MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

SACRAMENTO, CALIFORNIA

TUESDAY, JULY 12, 2011

10:08 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

APPEARANCES

COMMITTEE MEMBERS

Dorothy T. Burk, Chairperson, Ph.D.

Ellen B. Gold, Ph.D.

Carl Keen, Ph.D.

Hillary Klonoff-Cohen, Ph.D.

Linda G. Roberts, Ph.D.

La Donna White-Porter, M.D.

STAFF

Dr. George Alexeeff, Acting Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

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

Dr Shelley Green

Dr. Farla Kaufman

Dr. Allegra Kim

Ms. Cynthia Oshita, Proposition 65 Implementation

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

ALSO PRESENT

Dr. John Bucher, National Toxicology Program

Ms. Brenda Coleman, California Chamber of Commerce

Ms. Caroline Cox, Center for Environmental Health

Dr. Steve Hentges, American Chemistry Council

Mr. John Hewitt, Grocery Manufacturers Association

APPEARANCES CONTINUED

ALSO PRESENT

Ms. Trudi Hughes, California League of Food Processors

Dr. Sarah Janssen, Natural Resources Defense Council

Mr. Stanley Landfair, McKenna, Long & Aldridge

Mr. Gene Livingston, Greenberg Traurig

Dr. Jay Murray

Ms. Renee Sharp, Environmental Working Group

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PROCEEDINGS

ACTING DIRECTOR ALEXEEFF: Good morning. I'd like to go ahead and get this meeting started. I want to welcome everyone to the meeting of the Developmental and Reproductive Toxicant Identification Committee. I am George Alexeeff. I'm Acting Director -- okay. I'll move closer here.

I'll start again.

I want to welcome everyone to the meeting of the Developmental and Reproductive Toxicity Identification Committee. I am George Alexeeff, Acting Director of the Office of Environmental Health Hazard Assessment in the CalEPA.

And I'd like to start by thanking the members of the Committee here of taking time out of their busy schedule to be here to review the information, and to also provide the State advice on some very important matters.

Let me start by introducing the members. Directly on the left to me is Dr. Dorothy Burk. And she is the Chair. She is an Associate Professor in the Department of Anatomy at the University of the Pacific School of Dentistry.

Next to her is Dr. Ellen Gold, who is a Professor in the Department of Public Health Sciences at UC Davis.

And next to her is Dr. LaDonna Porter, Clinical

Physician of the California Hospitalist Physicians at Dameron Hospital.

Directly to my right is Dr. Hillary Klonoff-Cohen. She is a Professor in the Department of Family and Preventive Medicine at UC San Diego.

And next to her is Dr. Linda Roberts, who is a Senior Toxicologist at the Chevron Research and Technology company. And next to her is Dr. Carl Keen, who is the Chair of the Department of Nutrition and he's also a professor in the Department of Nutrition at UC Davis.

And unfortunately, not in attendance, are Dr. Kenneth Jones and Dr. Calvin Hobel.

Let me just also -- I may as well introduce the staff while I'm introducing people over here. Let's see, directly in front me is Allan Hirsch, who is our Chief Deputy Director. And next to him is Carol Monahan-Cummings, who is the Chief Counsel and will be providing us legal advice during the meeting.

And next to Carol is Lauren Zeise. And Dr. Zeise is the Chief of our Reproductive and Cancer Hazard Assessment Branch. And next to Lauren is Dr. Jim Donald, who is the Chief of our Reproductive and Developmental Toxicity Section. Okay, I should have briefed on that one. Anyway. He's our Section Chief.

And next to Jim is Dr. Allegra Kim. And next to

Allegra is Dr. Farla Kaufman. And next to Farla is Marlissa Campbell. And then over there is Rachel Broadwin. And next to Rachel is Dr. Shelley Green. So you might be hearing from various members of the staff during the meeting.

First, I have to give some important information about evacuation of this location here. So if you look around to your exits, you'll see that there are exits. The closest one might be right behind you. And in case of a fire, we're required to evacuate the room. Take your valuables with you. Do not use elevators. And while staff will endeavor to assist you to the nearest exit, you should know that you may find an exit door by following the ceiling-mounted lights. And then you go down the stairways to a relocation site across the street in the park.

If you can't use the stairs, you'll be directed to a protective vestibule inside a stairwell where someone can help you relocate.

A couple other housekeeping points. Drinking fountain and restrooms out the back and to the left. And then food service is available downstairs. There's the grand stairway, go downstairs, and sort of make a right as you exit that. There's a cafe there. And then we encourage recycling. There's a lot of recycling bins

downstairs, so please use those. And please silence your cell phones as well.

Okay. So I'll go ahead and I will -- let's see I guess we'll -- should I turn it over? Do you have any remarks, Dr. Burk, before we start or begin with the staff?

CHAIRPERSON BURK: Sure. Good morning, everyone. And thank you all for coming for, I think, our first ever two-day scheduled meeting. I made it in the nick of time, but tomorrow I will be earlier.

I wanted to, first of all, thank the Committee for attending, those of us that made it here. It's a smaller group than usual, but we will give it our all. And I very much want to thank the staff for all the work that they put into preparing the documents that we're using today.

I appreciate how much effort that took. And I'll even thank the presenters to come and also the commenters who have sent us information, because I think it was careful and thoughtful.

On the agenda today, and I just want to give you an idea of how we're going to approach this. The first thing we're going to do is consider sulfur dioxide as a chemical known to the State to cause reproductive toxicity. And that will, I think, take the bulk of the

morning. If we do not finish by noon, then we may have to continue it later today or tomorrow, because right after lunch, at 1 o'clock, we want to proceed to the third item the informational item about listing mechanisms, so that we can begin Item 4 at 2:30, when we will have a conference call with some representatives from NTP.

So depending how long that part goes in the afternoon, we'll either continue that the next day along with sulfur dioxide or maybe we'll get through all that today. If so, I'm pretty sure the prioritization portion, the last -- the second to the last agenda item and the staff updates will definitely be tomorrow. So just to let you know how we're planning to proceed.

One other announcement that George neglected, but I always say is when commenting, please speak directly into the microphone so that the stenographer can get everything, but I've also been told that since we're webcasting, side comments that you make may be picked up by the microphones, so just bear that in mind.

All right. So first up then is our consideration of sulfur dioxide. And the first person that usually speaks is Carol Monahan-Cummings to remind us of our charge.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you, Dr. Burk. A couple of items. Dr. Roberts is going to recuse

herself on this particular item. And so she's going to leave the group now. It's not because she doesn't like us, but she's going to recuse.

And also in terms of the webcast, hopefully people are listening on the webcast, if you want to -- anybody in the audience can let folks know that they have access to that. There's a link on our web page to the CalEPA webpage, which has a link to the actual webcast. We also have links to the materials, slides and stuff that will be used today for the presentations on the webcast.

And so also since it's webcast and people may or may not know the speakers, if -- particularly with staff and public speakers, if you could identify yourself and any affiliation you might have on the record and so also the people on the webcast know who's speaking.

So in terms of just a reminder, since the Committee only meets once a year and so it's kind of hard to remember from one meeting to the next, I just wanted to point out that sometimes we get a lot of comments from interested parties concerning what the standard -- you know, the clearly shown standard means in terms of your decision. And there's generally arguments about what the -- that it is a legal standard that you're applying.

And, in fact, that's not what you're doing. There is a legal interpretation one can do for clearly

shown, but this group was identified by the Governor and appointed as the scientific experts for the State. And I'm not aware that any of you are attorneys, and I am counsel for the Committee, and so I can give you advice in terms of legal issues. But from our perspective and even from your own guidance, it should be clear that the decision you make on sulfur dioxide, you know specifically, should be based on your scientific expertise and not a concern about whether you're applying a reasonable -- reasonably known type standard that you might in a court proceeding.

You also don't need to consider the logistical effects of a listing decision for a particular chemical. Sometimes people bring up issues like well, you know, there's going to be a warning everywhere for this chemical if it's listed. You know, it's in everything. And so what's the point of that?

The listing -- the actual effect of the listing is handled primarily through the statute, because it -- you know, it provides when a warning might be required, and also by businesses or those subject to the act that have to determine whether or not a warning is required under our regulations.

Your piece of the process is really the hazard identification piece. And that is, you know, does a given

chemical cause reproductive or developmental effects?

You are not required to look at whether or not actual or potential exposures in California to the chemical are -- actually occur, because you're only looking at the hazard piece of the process.

The exposure issues are dealt with in a different manner. They usually have to be looked at in terms of the actual exposure that a business is causing, and then they can usually -- if we adopt safe harbor levels, so that there's a, you know, a base line, so that they know whether or not a warning is required or a discharge is prohibited.

And so it really is up to the business that's causing the exposure to either look at our safe harbor or use our regulations for purposes of determining whether a warning is required. So, you know, it's just really outside your -- the requirements for your Committee to consider that information, even though you might hear it.

I also wanted to point out we have included in your materials the guidance that the Committee adopted some years ago in terms of how to consider the data that you hear about, you know, that's been presented to you in writing or will be presented today. And so it can be useful to review that. And it can help you decide some of the scientific issues that may concern you at the meeting.

