON BURK: Thank you.

I've asked Dr. Calvin Hobel to take the lead on this chemical.

COMMITTEE MEMBER HOBEL: Okay. The papers that I reviewed I think really point toward this whole issue of timing again. I think that the -- for example, the first paper was from Korea. And actually there are a lot of exciting papers coming out of Korea today on the epidemiology of low birth weight. And there are a lot of different conditions that seem to be related to low birth weight - maternal age, pollution, and psycho-social stress.

But it's interesting that consistently it's been very difficult for me to sort out which of the pollutants are we really talking about. Because as pointed out by the -- one person that put together the comments from the community pointed out that most of these issues with the downstream changes of sulfur dioxide leads to various

different types of pollutants.

And when people are studying this, they tend to look at several different compounds. And it appears to be two pathways involved. Oxidative stress seems to be very important. And today there's are some really very good bio-markers that can be actually used to study this.

And the other pathway that seems to be involved is in the inflammatory pathway. And I think I will point that out as we talk about some of these papers.

There seems to be sort of an international issue. There are papers from Korea, Canada, Brazil, the United States, and so forth. And each of these different types of substances, whether we're talking about particulate matter, carbon monoxide or sulfur dioxide, seems to have different patterns in terms of its effect in reproductive biology.

For example, the paper from Texas by Gilboa really points this out where they looked at the effect of these substances on cardiac abnormalities. And they found an increased incidence of tetrology of flow related to carbon monoxide, whereas atrial septal defects were related to a different particulate matter. And then ventricular septal defects were more associated with sulfur dioxide.

So there seems to be a different effect on

different organ systems. So one has to be careful what substance you're really looking at.

And there are also a lot of confounding other factors, as I pointed out - stress and other things.

One of the things that I found I thought was quite interesting is this issue of the timing of things. For example, in the paper presented from China by Xu, et al., looked at the issue of high pollution compared to low pollution. And in situations of high pollution was associated with a much earlier preterm birth rate with the very low birth weight deliveries. And this is classic for the inflammatory pathway.

And so it looks as if inflammation can be an important part of this pathway if it is related to a much greater exposure rate.

And it's interesting that as you look at the sequence of events over time, it looks like oxidative stress initially is probably the beginning of the pathway. And as oxidative stress leads to various biochemical alterations, leads to turning on the inflammatory pathway with all different types of cytokines that are produced. Whereas the initial oxidative stress results in a different profile of biomarkers.

And some of these papers begin to point the direction toward that, and other biomarkers like

methemoglobin as being a good biomarker of oxidative stress.

So I think this is a very complex issue. I don't know how you would address it in terms of listing sulfur dioxide as a significant toxicant, because it's so prevalent in terms of where it's coming from. According to a letter that was produced for us by Ken Kloc from the Golden State University, points out that about half of the emissions come from ships and commercial boats, 20 percent came from petroleum refineries, and 14 percent --

DIRECTOR DENTON: Dr. Hobel, we need for you to speak into the mike.

COMMITTEE MEMBER HOBEL: Oh, I'm sorry.

-- 14 percent from industrial sources.

Let me just repeat that again.

Half of these emissions came from ships and commercial boats; 20 percent came from petroleum refineries, 14 percent from industrial processes. And then the rest of it appeared to be coming from emissions from sulfur dioxide from other industrial sources.

So one would have to address this in a very comprehensive, complex way in order to try to reduce these emissions.

So, I think it's something that one should continue to provide surveillance, because I think it does

have a significant impact on all kinds of diseases, whether it's asthma, preterm birth, because it seems to have an effect on a lot of steps in the developmental pathway.

End of comment.

CHAIRPERSON BURK: Okay. I didn't receive any cards, but are there any public comments?

All right. Well, let me ask one thing to you, Calvin. In that same letter I noticed there was a suggestion that we should consider particulate matter too?

COMMITTEE MEMBER HOBEL: Yes.

CHAIRPERSON BURK: Did that make sense to you or --

COMMITTEE MEMBER HOBEL: Yes, because most of the papers particulate matter is one of the substances that -- downstream from sulfur dioxide.

And I think this whole area --

CHAIRPERSON BURK: Make sure your green light is on.