The last thing I wanted to point out is that we really encourage the Committee members to ask questions of the staff, including, you know, questions like is this a legal issue? Is it within our, you know, charge to deal with the scientific issues from the science staff who are very well versed in the chemical, and that sort of thing so that you're clear on those things. We're here to provide that and we really encourage that.

And to the extent possible, we will also address the public comments in terms of their characterization of the evidence or the legal standard.

So I think, at this point, the next person that's going to be speaking would be Dr. Donald, who is going to at least introduce his staff that will be speaking today.

Any questions on that before you start?

DR. DONALD: Good morning. My name is Jim Donald. And just for the record, I'm Chief of the Reproductive, Toxicology, and Epidemiology Section. My name has changed a lot, so sometimes it's hard to keep track.

Before I introduce the staff and we begin the technical presentations, I'd like to quickly address a question that's been raised about why OEHHA is bringing sulfur dioxide before this Committee, when it has been reviewed by Proposition 65 authoritative bodies, including

relatively recently by U.S. EPA.

Sulfur dioxide was identified as a candidate for consideration by this Committee through our prioritization process. And the hazard identification materials were prepared after a recommendation by this Committee that the chemical be brought forward.

Our prioritization process states that it is unlikely that chemicals will be proposed for DART IC review that have been recently reviewed by an authoritative body and found to have insufficient evidence of reproductive toxicity. It also states that exceptions to this generalization may occur. For example, if an authoritative body has evaluated a chemical, but failed to review all relevant data, or if compelling new data have become available since the evaluation.

The U.S. EPA Integrated Science Assessment for sulfur oxides published in 2008 focus primarily on the most sensitive effects of sulfur dioxide, such as bronchioconstriction and asthma. The OEHHA HIM summarizes approximately twice as many studies of developmental and reproductive toxicity as were reviewed by U.S. EPA.

Although it has been suggested that U.S. EPA was exhaustive in its review and analysis of the literature regarding sulfur dioxide and all health effects, the U.S. EPA document did not contain any evaluation of male

reproductive toxicity. The only mention of male reproductive effects was inclusion of two male reproductive animal studies in a summary table in an appendix to that document.

The International Agency for Research on Cancer reviewed the carcinogenicity of sulfur dioxide in its Monograph on Occupational Exposures to Mists and Vapors from Strong Inorganic Acids, and other Industrial Chemicals in 1997. IARC did not draw any conclusions regarding the developmental or reproductive toxicity of sulfur dioxide.

The Food and Drug Administration review that was brought to the Committee's attention was completed in 1976 and did not evaluate sulfur dioxide, the chemical under consideration today. Rather that document focused on ingestion of sulfiting agents in foods.

The evaluation by the National Institute for Occupational Safety and Health is contained in the Criteria for a Recommended Standard for Occupational Exposure to Sulfur Dioxide published in 1974. The document includes no assessment of developmental or reproductive toxicity data for sulfur dioxide.

The remaining authoritative body, the National Toxicology Program, soley as to final reports for the Center of the Evaluation of Risks to Human Reproduction,

has not evaluated sulfur dioxide.

So hopefully that clarifies that issue.

I'll now turn it back to George.

ACTING DIRECTOR ALEXEEFF: Good morning, Committee.

As the Committee is aware, much of the relevant information on this particular item comes from epidemiologic studies of sulfur dioxide as a component of air pollution. And a number of questions have come up regarding the use and interpretation of such studies. To help the Committee in its deliberation of those data, we thought it would be useful for staff of the Air Toxicology and Epidemiology Branch to make a brief presentation.

The staff who prepared and will make the presentation are OEHHA's experts in the evaluation and use of such data in the identification and regulation of criteria air pollutants.

The presentation will review the types of epidemiologic studies that can be used for that purpose. It will also cover the methodologic consideration that have to be taken into account in evaluating and interpreting the studies.

Dr. Shelley Green will make the presentation. And she and some of her colleagues from the air group will then be available to answer any questions of the

Committee.

(Thereupon an overhead presentation was Presented as follows.)

DR. GREEN: Well, thank you very much for that introduction.

Can you hear me now?

How about now?

Is that too close.

Okay. Well, thank you, Dr. Alexeeff, for the introduction. And so I'm here today, as he said, to talk to you a little bit about how our section does air pollution standards, and how we use epidemiologic studies in setting air pollution standards.

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DR. GREEN: So today I'm going to talk to you about OEHHA's role in air quality standard setting for criteria pollutants. OEHHA's previous history looking at SO2 as an air pollutant, the study types that we use in our recommendations, the epidemiologic study designs relevant to SO2, and how we evaluate the quality of air pollution epidemiologic studies.

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DR. GREEN: So for OEHHA's role in setting air quality standards for criteria air pollutants, we're tasked to create health-based recommendations for air

quality standards, which is the legal definition of clean air. And the standards have a pollutant definition, a concentration, an averaging time, a monitoring method and a form of the standard. And they're based solely on health considerations.

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DR. GREEN: It's been a long time since OEHHA has evaluated SO2 as an air pollutant. The California standard was last revised in 1994. At that time, the 24-hour standard was set at 40 parts per billion and the one-hour at 250 parts per billion. But a review in 2000, which was mandated by the California Senate Bill 25, which mandates consideration of infants and children in setting air quality standards. At that time, the standard was reviewed and it was determined that it was not adequate to protect all members of the community. And since then, very recently, U.S. EPA has revised the federal standard to give a one-hour standard of 75 parts per billion.

And, of course, California has to abide by that standard as well. So this would actually update California's standard, because we have to comply with the federal standard.

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DR. GREEN: So when we do our air pollution review of a pollutant, we basically usually uses three

types of studies to base our health-based recommendations. We look at controlled human exposure studies, animal toxicology studies, and epidemiology studies.

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DR. GREEN: So the controlled human exposure studies are exposures of human volunteers in a laboratory setting. And the advantages are that you get precise measures of exposure and response. And limitations are that there are few studies on vulnerable populations, because they don't -- when they do chamber studies and expose people, they usually do not choose individuals with severe asthma, for example. They might look at mild asthmatics. And they certainly don't study children. Most of them -- they're all adult volunteers.

And there's usually small sample size. And then the researcher will define the doses. And also, you can't predict the effects of chronic exposure. These chamber studies are usually anywhere between two and six hours. So they're used mostly for the shorter term standards, not the annual averages.

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DR. GREEN: Then, of course, there's animal studies or what we call toxicology studies. And the advantages of looking at animals are that you can give them higher doses, and you can study more endpoints, and

with higher severity.

The limitations are that as always with animal studies it might be difficult to extrapolate the effects to humans.

And finally, we look at epidemiologic studies. And the previous study designs I mentioned were experimental. But epidemiologic studies are what we call observational. They're not experiments. The advantages are though that they can evaluate exposures and responses of free living populations over a wide range of individuals, behaviors, and subgroups. And that often includes susceptible individuals, such as infants, children, the elderly. And you can examine both short- and long-term exposures with epidemiologic studies.

There are some limitations, of course. Sometimes it's difficult to determine specific exposure averaging times. And you need to account for other factors, particularly co-pollutants, because the air pollutants usually occur as a complex mixture. Not always, sometimes there are source-specific exposures. But most often they are a mixture. And also, the exposures are limited to real world doses, so you can't experiment with a dose. You just have to take what people are exposed to.

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DR. GREEN: And there are five epidemiologic

study designs relevant to SO2 that I'm going to talk about today very briefly.

The first is the cohort study. And that could be either prospective and retrospective. And I'll explain that in a minute. There's case control, time series, cross-sectional, and finally ecologic studies.

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DR. GREEN: So the first study design is the cohort study. And this follows a group of people with and without a common exposure over time, and identifies those who develop a disease during the follow-up period. And so the exposed and unexposed people, they could be selected from the same population or separate populations. But if so, the two populations must be comparable with respect to other exposures. Other than the ones that you're interested in looking at.

And we have two different types of cohort studies. One we call prospective. And this -- and that type of study, the study begins in the present and follows subjects over time. And in a retrospective cohort, the study begins in the past and it follows subjects over time. And they use information collected on past exposures and disease.

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DR. GREEN: One type of study that is often used,

obviously for reproductive hazards, is a birth study. And there are birth cohort studies. What they do is they follow pregnancies from conception and then to the endpoint, which would either be miscarriage, stillbirth, or live birth.

And often the researchers are interested in windows of exposure in birth studies, because there could be certain critical -- because the infant or the fetus is going through critical stages of development, there could be times during the pregnancy when the fetus could be more susceptible than others to the effects of the pollutants.

So a lot of the air pollution studies look at different windows of exposure, such as the month of pregnancy or a trimester of pregnancy, and then determine these separately for each window of exposure.

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DR. GREEN: And a couple of cohort studies that are examples of SO2 studies that were reviewed by the Committee were the Xu study of preterm birth and the Dejmek study of male reproduction.

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DR. GREEN: Okay. So the second type of study design is what we call the case control study. And in this instance, subjects with a particular disease are identified first. And these are, what we call, the cases.

And then control subjects come from the same population as the cases, but they do not have the disease.

And then the exposure of interest is what's measured in both the cases and the controls. And the controls are often matched to cases on factors that might be associated with both the disease and the exposure of interest.

And this is good for studying rare diseases, where you'd have to study just too many people, if you used a cohort design. Often, it's used in cancer studies, where it's more economical to select cases first and then find controls, rather than to do a study of a million people and see who develops cancer. Although, that's also done in some large-scale studies.

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DR. GREEN: And the next study design is, what we call, the time-series. And this examines associations over time in one area between daily changes in pollution and daily counts of an outcome. And the outcome could be anything from hospital admissions to mortality or just preterm birth. In other words, how many preterm births occur every day.

And when we do the time-series studies, individual level variables, like smoking and body mass index, they don't change appreciably in an individual from

day-to-day, so these factors don't have to be controlled.

There are some variables that do vary daily with pollution and in the health outcomes. And they can be add to the model, such as weather, and day of week. And you can control for season by adding, what we call, a smooth for time. So you smooth over the little ups and downs of what happens over the years with the outcome and the pollutant.

And one example of an SO2 time-series study was the Sagiv study of preterm birth in Pennsylvania.

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DR. GREEN: And this slide just shows you how the outcome can be smooth. This example is for mortality in Sacramento county. And you can see there's some periodicity in the outcome where there's seasonal changes in mortality from year to year. And so -- but this could be any outcome. This could be preterm births or whatever.

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DR. GREEN: Okay. The next study design is what we call the cross-sectional study. It's also called the survey or prevalence study. And in this case, the study population selected from a single target population by random sampling. You measure the individual's exposure and disease at one point in time.

And a good example of that would be the Robbins

et al., study of sperm aneuploidy for SO2.

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DR. GREEN: The last study design is called the ecologic. And this is most often used to compare disease rates in separate geographic areas with different exposure composition. No individual level data is gathered. And on a group level, you know, the number of exposed and the number of cases, but you do not know which individuals were exposed.

And these studies are good for hypothesis generation or to confirm findings of other studies.

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DR. GREEN: Okay. So when -- now, I'm going to talk about evaluating the quality of air pollution epidemiologic studies. There are several factors that we look at, but three important ones would be exposure assessment, what we call confounding, which I'll explain, and multiple comparisons.

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DR. GREEN: So for exposure assessment, when you're looking at air pollutants, often the exposure is determined either through personal monitoring or ambient air quality monitoring. So for personal monitoring, this is very good, because it introduces the least amount of exposure misclassification, but it's very expensive and it

necessitates small studies. But there have been studies of this type, where -- like pregnancy outcome studies, where women will wear a backpack over like a few -- two- or three-week period.

And these type of studies have been done, especially in New York City. There have been quite a few reproductive health studies there looking at different groups of women.

There's also, of course, the ambient air pollution monitoring. And these are usually -- they're central site monitors that are used for regulation purposes. And they're set out by EPA and the ARB regulating them, and take care of them.

And even when we use those, we still try to minimize bias from exposure misclassification, such as using inverse distance weighting, so that the distance between the monitor and the subject's residence then will be used to adjust exposure or you could only include subjects who live within a certain distance of the monitor, just so that you feel that you're getting the best possible exposure assessment you can, given the limitation of the central site monitor.

And usually then this type of misclassification would bias your study toward the null, if you assume that it's non-differential. In other words, that the

likelihood of exposure misclassification is not affected by the disease status.

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DR. GREEN: Another issue that we deal with are that of confounders in the air pollution studies. And those are factors, such as other air pollutants, lifestyle factors, demographic characteristics of people that can distort the relationship between the exposure and the outcome.

And that's because they're associated with both the exposure and the outcome. But also they're not a confounder if they're in an intermediary step in the causal pathway between exposure and the outcome. Then we don't want to control for them.

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DR. GREEN: And this just diagram just shows you, for example, just what a direct causal effect would be. Increasing SO2 would increase the risk for the outcome. But if you have confounding, then here's your confounder, and it's related to the SO2, and it's related to the outcome. And so then the relationship between SO2 and the outcome will change because of that confounder. And it could be either higher or lower. It could be -- go in either direction, what we call the bias introduced by the confounder.

But, I mean, even if you have a confounder, it might lower the association but you could still see an association between the exposure and the outcome. It doesn't mean it takes it away. It just means it changes it.

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DR. GREEN: And so methods that we use for adjusting for confounders include adding a term in the model for the potential confounder. That's in a statistical model. You could match the exposed and unexposed subjects on the potential confounder or you could stratify your analysis by the confounder.

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DR. GREEN: Okay. So another issue that is brought up with the epidemiologic studies is multiple comparisons. And that just means when you do a study if you look at a lot of different exposures or outcomes in one study, you might think, well, by chance at least one of them will be significant.

So if you adjust for this, it would reduce the error of finding a false association, but it will increase the error of not finding a true association. And so in the epidemiologic field right now, most people do not recommend adjusting for the multiple comparisons. But what we do is we look at the general body of evidence

across human and animal studies. And if we see consistency, then we're more assured that the effects are real.

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DR. GREEN: And so finally, although these air pollutants occur as mixtures -- and this slide shows you just a picture of the -- some of the air pollutants that we regulate in the State of California and by U.S. EPA, we still have to regulate them individually. And we do this by comprehensive reviews of the epidemiologic and experimental studies. And the epidemiologic studies can be instrumental in determining harmful levels of a given pollutant.

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DR. GREEN: So do I ask for questions now or later?

CHAIRPERSON BURK: Yeah. Are there any questions right now?

DR. GREEN: It was clear?

(Laughter.)

CHAIRPERSON BURK: No, it was very clear. I'm trying to think of a question just to -- but no, nice job.

ACTING DIRECTOR ALEXEEFF: So we'll turn it over to Dr. Donald to introduce the staff presenting the report.

DR. DONALD: Thank you. The presentation is going to be made by Drs. Farla Kaufman and Allegra Kim who are the epidemiologists in our group, since most of the data are epidemiologic. After the presentation, Dr. Marlissa Campbell, who prepared the information on the relatively small amount of animal data will also be available to answer questions.

So Dr. Kaufman is going to being by presenting male reproductive toxicity data and some of the developmental toxicity data. Then Dr. Kim will present the remainder of the developmental toxicity data and the female reproductive toxicity data.

CHAIRPERSON BURK: Okay. May I ask something before you start. Are you going to give all your presentation at once or...

DR. DONALD: Oh, I'm sorry. I should have mentioned that.

CHAIRPERSON BURK: I thought we might break it up, so that we could digest it better.

DR. DONALD: Yes, I should have mentioned that. Each section, the male reproductive toxicity, developmental toxicity and the female reproductive toxicity will be presented separately. And there will be an opportunity for public comment and Committee discussion after each of those presentations.

(Thereupon an overhead presentation was Presented as follows.)

DR. KAUFMAN: Thank you. So as Dr. Donald said, I'm now going to present the evidence on the developmental and reproductive toxicity of sulfur dioxide.

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DR. KAUFMAN: Sulfur dioxide is a colorless, non-flammable gas with a pungent odor. In air pollution it is found in combination with sulfuric acid, sulfur trioxide, ozone, nitrogen dioxide and particulates.

It's also an important precursor for the formation of particulate matter. It is present in ambient air, primarily as a result of fossil fuel consumption at power generation and other industrial facilities, and it's also emitted from wildfires.

Exposures in California result from the combustion of sulfur-containing fuel by mobile sources, such as locomotives and ships. Exposure can result from other uses, such as pesticidal and sterilant applications. It's also a component of residential wood smoke.

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DR. KAUFMAN: So SO2, as I will now refer to it, is one of six criteria air pollutants identified by the Clean Air Act. As mentioned earlier, U.S. EPA recently replaced the previous standards with a one-hour standard,

which was stated -- which they stated was specifically to be more health protective by reducing people's exposure to high short-term concentrations. The new standard is based on adverse respiratory effects, including bronchoconstriction, and increased asthma symptoms.

So the primary root of exposure is inhalation of gaseous SO2. However, the percentage absorbed is smaller at low air concentrations than at high concentrations. Although, the mechanism for this has not been identified.

In the interests of time, I haven't included the chemical non-DART toxicities, which are included in the hazard identification materials, or as referred to as the HIM document.

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DR. KAUFMAN: Although I won't be reiterating all the data in the HIM, I will review some of the important -- more important studies and information. However, details of all the studies are included in the document. So starting with the male reproductive toxicity studies.

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DR. KAUFMAN: All human studies were from the Teplice program, which was an international scientific effort to study the impact of air pollution on human health between the years 1991 and 1999. This

collaborative effort between the Czech government and the U.S. EPA focused on a polluted mining district in northern Bohemia.

Teplice was a very heavily polluted area with one of the chief pollutants being sulfur dioxide. That was coming from burning brown coal where the effects of acid rain, as you can see here, actually killed whole forests.

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DR. KAUFMAN: So studies of SO2 and other pollutants compared people living in the very polluted area of Teplice with people living in the relatively clean area of Prachatice in the south.