COMMITTEE MEMBER HOBEL: I think this is a very important area that everyone needs to become aware of, because -- there's an article in Science magazine recently, October 5th, 2007, on the issue of life with oxygen. It goes through this whole issue of the role of oxygen in biology and in systems where there is decreased

oxygen availability and what it does to all systems within the body. And I think it's a great article, because it tells us that probably there are various genes that people have that leads to increased susceptibility of disease through oxidative stress.

So, again, I point out this issue of there seem to be some people more vulnerable than others that are susceptible to this. And so I think this issue is very, very important.

CHAIRPERSON BURK: Any other comments from the Committee?

All right. I will read the last one then.

Do you advise OEHHA to begin preparation of the hazard identification materials for sulfur dioxide?

All those advising yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: 1, 2, 3, 4, 5, 6, and Linda is recusing herself.

So 6 and 1 abstain -- or a recuse.

All right. Now, that concludes the chemicals.

The next item on the agenda is listed as Other Chemicals Proposed for Committee Consideration. My understanding is that this just means time for the Committee to give input or make any further recommendations.

The only note I took along the way was the possibility that we might want to ask for total trihalomethane as a screen. Is that something that we agree on?

And is there anything else? Did you want to ask for particulate matter to be screened?

COMMITTEE MEMBER HOBEL: Yes, I think it should be -- yes, it should be.

CHAIRPERSON BURK: We're in agreement?

Okay. Is there anything else? I don't know what's in this category. I don't know what it means exactly.

DIRECTOR DENTON: Dr. Burk, in our prioritization procedure there's actually -- this is this Committee -- Consultation on Committees for Review. There is a sentence that says, "The committees may also suggest other chemicals that should undergo hazard identification materials preparation." So that's what this item is.

Carol, did you have anything else?

CHIEF COUNSEL MONAHAN-CUMMINGS: I just wanted to mention that you should also ask if there's any members of the public that wanted to suggest chemicals.

CHAIRPERSON BURK: All right. That's a good idea.

So are there any members of the public that would

like to suggest chemicals to be included or have hazard identification materials prepared?

Seeing none.

Oh, Linda.

COMMITTEE MEMBER ROBERTS: I have a question. Are we going to try to do all seven chemicals at the same meeting?

DIRECTOR DENTON: I'm sure that will not happen. That will not happen. Some of these are much more complex than others.

CHAIRPERSON BURK: Okay. Next on the agenda then, Discussion of Next Prioritization Data Screen. And that would be Jim Donald.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: Thank you, Dr. Burk. My name, again, is Jim Donald.

Thank you also for the Committee's advice to us. You've certainly given us plenty to work on.

But we would like at this point also to ask your advice about future screens to apply and our ongoing iteration of this process. And we'd like to make -- we'd like to suggest a few possibilities to you.

Since apparently the screen that we applied this time identified chemicals that the Committee thought were worth proceeding with, one possibility would be at some

point in the future, either the near future or the slightly more distant future, to reapply this same screen, because the expectation that other chemicals would have had data developed in the meantime that would lead to them also passing that same screen.

A second possibility we'd like to suggest is that if you're still interested in focusing initially on the availability of human data, that we might implement a screen with a slightly lower bar, such as the availability of one study -- one analytical study of adequate quality, along with some other type of human data such as perhaps an ecological study or a case series.

A third possibility would be to implement a screen that was either based entirely or in part on the availability of animal data. And one possibility there would be to perhaps try and identify chemicals where there appeared to be greater sensitivity for developmental or reproductive toxicity than there was for maternal or systemic toxicity. And just, again, as a possibility, we might look for chemicals where we could identify perhaps two or three studies with the same endpoint where the developmental or reproductive effect occurred at a lower level of exposure than the maternal or systemic toxicity.

CHAIRPERSON BURK: All right. Any comments?

Yes, please.

COMMITTEE MEMBER HOBEL: I just wanted to make a comment about the national children's study, which will be starting in the Vanguard Center. There's one Vanguard Center in southern California which is Irvine. They start recruiting patients July of 2007. And I'm one of the co-investigators of one of the more recent centers in Los Angeles, which will start recruiting patients in July of 2009.

And this is a tremendous opportunity, because there are going to be many people involved in the State of California - UC Davis, UC Irvine, UCLA, and then UC San Diego, UC Riverside.