This graph shows the SO2 levels in parts per billion from the years 1992 to '99. SO2 levels were very much higher in Teplice as shown in the solid line, as compared with Prachatice shown in the dashed line.

Also evident is a substantial decrease in SO2 levels in Teplice starting the late 1990s. This is a result of government projects to reduce pollution.

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DR. KAUFMAN: So almost all the studies of male reproductive toxicity came from the Teplice project. The epidemiologic study by Dejmek et al., a retrospective cohort study, examined fecundability, and I will review the study in more detail in a moment.

Other studies examined measures of sperm quality and genetic integrity, such as abnormal chromatin structure, aneuploidy, and found associations with higher SO2 exposure. That is decreased sperm quality, increased DNA damage, and increased aneuploidy.

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DR. KAUFMAN: So we can examine a possible frame work for integrating the data. There is empirical evidence in humans that for increases in SO2 exposure, there was increased -- there was decreased fecundability or fertility. There's also evidence that increases in SO2 exposure result in increases in DNA damage. These increases in DNA damage were seen in human sperm and in animal germ cells. DNA damage is an endpoint in and of itself.

Supporting evidence of direct damage of SO2 was also seen in human lymphocytes. The association between DNA damage in sperm and reduced fertility is well established in many human and animal studies. So as shown in this framework, if SO2 causes decreased fertility, it may be doing it through the mechanism of DNA damage.

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DR. KAUFMAN: So I'll review some of the details of the fecundability study Dejmek et al. In this graph from the study, the X axis is time from 1993 to 1997 in

four-month periods. Monthly mean SO2 levels are shown in green. Thirty day maximum daily temperatures are shown in red, and fecundability shown in blue was measured as the proportion of women who became pregnant in the first menstrual cycle in which couples were not trying to prevent pregnancy.

The highest SO2 levels occurred in the winter months, along with the lowest prevalence of conception. Therefore the authors controlled for season in their analyses.

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DR. KAUFMAN: This figure shows the annual levels of SO2 in red and PM10 in blue in micrograms per meter cubed for the years 1992 to '99. Decreases in the levels of these pollutants occurred around 1994 as a result of the change in home heating from lignite or brown coal to natural gas, as well as around 1998 when coal-heated powerplants were desulfurized.

Since SO2 levels decreased markedly over time, the Dejmek study evaluated the potential of secular changes by examining two two-year periods, as you can see here. They range from 1994 to '96 and from '96 to '98.

Many studies show correlations with pollutants. Here, we see a dissociation where SO2 decreased dramatically during this time, especially during the

second period, the second two-year period, while PM levels did not change substantially over this period.

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DR. KAUFMAN: This table presents the adjusted odds ratios of conceiving in the first unprotected menstrual cycle. SO2 levels were either classified as medium or high exposure. On the left is the month before conception. In the first two-year period, the odds ratio of conceiving were significantly de -- reduced during the second month or the 30- to 60-day period before conception for couples exposed to both medium and high exposure levels.

So the adjusted odds ratio of 0.49 and 0.43 indicate a lower likelihood of conceiving. During the second two-year period, when SO2 levels were lower, as shown in the previous graph, the odds ratios were reduced, but not significantly during the second, third, or fourth months before conception.

The authors analyzed these pollutants, including particulate matter, a number of nitrogen oxides, polycyclic aromatic hydrocarbons, and observed that SO2 was the only pollutant consistently associated with fecundability -- decreased fecundability.

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DR. KAUFMAN: As mentioned earlier, various

methods can reduce the degree of misclassification in exposure assessment, such as including a factor for the distance from the air monitor to the subject's residence or employing statistical methods, such as spatial averaging. In examining the influence of distance from the air monitors within the region assessed in this study, the adjusted odds ratios of conceiving in the second month before conception were significant when couples lived less than three and a half kilometers from the monitors.

The adjusted odds ratio of 0.56 was of borderline significance at medium exposure. While the adjusted odds ratio of 0.36, under high exposure, was highly significant. At greater distance from the monitor, the odds ratios were not significant even under high exposure.

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DR. KAUFMAN: So in reviewing the results of the study, the evidence of a causal association includes the reduced odds of conception with SO2 exposure greater than 15.3 parts per billion in the second month before conception.

This timing of the effect coincides with critical period of sperm maturation. A dose response association was evident with increasing SO2 exposure. The association was strengthened when distance from monitoring stations was considered. Decreased fecundability was only seen

with SO2 exposure not with other pollutants. And effects on sperm motility and morphology appeared reversible with improving sperm quality after episodes of elevated pollution.

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DR. KAUFMAN: In human studies of sperm, one study reported exposure of air pollution with SO2 as an indicator variable. That was associated with adverse effects on sperm quality and sperm chromatin.

Another study showed increases in DNA damage were associated with increased SO2 exposure during -- or using repeated sampling in a relatively small cohort of 36 young men. They did not find changes in sperm quality. However, the authors noted this is not surprising since sperm genetic integrity is considered an independent measure of sperm function. The DNA damage was significantly associated with SO2 levels. Correlations with either PM10 or PAHs were of borderline significance.

And lastly, the risk of aneuploidy in sperm was also shown to be increased in association with increased exposure to SO2, which was used as an indicator variable.

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DR. KAUFMAN: In animal studies of male reproductive toxicity, mice exposed to SO2 by inhalation showed adverse effects in a number of organs. The ones

relevant to reproduction include the testis.

One study showed altered testis basement membranes, as well as damaged to Sertoli cells and spermatids. Two studies showed altered testicular biochemical parameters. One study also examined comet tails and found increased frequency of cells with longer comet tails, indicating increasing DNA damage with increasing concentrations of SO2.

The authors concluded that SO2 exposure can influence glutathione oxidation and reduction, and damaged spermatocyte DNA.

And lastly, a study showed increased levels of lipid peroxidation, altered intracellular redox status in mouse organs, including the testes.

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DR. KAUFMAN: In summary, there's evidence strongly supporting a causal association between SO2 exposure and decreased fecundability in humans. In addition, SO2 exposure was associated with decreased sperm quality in humans, toxic effects in the testis in animals indicative oxidative damage, and increased DNA damage in the sperm sells of humans and animals.

Taken together, the data provide important evidence of an association between SO2 exposure and male reproductive toxicity.

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DR. KAUFMAN: I'll stop here and answer any questions the Committee members may have.

Thank you.

CHAIRPERSON BURK: No questions?

We have another chance to ask, I'm sure. But I wanted to open it up to public comments. We have determined that at least based on our last meeting that we would limit the time for comments to three to five minutes. And we're going to hold strictly to that. But the beauty is we're going to discuss each endpoint, so that gives you multiple chances to make hopefully relevant comments.

I will say we received the materials that were submitted. And at least I know I read them carefully, so there's no need to repeat everything.

So if anyone would wish to make a comment, do we have any cards submitted?

Nothing.

Okay. All right. Any discussion, at this point, with the Committee? I think the idea of breaking it up is so that we can start to hash it out and not have to do it all at the end. So I'd like us to start thinking about it now.

And I personally have to say, I think of all the

ones -- the endpoints we're looking at, this may be the strongest. And so I want to be sure that we're comfortable with essentially one epidemiological study, which our guidance will support, if we do, you know, backed up with some potential mechanism.

Dr. Keen.

COMMITTEE MEMBER KEEN: Yes. If I could ask Dr. Kaufman maybe just expand a little bit, if there's any additional information they ran across? I realize that we're not focusing on concentrations per se.

But with that said, I am struck by the fact that the concentrations of SO2 that were in the Teplice study seemed to be, if anything, modest at around 25 parts per million. In fact, later down to 15, which is one quarter of what the initial OEHHA apparent 24-hour level of exposure was, which was at 40 parts per billion. So one gets the sense they're quite low.

And then when looking at the experimental animal literature. And I did some reading on my own, it seems as though most of it is 80,000 parts per billion and on up. So one is left with this position of wondering if there's other secondary effects that could be influencing it.

There's been a series of recent reports, for example, that even short-term fasting can result in experimental animal models with whole body increases in

oxidative damage, including potentially damage to DNA and testicular.

So in my own mind, I'm really struck by the very large divergence of what was the concentration that if I just looked at the numbers, I'd say Teplice looks like a pretty good place to live, which then leaves me to wonder if it's other co-contaminants, which were pollutants that might be driving it.

It's a long question, but it's, I think, maybe at the core of what we need to be considering. Was there additional information you can provide in this area?

DR. KAUFMAN: Well, in answer to the first point, yes, the levels were more modest than what you see in animal studies. However, as you saw from the graph with the green levels, they do vary and they're very high points.

So although that's a -- the 30 parts per billion is a mean or where they cut it off actually. That doesn't mean that's all they were exposed to, but I think one important point to bear in mind, they were exposed to them a lot constantly over time, you know. Although, they did vary by season, you see that they were there all the time living in it.

And when you mentioned the standard, it's for -- the new EPA standard is for one-hour exposure. So there's

this chronic exposure where these people in Teplice were living.

Also, I think the differences you see it decreases over time with SO2. And changes in their effects that speak to it being more of SO2 than other pollutants. Although, there were other pollutants there. They just weren't changing over time in the same way.

In terms of the animal studies, yes, the levels were high, but you did see effects in those studies. And, yes, I think a lot of the evidence points to the oxidative damage. And there were studies in humans, if you remember the triangle of the bottom angle of the triangle shows studies in humans that do show oxidative damage relating to fertility.

So there's oxidative damage that in -- that impairs or affects the DNA, which then again affects the fertility. So the mechanism is there.

The levels, per se, you know, that's all I can tell you about them. There is no other information in terms of further studies. The one other piece of information that showed up recently or came to my attention was this issue of a -- the sulfide oxidase deficiency, where Gunnison had done a study looking at the effects on the testes in animals, when he impaired the oxidative -- the sulfide oxidative enzyme he saw effects.

And it speaks to the sense -- the idea of sensitivity across population. So there may be people who are more sensitive because they have different enzyme levels, different polymorphisms. So that's the only other piece of information that would look at, well, is it the problem with a specific population that are most sensitive to lower levels.

COMMITTEE MEMBER KEEN: So maybe just to expand on that slightly, because there may be information that I'm just not familiar with. So if I'm following the SO2 and I appreciate in the Teplice study you can see that there's seasonal variations, are not pretty much the same seasonal variations, say showing up for ozone. I mean we talked about the PM10 which seems to track with it relatively okay, except for one small time point.

But if you use two or three other, you know, markers, what I'm struck with, you may have the most -- the strongest seasonality change in SO2, but that doesn't necessarily imply that other factors aren't driving it. So it's -- I guess that's why I'm kind of struggling with.

The sulfide oxidase issue is really quite different, in my mind. We're talking genetic sensitivities, but it's...

DR. KAUFMAN: So with the changes -- you know, of all the literature that I've read on Teplice, I did not

see much on ozone. I've seen more on PM or PAHs. And I notice that the authors of, I think, it's Rubes et al., and there's an overall Teplice project document that has a lot more information in it. They were struck by the idea that the PM did not change as much as the SO2. And that was over time with the amelioration of the pollution, especially the desulfurization of the coal plants.

In terms of seasonality, I think they track closely together. However, when they looked at PM, for instance, in the Rubes study, they did look at PM and PAHs. And they saw a borderline significant relationships. They weren't -- there were studies that didn't look at the other co-pollutants, they just used SO2 as an indicator, but that is the data that we have available.

COMMITTEE MEMBER KEEN: Thank you.

CHAIRPERSON BURK: Other discussion?

Dr. Klonoff-Cohen, were you happy with the study design, being you're our epidemiologist, I want to get in -- oh, yes, both you I'll ask.

COMMITTEE MEMBER KLONOFF-COHEN: I just wanted to say something just -- I think you probably mentioned it, but I just wanted to say in terms of the study we were just talking about, in terms of Carl's questions.

So it said that the authors note that in previous

studies of the fecundability, and they list the sulfur dioxide hydrogen dioxide, the PM10, blah, blah, blah were highly correlated with coefficients ranging from 0.55 to 0.83.

However, in single pollutant models in the study only sulfur dioxide was consistently associated with fecundability. So they actually notate that.

I think it's one of these -- you know, in terms of for this particular study, and Ellen and I had talked about this before, the beauty of an epidemiologic study is sometimes also has its disadvantages. I think the advantages of the study are certainly that there were -- it seems like they were strong results. I mean, you have a large grouping in terms of parental pairs, 25,858 pairs with 587 that conceived. It is a retrospective cohort, but there are -- it does appear that, to me, that it's important information.

The disadvantages, of course, are the disadvantages in terms of many studies, in that there could be other factors, and you're dealing with real world doses, rather than, you know, in experimental animal studies, of course, you can actually adjust those doses accordingly. But in reality with an epidemiologic study, the doses are what the doses are. And so these real world doses are what, in fact, are in the study. So I think

that's something that we deal with in epidemiology every day.

COMMITTEE MEMBER GOLD: Well, I agree with what's been stated. I guess, you know, what our charge is here is to evaluate the evidence that's before us and try and make a decision in the absence of perfect knowledge. I think we could certainly figure out ways to tweak the studies and try and do them better.

Still a problem, can't hear me?

Is that better?

So, I mean, it would be -- it's easy game to try and pick apart the designs and find fault, but -- so what I tried to do is assess the quality and then look sort of at the weight of the evidence. And I think the evidence is not perfect, but it's reasonably good, and relatively strong. I think when we look in epidemiology at causal criteria, we look at the strength of the associations, and some of these associations are moderately strong. We look at the temporal relationships. Those seem to be appropriate, though not perhaps perfect. We look at dose response. There is some evidence of dose response. We look a biologic plausibility. We look at the consistency of the data. And so it's that total picture, I think, that is helping us to evaluate these for this particular outcome and the other outcomes.

CHAIRPERSON BURK: Are there any other comments on this? Again, we're not going to vote until the end, but I think it's good to break it up this way.

Okay. Hearing none.

COMMITTEE MEMBER KLONOFF-COHEN: Just to sort of add to what Ellen was saying in that what was mentioned in the talk certainly was -- certainly that the timing did correspond with the sperm maturation, and that the weakening effect in terms of in the second year when they thought the sulfur dioxide actually decreased in the region, was certainly important also, and that the effect on the sperm motility morphology actually six months later there were improvements. So all of those add to what Ellen was, in fact, stating in terms of the study.

CHAIRPERSON BURK: I agree. And I'm, you know, not an expert in epidemiology, but I like biological plausibility. And, at least, I think we have that here.

All right. If there are no other comments, I guess we'll --

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk.

CHAIRPERSON BURK: Go right ahead, Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just A clarification. I'm sorry. When I did my earlier discussion about your criteria, I failed to mention that you can use only animal data to make a determination. You

know, this chemical has a lot of epidemiology information, but you are allowed to just look at animal data in terms of determining whether or not a chemical causes an effect.

CHAIRPERSON BURK: All right. Well, would anyone want to comment on the animal data?

COMMITTEE MEMBER KEEN: Yes. That's actually why I did mention it, because my understanding is that the doses that were being used, that were clear, again as I read the papers, signs of toxicity. So when you start having, for example, reductions in food intake, and it was not that quite clear to me how severe they were, that by itself can trigger whole body oxidative damage. And there's been reports on that.

So there could be secondary effects. So I was -- you know, if the animal data had used lower doses where one saw no other signs of toxicity, they would be much more comforting. But as was already noted, those studies apparently haven't been done.

The real thrust of my question was that in case you were aware of any other data that might have been out there where lower doses have been used, but it would appear not.

DR. KAUFMAN: No. I think the lowest dose is indicated on the slides was about 8,400 parts per billion.

I might add that, you know, there are studies

noted in the HIM where humans were exposed to very high levels, as well, and saw effects, but not, you know, systemic chronic toxicity.

CHAIRPERSON BURK: Well, I think if we were basing a decision on animal data only, it would be more challenging actually, because, I mean, it's not inconsistent with Epi, but by itself, it seems not the way we'd like a study to be laid out, I don't think. And actually, I always wonder why do they pick such high doses? I guess they take things that are possible and just --

DR. KAUFMAN: Yeah, I think being an epidemiologist, I have a slanted view of animal experiments, but they do -- you know, they want to see an effect, so they look for it at high doses.

COMMITTEE MEMBER GOLD: I think that's not to say that if they did study lower doses that they wouldn't see anything, it would just -- it might just take, you know, thousands of animals to see it. And so from a practical point of view, they don't do that.

CHAIRPERSON BURK: All right. I think we're ready for the next section, which will be -- are you going to do all of development? Are you going to do female? What's next?

DR. KAUFMAN: Well, we're going to start with

developmental toxicity, and then do female reproductive toxicity.

(Thereupon an overhead presentation was Presented as follows.)

DR. KAUFMAN: All right. Developmental toxicity included studies on preterm birth, low birth weight, congenital malformations, pregnancy loss, asthma, and as well as developmental -- other developmental effects that we'll go into after.

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DR. KAUFMAN: The preterm birth studies there were 10 epidemiologic studies examining preterm birth, eight of which reported significant findings, seven of which were statistically significant with one of borderline significance.

Studies with higher exposure levels of SO2 were more likely to report increased risk of preterm birth. Three studies reported exposure response associations between SO2 and preterm birth, two of which were statistically significant.

Studies of preterm birth varied as to the important windows of exposure, whether there was adjustment for distance from the monitors, and as to the level of SO2 exposure.

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DR. KAUFMAN: This graph shows the reported SO2 levels for each of the 10 studies of preterm birth, ranked from lowest at the top to highest at the bottom.

All the blue circles represent mean values with one blue triangle in the middle, the Leem study it represents a median value. The lines represent either the range or interquartile range of the values. As you can see, there's considerable range in these exposure levels between studies with the study of Brauer at the top with a mean of 2.17 parts per billion, and the study of Xu et al., at the bottom, with mean exposure levels of 35 and 41 parts per billion in different districts.