And just in the Los Angeles we're going to recruit 6,000 patients. And these women will be followed over five to six years, and then their children for twenty years. We'll be collecting biological samples. A third of patients will have samples collected before pregnancy. And then during pregnancy they will have biological samples collected in the first trimester and second trimester. Third trimester we'll be collecting placentas, cord blood. And then there will be samples throughout the new -- for the child for twenty years.

So it's a great opportunity to do ancillary studies. So I just mention this because I think all of us are now beginning to think about what type of ancillary

studies should be done. And I think this whole issue of collecting samples -- there are plans for collecting dust samples, air samples as part of the study. But I think -- beginning to think of what one should begin to look at will be very important, and makes certain we got the right number of urine samples, blood specimens, placentas, to make certain we have something planned that could be available to monitor this for the next twenty some years.

CHAIRPERSON BURK: Very good.

Does anyone have any comments on the three suggestions that Jim made?

COMMITTEE MEMBER JONES: Yeah, I do.

I think to take one end of your spectrum, Jim, and look just at epidemiol -- look just at animal data, in other words after you get through the epidemiologic data and that includes animal data as well and so forth, you're going to have to change to a certain -- and if you're just going to be looking at animal data, you're going to have to change the mix of this Committee a little bit, because there are at least three of us for sure who are primarily clinical investigators. And I think you're going to have to have more people who have expertise with animal data and interpretation of animal data if you're just going to be doing animal studies.

CHIEF DONALD: Okay. I'm sorry. I think I gave the wrong impression. I was talking only in terms of identifying chemicals for consideration by the Committee.

COMMITTEE MEMBER JONES: I'm sorry.

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CHIEF DONALD: We would not be selecting chemicals necessarily that only had animal data, though there would be a possibility that that might occur. But the intent would be still to bring the Committee as complete a representation as we could of the entire spectrum of data including whatever human data were available.

But you're absolutely right. It does raise the possibility that we might identify chemicals for which there only were animal data.

CHAIRPERSON BURK: Well, that wouldn't be the first time that we had done that. But I tend to think this worked fairly well. Now, if you went back and screened again for human studies, would you find similar to what we had today?

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION

CHIEF DONALD: Well, Of course the only way to know is to do it. But we would expect that since there was, you know, some time lag involved in preparing these materials and sending them out and there would be presumably some additional time lag before we ran the screen again, that

it's very likely that there would be additional chemicals that would make the screen.

CHAIRPERSON BURK: Okay. Because there would have been more studies published in the meantime?

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: Exactly.

CHAIRPERSON BURK: Well, I thought that was good. I actually am not so much in favor of dropping the standard to just one analytical study, because I'm afraid that sometimes is too easy to criticize. Even though I think case reports, ancillary material can be very helpful personally. But I know we heard today some think, you know, one study just wouldn't be enough.

But, yes, if you do start screening animal, it certainly would be nice to find the ones where there were DART endpoints in the absence of maternal toxicity. That certainly would be a good thing.

Does anyone else have any -- Ellen.

COMMITTEE MEMBER GOLD: I would interject a note of caution about using case series and ecologic data, because I think in the -- without any sort of comparison group as would be the case in a case series, we'd be treading on very iffy ground for making any kind of recommendations.

And similarly with ecologic data where we

wouldn't have data on individuals with regard to exposure and outcome, I would be very hesitant to go that direction and set the bar that low. I think it's okay to include those if you meet the bar in addition that we currently have. But I wouldn't lower the bar to use those kinds of studies to prioritize anything.

COMMITTEE MEMBER HOBEL: The reason, Jim, I mentioned the national children's study is that there are a lot of people involved at the various universities now who are beginning to think about what things we should be looking at. A lot of them are doing studies that may have preliminary data about some issues that would be very helpful for us to begin thinking about. And I can supply at least two names to you of people who I think should be contacted or at least aware that you are interested in what might -- what should be on the radar screen.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: Thank you. We'd appreciate that information.

CHAIRPERSON BURK: Are there any public comments on the next prioritization data screen?

No?

COMMITTEE MEMBER JONES: May I have -- I just have --

CHAIRPERSON BURK: Sure.

COMMITTEE MEMBER JONES: Jim, Linda and I, you'll remember perhaps, were on that -- we contributed to the discussion of how to prioritize. And I must tell you I don't really remember the step that we took today. What I remember was that you were going to -- correct me if I'm wrong -- and, Linda, you may want to correct me. What I remember was that you were going to come up with this prioritization process that we all agreed on in which you would look for agents that had epidemiologic data. And then based upon that, you were going to prioritize. And based on that prioritization, you were going to -- we were going to start looking at those agents that were of the highest priority based on having decent or even good human epidemiologic study.

And that this step of having the Committee recommend to you whether you were right, I don't remember being part of this.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: We had a number of meetings. And I have to confess, I don't remember whether you attended all of them or not. But --

COMMITTEE MEMBER JONES: Oh, I did, Jim.

(Laughter.)

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: In previous iterations of prioritization we

had offered the Committee the opportunity to have this advisory role. And the Committee had declined to do it. So we are quite certain that this time around the Committee did agree to take on this role, because there was a fairly radical change from a previous position. As to exactly when we reached that decision, I'm afraid I can't tell you.

COMMITTEE MEMBER JONES: Do you remember it, Linda?

COMMITTEE MEMBER ROBERTS: I don't remember one way or the other. But now that we've done it, what do you all think? Should we --

CHAIRPERSON BURK: That's what I want to know. What's the feedback?

DIRECTOR DENTON: Well, this is all -- just to remind the Committee, this is all part of this written document here. So we're following pretty much to the letter of what we would do and how we would do it and when we would bring it to the Committee, and flow charts and everything. So this is our final prioritization process that we did adopt back in 2004.

COMMITTEE MEMBER JONES: Okay.

COMMITTEE MEMBER ROBERTS: I guess I'd suggest that I think -- well, part of me feels it would be nice if this meeting was actually held separately by OEHHA, and we

just got the final products. It seems to have worked. And now we have I think at least a year's worth of chemicals to take a look at before we'd be having another prioritiza -- four years. No, I think we can do more than one at a time this time around. And so I guess maybe a check in at one of the other meetings where we're actually looking at a chemical with a hazard identification document might be a good idea before our next meeting to look at the results of screens.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: And to clarify, you know, we see this meeting as being probably somewhat unique because we had run out of candidate chemicals for the Committee to consider. Now that we hopefully have a fairly strong list of chemicals, in the future hopefully further consultation about additional chemicals will be part of a meeting in which you are actually considering chemicals and making listening decisions.

DIRECTOR DENTON: And it's always been my intent to get away from these December meetings.

CHAIRPERSON BURK: I'll vote for that.

I like coming to Sacramento better at other seasons. Although it's not bad now.

One more comment.

COMMITTEE MEMBER HOBEL: I think I remember when

we had the meeting -- we had a lunch at a different place rather than close by. It was a very nice lunch, I recall.

(Laughter.)

COMMITTEE MEMBER HOBEL: And you had a slide presentation or a PowerPoint presentation and you actually showed a whole series of slides pointing out this process, as I recall.

REPRODUCTIVE & ECOLOGICAL TOXICOLOGY SECTION CHIEF DONALD: Yes, that's correct. I did do that.

COMMITTEE MEMBER HOBEL: So maybe we ought to go out for lunch again.

(Laughter.)

CHAIRPERSON BURK: Oh, yes.

All right. So are we up to the last agenda item?

DIRECTOR DENTON: Maybe I could just summarize the Committee's recommendations on this next prioritization data screen.

From my understanding of the discussion, OEHHA would go forward again to do the epidemiology screen using the same criteria that we used in this screen that we brought to you today. And then at some point when we would go on to the animal studies, then the animal evidence, we would look for DART endpoints that do not involve maternal toxicity.

CHAIRPERSON BURK: I agree.

All right. Staff updates. We have two.

First, Cynthia Oshita.

MS. OSHITA: Good afternoon.

OEHHA has administratively added four chemicals to the Proposition 65 list, one chemical as known to cause reproductive toxicity, and that was di-isodecyl phthalate; and three chemicals as known to cause cancer, and they were propoxur, iprovalicarb, and anthraquinone.

And in addition to these, three chemicals were removed from the Proposition 65 list. They were isosafrole, 5-nitro-o-anisidine, tris(aziridinyl)-p-benzoquinone. These chemicals were added as known to cause cancer to the Proposition 65 list in October of 1989 by operation of law based on the Labor Code sections 6382(b)(1) and (d) that incorporates by reference chemicals that require the inclusion of substances listed as human or animal carcinogens by the International Agency for the Research on Cancer, or IARC, and also those that required the inclusion of chemicals within the scope of the federal Hazard Communication Standard, which establishes that a chemical is a carcinogen or a potential carcinogen for hazard communication purposes if it is identified as such by IARC or the National Toxicology Program.