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DR. KAUFMAN: So in this forest plot, the studies are still listed in the same order as the previous plot. That is by exposure level with the lower exposures at the top and the higher exposures at the bottom.

But now we're looking at the risk estimates with the 95 percent confidence intervals. These values are not standardized and the plot does not represent a meta-analysis. The studies varied by window of exposure examined. And there are numerous risk estimates, under Jalaludin, represent the estimates of different seasons and windows of exposure.

The plot does however show that generally studies

with higher levels of SO2 exposure were more likely to report a significantly increased risk of preterm birth. Most studies considered many covariates, including season and co-pollutants.

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DR. KAUFMAN: So I'm going to describe more about the study of Xu et al. As you saw in the previous slides, there was a high level of SO2 exposure with an annual mean concentration of approximately 41 parts per billion, and a large gradient of exposure, approximately 15 to 115 parts per billion across months.

The authors monitored and included adjustments of seasonal changes, as well as other potential covariates such as temperature and humidity.

The analysis did control for total suspended particulates, but not for other co-pollutants. These districts are densely populated, and all subjects resided within five kilometers of the air monitoring stations, so they did not adjust for distance. A number of different lag days were investigated.

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DR. KAUFMAN: In this figure, if Y axis is adjusted gestational age for SO2 on the left and TSP on the right. And as you can see, the study showed a dose response relationship of gestational age with SO2 and TSP

concentrations after adjusting for temperature, humidity, day of the week, season, maternal age, gender of child, and residential area.

The estimated reduced length of gestation was 12.6 hours for each 100 microgram per meter cubed or 38 parts per billion increase in SO2 and 7.1 hours for TSP.

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DR. KAUFMAN: This figure shows gestational age distribution by tertile of SO2 concentration. The log scale is used to emphasize the tail of the curve. The solid line represents the most polluted days, with the dashed and dotted lines being the moderate and least polluted days respectively.

The authors reported that the gestational age distribution of high pollution days was more skewed to the left, as you can see here. That is towards very preterm and pre-term births, compared with low pollution days, suggesting that more babies are born preterm on high pollution days.

This suggests that pregnancies at high risk for preterm delivery may be particularly susceptible to effects of air pollution.

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DR. KAUFMAN: So the findings in the Xu study included dose response relationship between gestational

age and SO2 exposure. When both SO2 and TSP were included simultaneously in a stratified analysis, the effects of both pollutants were reduced but remained statistically significant in winter.

The adjusted odds ratio for preterm birth was 1.21 for each log increase in SO2 when examining SO2 as a continuous variable. There was evidence that pregnancies at high risk for preterm birth may be particularly susceptible to effects of air pollution.

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DR. KAUFMAN: Dr. Allegra Kim will now describe the remaining evidence for developmental reproductive toxicity.

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DR. KIM: Good morning.

As Dr. Kaufman said, I'll be talking about the studies of the effects of SO2 on low birth weight and other measures of fetal growth or growth restriction.

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DR. KIM: The vast majority of data on fetal growth and fetal growth restriction are from epidemiologic studies. These studies examined a variety of outcomes that represent fetal growth or fetal growth restriction, including the terms listed on this slide. And by the way, I am using the word "restriction" rather than

"retardation", because the American College of Obstetrics and Gynecology is using this terminology now.

First of all, low birth weight is the most common. And it's defined as birth weight less than 2,500 grams. This was usually, but not always, limited to infants born at term, defined as at least 37 weeks gestation, sometimes with a maximum gestational length of 41 to 44 weeks as well.

Birth weight is a continuous variable. Intrauterine growth restricted, IUGR, and small for gestational age, SGA, are conceptually different outcomes, but were generally operationalized in the same way as infant weight below the tenth percentile for sex and gestational week.

Very low birth weight, defined as less than 1,500 grams, was also examined in one study, although the study did not adjust for gestational age.

Another study examined measurements taken from fetal ultrasound scans. Examples of these measurements include femur length and head circumference or biparietal -- and biparietal diameter.

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DR. KIM: In all, 22 studies examined the relationship between SO2 and indicators of fetal growth or growth restriction, and had SO2 measurements. This table

is intended only as a very broad overview of the data set, and I'm including it simply because of the large number of studies.

Starting with the blue row, 13 studies found that SO2 was associated with indicators of fetal growth restriction. That is higher SO2 exposure was associated with increased risk of low birth weight or other measures of fetal growth restriction. Two of these studies examined birth weight as a continuous variable and found higher SO2 exposure was associated with lower birth weight. The exposure periods associated with increased risk varied across the studies.

Please note that inclusion in this count means that for a given study, the only statistically significant associations were in this direction.

Moving now to the yellow row. There were two studies that found the opposite, that is that higher SO2 exposure was associated only with decreased risk of intrauterine growth restriction or slightly increased birth weight.

And in the pink row, another two studies each had mixed findings with SO2 associated with both increases and decreases in risk of fetal growth restriction or birth weight, depending on the population exposed or the trimester of exposure.

Finally, the five studies in the white row found now association -- significant associations between SO2 and fetal growth. Two of these found associations, but they did not reach to statistical significance. Two others were well designed, but had very little exposure gradient. The Brauer study had a mean SO2 level at the limited detection.

Now, I address some of the methodological issues as they relate to the fetal growth restriction studies. As highlighted in the hazard identification materials, or HIM, an important distinction among these studies was exposure assessment. Most studies assessed exposure to SO2 temporally, such as by analyzing average daily SO2 levels for each trimester of pregnancy. And some studies also assessed spatial variation, for example, by using SO2 readings for the monitor closest to a mother's residence.

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DR. KIM: Six studies assessed exposure both temporally and spatially. All of these are shown on this slide. Of these, five studies, those in the blue rows, found that SO2 was associated with increased risk of fetal growth restriction or with decreased growth.

The Lin study found that whole pregnancy and third trimester exposure to SO2 was associated with low birth weight at medium and high SO2 levels.

Dugandzic at al., study observed a first trimester association with low birth weight. The study by Williams et al., found a very large association, that this study was interesting for its statistical methods. It is an outlier both in the methods and the findings.

The study by Yang et al., found a small decrease in birth weight associated with the first trimester SO2. And Hansen et al., found SO2 exposure, which was very low in their study, about one part per billion. They found SO2 exposure was associated with reductions in two out of four kinds of measurements from fetal ultrasound scans. Abdominal circumference was associated with early pregnancy exposure and biparietal diameter for exposure in the first month of gestation, though it was not clear that these measurements would translate to lower birth weights or other clinically important outcomes.

And finally, in the white row at the bottom, is a study Brauer at al., which found no associations between SO2 and fetal growth restriction. Though this was a stronger study in terms of its methods. The mean SO2 levels were at the limit of detection of two parts per billion as both Dr. Kaufman and I pointed out. This was confirmed with the author. Also, the interquartile range for SO2 levels was one part per billion. So this study lacked both reliably detectable SO2 levels and an exposure

gradient.

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DR. KIM: Another important methodological concern is confounding by co-pollutants. Based on the literature and as observed in this data set, the main co-pollutants of concern for fetal growth restriction are carbon monoxide, particulate matter including particulate matter less than 10 microns in diameter, less than 2.5 microns and total suspended particulates, TSP. And to a lesser extent, NO2 could also be a concern.

In this data set, carbon monoxide was more consistently associated with fetal growth restriction than particulates and NO2. As most studies looked at various air pollutants, not just SO2, they typically considered at least one co-pollutant. Although, high correlations among pollutants often prevented multi-pollutant modeling.

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DR. KIM: I'm showing you this slide again to point out the fact that CO was associated with increased risk of fetal growth restriction. And in both of the studies that found -- excuse me. Both of the studies that found SO2 was associated with lower risk of fetal growth restriction, these in the yellow row, as well as the two studies with mixed findings in the pink row.

PM10 was also associated with fetal growth

restriction in one of the studies in the yellow row, that found that SO2 was associated with decreased risk of IUGR.

Among these four studies in the yellow and pink rows -- I lost my cursor here -- here we go -- CO and/or PM had stronger associations with fetal growth restriction than SO2. In these studies, co-pollutants were not analyzed in the models with SO2, so they could easily confound the relationship between SO2 exposure and fetal growth.

There is a possible exception, the study by Gouveia at al., which actually reported including co-pollutants in statistical models with SO2, but I'll get back to that study by Gouveia again in a moment.

Although multi-pollutant models were often not possible due to high correlations among co-pollutants, as I mentioned a moment ago, multi-pollutant analyses were reported for seven studies, including the Gouveia study.

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DR. KIM: This table shows the seven studies that examined fetal growth restriction and included multi-pollutant statistical analyses. The right-hand column shows the co-pollutants that were analyzed in the models with SO2.

Returning again to the study by Gouveia in the pink row at the top, Gouveia found SO2 was associated with

slightly decreased risk of low birth weight and greater birth weight in single pollutant models. However, when analyzing a multi-pollutant model with CO and PM10, the association disappeared.

The correlation between CO and PM10 was 0.9, which is very high and suggests that proper adjustment may not have been possible in statistical models. These multi-pollutant analyses might therefore be invalid and the authors did not report them in detail. Correlations were not reported for SO2.