The change in classification of isosafrole and

tris(aziridinyl)-p-benzoquinone by IARC and the removal of 5-nitro-o-anisidine by NTP required that these chemicals be also removed from the Proposition 65 chemical list.

A summary sheet of these latest changes to the Prop 65 list are in the staff updates in your meeting materials binder. And in addition to these listings and delistings, there are several chemicals that are under consideration for administrative listing, and they include: Hexafluoroacetone, nitrous oxide, vinyl cyclohexene dioxide, and methanol. And these are all listed as chemicals known to the state to cause reproductive toxicity. Also gallium arsenide is under consideration as a chemical known to cause cancer.

Comment were received on all these chemicals and they are under review.

Also in your binders is a summary sheet of the safe harbor levels that we've adopted since you last met in May of 2006. And there were three maximum allowable dose levels that are adopted effective September 30th, 2007. They were for ethylene glycol monoethyl ether, ethylene glycol monoethyl ether acetate, and potassium dimethyldithiocarbamate. And in June of this year OEHHA issued a notice of proposed rule-making announcing a proposed MADL for di-n-butyl phthalate. Written comments were received and they are being reviewed, and we will

respond to them as part of the rule-making process.

Thank you.

CHAIRPERSON BURK: Yes. And then Carol has an update.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, I just have a very brief update.

One of the chemicals that Cindy mentioned that we listed this year, one of the phthalates, DIDP, was also the subject of some litigation. Subsequent to the listing we were sued by Exxon-Mobil Corporation challenging our authority to list the chemical administratively. The hearing on that case was held November the 13th in Los Angeles, and the trial court decision was just announced on December the 5th, and the Court upheld our authority to list the chemical using the authoritative body method.

CHAIRPERSON BURK: Okay. Last on the agenda, Summary of Committee Advice and Consultation.

DIRECTOR DENTON: I want to thank Dr. Burk and all the members of the Committee for participating and very methodically and very conscientiously considering the evidence and the chemicals that were brought for your consideration today. I think it's just so important that such a sober and considerate meeting be held on these important chemicals.

I would also like to thank my very able and

talented and long suffering staff, who have done yeoperson's work and continue to do yeoperson's work throughout the Prop 65 process under the able leadership of Jim Donald and Lauren Zeise. So thank you for the materials that you presented today and your most positive reflection on the Department.

And also thank you to the audience for coming today and for your participation. It's also very important in this process that all sides be heard, both in the written and also in the verbal comments.

So with that, I'll summarize the Committee's action.

Essentially the Committee endorsed the moving all of the chemicals forward to preparation of hazard identification materials.

The votes were unanimous for that for Bisphenol A, Chlorpyrifos and DDE.

The votes were 6 to 1 recused for hexavalent chromium and sulfur dioxide.

The vote was 6 yes and 1 no for methylisocyanate.

And the votes were 4 yes and 3 no for bromodichloromethane and caffeine.

The Committee is also recommending that THM -- that hazard identification materials be prepared for the class of THM and also for particulate matter.

Finally, as far as our prioritization screen, the next screen, as I mentioned earlier, the Committee recommends that we go forward with the same epidemiology screen and do it again for other studies which may have come out since the last screen was done; and then moving on into the animal evidence, consider DART endpoints for which there is an absence of maternal toxicity.

So with that, it looks like Jim may have a question.

Do we have any --

DEPUTY DIRECTOR ALEXEEFF: Just as a clarification. George Alexeeff here.

For particulate matter and THMs, it was simply to run the screens, not to actually prepare any materials.

DIRECTOR DENTON: I'm glad for that correction.

(Laughter.)

DIRECTOR DENTON: It's like 3, 4, 5 person-years worth of work that I just committed to and just decommitted to.

So let me correct myself. We would be doing the epidemiology data screen for particulate matter and THM.

So thank you, Jim.

With that, that -- do you want the microphone back, Dottie?

CHAIRPERSON BURK: Oh, I get the pleasure.

No, I also want to thank everyone, certainly the audience comments, the staff, and the Committee for their serious consideration.

And the meeting is adjourned.

(Thereupon the Carcinogen Identification Committee adjourned at 4:12 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 21st day of December, 2007.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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