And NO2 and O3, which were in the parentheses, were not considered in the multi-pollutant models, because they were not significant in single pollutant models.

And also, this study averaged daily pollutant levels across all sites in São Paulo, a very large city, increasing the potential for exposure misclassification.

So the remaining six studies with multi-pollutant analyses, shaded in blue, found that SO2 was associated with increased risk of fetal growth restriction after adjusting for the co-pollutants shown. Recall that carbon monoxide and PM were the co-pollutants of greatest concern for confounding.

Two of the studies, those by Lin et al., in 2004, and Liu et al., in 2003, examined CO together with SO2 in multi-pollutant statistical models. Liu at al., who

examined low birth weight and intrauterine growth restriction in Vancouver, British Columbia also had data on PM10, but only for five of the 13 years in the study period. So they did not include PM10 in multi-pollutant analyses.

They did report, however, that PM10 was not associated with birth outcomes. Liu et al., observed associations between early pregnancy exposure and low birth weight and IUGR. And adjustment for co-pollutants either strengthened or caused no changes in observed associations for SO2. Correlations among pollutants were also relatively high in this study.

Lin et al., in the -- right here -- 2004, included both PM10 along with carbon monoxide and other co-pollutants in models with SO2.

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DR. KIM: So now I want to talk more about the study by Lin et al. This study examined birth outcomes in residents of Taipei and Kaohsiung, the two most populous metropolitan areas in Taiwan. Kaohsiung is surrounded by several petrochemical plants and industrial parks. And coal combustion is common among the steel factories in that area.

This study is highlighted because it assessed both spatial and temporal variation in SO2 exposure with

five monitors in each city. Restricted the cohort to births to women within three kilometers of monitors, reducing the risk of exposure misclassification. Statistical models also included multiple pollutants, as I've mentioned, including CO and PM10.

This study also included adjustment for season. The authors report that they examined seasonal patterns in this cohort, and they also evaluated season for effect modification and found none.

This study also had relatively high SO2 levels, which were well above the expected limit of detection. And finally, the study had an exposure gradient for SO2. Among the 10 monitors, the average annual SO2 levels range from 3.7 to 29 parts per billion.

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DR. KIM: This table shows the results for exposure to SO2 averaged over the entire pregnancy by exposure levels. So you can see in the second column, they had relatively high SO2 levels and an exposure gradient. The adjusted odds ratios, AORs, adjusted for potential confounders, including CO, PM10, NO2 and O3 were 1.16 for the medium exposure level, and 1.26 for the high exposure level. And they were statistically significant. On this and the next slide, you can see higher adjusted odds ratios with higher exposure.

So Lin et al., also reported analyses by trimester-specific exposures. The last slide was entire pregnancy exposure. This table shows results for SO2 exposure in the third trimester. The exposure categories are slightly different reflecting the differences in average SO2 concentrations for the third trimester versus the entire pregnancy.

Here the AORs, the adjusted odds ratios, are smaller than for exposures averaged over the entire pregnancy. But the OR for median exposure level is nearly statistically significant, and the odds ratio for the highest exposure category is still significant.

Odds ratios were not significant for the first and second trimesters. The authors did report, however, that analyses suggested an exposure response relationship between the trimester-specific SO2 exposure, and risk of term low birth weight.

Of course, the Lin study had some limitations. The high SO2 levels were generally from Kaohsiung, and the low levels were generally from Taipei.

It is possible that differences between these two cities could confound the associations observed. One possible source of city-related confounding could be differences in the two cities' populations. For example, maternal characteristics might have confounded the

findings. The maternal characteristics included in the analyses were education level, age, and parity.

The authors did not have information on factors, such as maternal occupation, maternal nutrition, smoking body size and so forth.

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DR. KIM: However, the prevalence of smoking among adult women in Taiwan was estimated at three to four percent during that period. And the prevalence among pregnant women was expected to be lower.

The authors also conducted phone interviews to examine smoking, alcohol use, maternal height and weight -- and maternal height and weight in a convenience sample of women from one medical center in the study area, and found little or no variation with maternal SO2 exposure levels. So such characteristics aren't likely to confound the observed associations.

Carbon Monoxide was associated with the reduction in risk of low birth weight, leading the authors to suggest the possibility of residual confounding, for example, by maternal characteristics.

And the authors reported that pollutants were correlated but they also reported that they examined them carefully co-linearity, included that they should be less of a concern. They did not report correlation

coefficients.

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DR. KIM: The toxicological data were quite sparse, but did show that inhalation of very high concentrations of SO2 reduced fetal growth. A study in mice found that SO2 was associated with a decrease in birth weight in a concentration-dependent manner. Reduced birth weight was observed at 65,000 ppb, but was not significant at 32,000 ppb. The authors noted no visible signs of maternal toxicity.

Another study found no effective SO2 at -- excuse me. Another study found gestational exposure to 25,000 parts per billion SO2 was associated with decreased fetal weight in mice, but no change in crown-rump length. And the same study found no effective SO2 at 75,000 parts per billion on fetal weights of rabbits.

Another paper mentioned the lack of effect on birth weight, but did not report actual data on this endpoint.

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DR. KIM: Now, I'm moving on to summarize the studies on effects of SO2 on congenital malformations.

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DR. KIM: The epidemiological literature on air pollution and congenital malformations is relatively new.

Six of the seven studies were published in 2008 or later. Three of the studies were U.S. studies in New Jersey, Texas, and Georgia. Some of the studies appear to be very rigorously designed and conducted, but they were still subject to challenges.

Challenges that are particularly important in studies of birth defects include lack of control for potentially important confounders. In the case of malformations, potential confounders might -- or could include occupational exposures, alcohol use, a sibling history of defects and specific nutrients.

Many of these studies looked at numerous defects and groupings of defects, in addition to multiple pollutants, so they were especially subject to multiple comparisons concerns.

Case identification can also be a problem, for example, with heart defects, because they can be difficult to reliably identify. And defining case groupings and dealing with syndromes are also concerns, and they varied in how they did these across the studies.

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DR. KIM: The case groupings used in human studies were any and all birth defects, chromosomal versus non-chromosomal defects, cardiovascular malformations, oral clefts, including cleft lip, with or without cleft

palate or cleft palate only.

Although this was a relatively sophisticated group of studies, the findings were highly inconsistent. There were numerous associations of SO2 with decreases and risk of malformations, sometimes large decreases, in risk of a given defect or group of defects. But for these, there were often -- there was often at least one other study finding an association with increased risk.

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DR. KIM: An animal toxicological study in two species found no association with specific or aggregate malformations in mice at 25,000 ppb or rabbits at 70,000 ppb. The same study reported delayed ossification of the sternebrae and the occipital bone in mice and minor skeletal variations in rabbits exposed to SO2, but the data were not reported.

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DR. KIM: Now, I'm moving to another outcome, pregnancy loss. As noted in the HIM, pregnancy loss may be manifestations of direct toxicity to the conceptus that may be mediated through toxicity to the reproductive system of the mother.

Thus, the pregnancy loss studies can be viewed in the context of identifying developmental or female reproductive toxicity. Again, I'll start with the

epidemiologic studies.

This group of four studies is generally older, with half being from the early 1980s and the others published in 2000 or earlier.

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DR. KIM: First, spontaneous abortion. A cross-sectional occupational study in Finland found no association between SO2 exposure and spontaneous abortion.

Stillbirth was variously defined as fetal death after 28 weeks gestation or over 1,000 grams or it was not defined. There were three studies, all ecologic in design. Two studies found no association. One study found a correlation between SO2 and stillbirth of the correlation was 0.7, but it did not estimate risk. And this study published in 1984 did not consider covariates.

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DR. KIM: Animal studies also did not provide evidence for effects of SO2 on fetal death. A study found that gestational exposure to SO2 at 25,000 parts per billion for mice or 70,000 parts per billion for rabbits, did not result in changes in mean litter size, or resorption frequencies.

Another study found that exposure to 32,000 parts per billion or 65,000 parts per billion SO2 was not associated with changes in litter size.

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DR. KIM: Risk of asthma was explained -- was examined in a recent study. Clark et al., in 2010 examined the associations of prenatal and first-year exposure to air pollution with risk of early childhood asthma.

Despite low levels in this British Columbia study, the authors reported a small increase in risk of asthma associated with prenatal exposure to SO2. However, postnatal exposure had the same association as prenatal exposure. And due to high correlations, the authors could not separate those effects.

Also, there were high correlations between SO2 and co-pollutants, so the authors were not able to examine the risks associated with SO2 independent of co-pollutants. Associations with traffic-related pollutants were stronger than those for SO2.

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DR. KIM: There were some toxicological studies of other developmental outcomes. One study in mice found effects on male-to-male social behavior at 12,000 and 30,000 parts per billion. These effects included increased body sniffing and non-social activities, and decreased freezing, tail rattling and defensive postures in a concentration-dependent manner.

Another study in mice reported delays in acquisition of certain postnatal reflexes, such as increased time to righting reflect on postnatal day one, and for negative geotaxis on postnatal day 10 at 32,000 and 65,000 parts per billion in a concentration-dependent manner.

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DR. KIM: So in summary for developmental toxicity, the majority of the studies of preterm birth found an association with prenatal SO2 exposure. And the same is true for studies of low birth weight and fetal growth restriction.

For both of these two outcomes, the relevant exposure period varied. While the quality and sophistication of the studies also varied, most of those with reliably detectable SO2 concentrations and an exposure gradient found SO2 to be associated with preterm birth and/or fetal growth restriction. Some studies also observed dose response relationships.

In addition, studies with multi-pollutant models in both spatial and temporal exposure assessment were more likely to find an association between SO2 and fetal growth restriction. Animal data are sparse, but did show effects on fetal growth.

The epidemiologic data do not suggest

associations with congenital malformations, pregnancy loss, or asthma.

Animal data did show effects on social behavior and some reflexes at high exposure levels.

And now we'll take your questions.

CHAIRPERSON BURK: Are there any questions yet? We have to digest and mull over some of this.

Are there any public comments?

All right. And I would ask that any of the commenters, you know, identify themselves and their affiliations and please try to stay to the time maximum that Dr. Alexeeff will be the monitor for.

MS. SHARP: No problem. My comment is short. I'm Renee Sharp and a biologist with the Environmental Working Group. And I'm actually going to address the other endpoint that you were speaking about earlier as well, because I didn't speak then.

And I think it's just notable to say that, I mean, looking at these two sort of different groups of studies together, you have, you know, quite a variety of different evidence kind of pointing to SO2 being a chemical that you would list. I mean, you have animal studies. You have human studies. You have mechanistic studies. You have dose response. You have many different endpoints.

So, you know, I'm not going to get into the technical matters. I think you guys probably know it better than me quite clearly.

But it just seems like, I mean, this is one of those cases where you actually have, you know, lots of different studies pointing in, you know -- you know, not uniformly consistently in one direction. Of course, you never get that. But it's -- I think it's just quite significant to note that. So I encourage you to list the chemical, even just -- you know, not that you're going to vote no, but I would just suggest that even if you were to vote now, that you would vote to list the chemical. Thank you.

CHAIRPERSON BURK: Are there any other public comments?

Two options right now. We can start discussing or we can hear the female presentation. We're going to have to break at noon for the stenographer and for lunch. So it's sort of up to the Committee.

COMMITTEE MEMBER KLONOFF-COHEN: Let's discuss it now.

CHAIRPERSON BURK: You want to discuss now. Okay.

Shall we split this discussion up into -- are we safe in saying we probably won't be discussing pregnancy

loss and/or asthma and/or -- well, I don't know, malformations. Does anybody think that's -- all right.

So I think that, you know, the main two areas we're going to talk about are preterm birth and the growth issues. So why don't we start with preterm birth just to try to organize ourselves a bit. Again, we have several studies. The Xu et al., seems to be one that perhaps has the best study design. Any comments on any of the studies?

COMMITTEE MEMBER KLONOFF-COHEN: There were seven studies, but since the staff chose Xu, we can certainly start with Xu in terms of for the advantages. So certainly they showed a dose response effect, and they have high levels of sulfur dioxide and large gradient of sulfur dioxide exposure, and they had a homogenous population, and people lived close to the air monitoring stations. And gestational age was collected prospectively, and they monitored seasonal changes.

So it's a very nice study, but it also has several other studies that collected different types of information, yet did, in fact, find an effect. So to me that's quite convincing, when you put the other studies. I'm happy to talk about the other studies or not.

CHAIRPERSON BURK: Well, I'm happy to hear about what you have to think about them, as long as we're at it.

COMMITTEE MEMBER KLONOFF-COHEN: Well, you have, let's see, Bobak study had about 108,000 people and they were looking at less than 37 weeks preterm cohort. And they had a monitoring system in the Czech Republic. And they had an adjusted odds ratio per 19.1 parts per billion increase in sulfur dioxide by trimester. So for the first trimester, it was 1. -- basically, all of the first, second, and third trimester has found an effect with increasing sulfur dioxide.

Let's see. There's the Jalaludin one, which was also statistically significant. There were about 123,000 Singleton births and about 4.9 percent were preterm. And they basically looked at analysis of mothers within five kilometers of the monitors. And they had high sulfur dioxide was correlated with the preterm risk in the first trimester with an odds ratio of 2.31.

Also, in the final month 1.56. And the final three months of 2.33. And they adjusted for gender, paternal age, maternal smoking during pregnancy, gestational age at first prenatal care visit, and some other things, including season and parity.

There is Jiang, but they didn't give the total sample for the number of births. They did say there were 3,346 that were less than 37 weeks preterm. They had six monitoring stations in Shanghai, China. And they also

found an increase in preterm birth correlated with 3.81 parts per billion sulfur dioxide.

There is Leem, who had 52,000 Singleton births and four percent were preterm, so that was about 2,000. And they found a dose response relationship between the first trimester of sulfur dioxide and risk of preterm delivery, with a relative risk of 1.21.

There is Lin who had 229,085 Singleton live births, and about 5.3 percent were preterm. And they used 13 census subdivisions in Vancouver, British Columbia. And the adjusted odds ratio for the last month of pregnancy was 1.09.

There is Mohorovic, where there were 704 women living near a coal power plant. And they broke them down less than 28 weeks, 29 to 32 weeks, 32 to 37 weeks. And that was a retrospective cohort. And there was the correlation between sulfur dioxide exposure and gestational length at the end of the first month, so it's probably appropriate for that.

I think that's it.

(Laughter.)

CHAIRPERSON BURK: Well, very good. We're going for speed records here, I think, but -- well, I wanted to get folks comments on the various criticism that we were presented. And one was the inconsistencies in the

critical exposure window.

Does anyone have any thoughts on that? Does that bother anybody?

COMMITTEE MEMBER GOLD: I'm not sure I'm going to directly answer your question, but I found for myself that I needed to kind of be able to summarize this study, so I came up with a grading system of the studies. And we could sort of argue about this, I'm sure, and not have perfect agreement.

But I sort of ranked them sort of high, medium, and low, in terms of their quality. High, being good sample size, control of confounding, adequate control of confounding, which would include considering seasonality in timing and all those kinds of things.

And so with pre -- I did this, by the way for each of these outcomes. And for the preterm births, it seemed to me that the likelihood of a positive finding was related to decreased quality of the study.

And so given that the effects are relatively modest, that some of the timing is inconsistent and that because the effect estimates are modest, the lack of control for confounding could easily account for some of those findings, for this particular outcome, I was a little bit more on the fence than say for fetal growth which we'll talk about next.

So, I mean, I think we have a good summary of the studies, but I think the evidence is not quite as convincing as perhaps for some of the other outcomes given the limitations of the study design. And as I said, some people could argue with me about my ranking system. And I'm sure that we wouldn't have a hundred percent agreement among epidemiologists on that.

COMMITTEE MEMBER KLONOFF-COHEN: Ellen, do you want to talk about what studies you ranked in what order, just to give an example.

COMMITTEE MEMBER GOLD: It's a little bit harder. That would be difficult for me to do quickly.

COMMITTEE MEMBER KLONOFF-COHEN: Okay. Give me like an example of a high rated one versus a low rated one.

COMMITTEE MEMBER GOLD: All right. Let me -- so I did make notes, so just a second.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Gold, if you could just move the microphone closer to your mouth.

COMMITTEE MEMBER GOLD: Excuse me?

CHIEF COUNSEL MONAHAN-CUMMINGS: Just move the microphone closer to your mouth. I think that would probably help.

COMMITTEE MEMBER GOLD: So my rankings in terms of high quality studies, I would put -- I put the Brauer

study and Jalaludin study. But the Brauer study was negative. And the Jalaludin I had as sort of inconsistent, just as two examples. Let me see if I can find some more positive ones.

Actually, I would disagree with the assessment made by the staff about the Xu study, because of the control of confounding issue was -- I mean, they made the argument that the pollution would not be related to socioeconomic status and so forth. And I'm not sure I'd agree with that.

It's true they have a relatively homogenous population, but, in fact, high pollution, at least in this country, tends to be in lower SES areas. And that's also -- lower SES is also related to smoking. So all of that considered, I would not rank that study as highly again epidem -- you know, conscientious epidemiologists can disagree on this.

Does that kind of get at your question?

COMMITTEE MEMBER KLONOFF-COHEN: I was just looking at those studies, yeah.

COMMITTEE MEMBER GOLD: That's all.

CHAIRPERSON BURK: I'm curious what you thought of the other sort of negative study, which was Darrow.

COMMITTEE MEMBER KLONOFF-COHEN: Well, I just want to go back and ask her, just in terms of -- I'm so

sorry, did you say the Gouveia study you rated that highly, is that what you were saying?

COMMITTEE MEMBER GOLD: The Jalaludin study.

COMMITTEE MEMBER KLONOFF-COHEN: Oh, Jalaludin.

Go ahead and ask your other question, and I'll just look.

CHAIRPERSON BURK: Well, you know, I kind of summarized each one too. And I go more for the probably the author's conclusions. And I was just curious about the other one that I thought was essentially negative, which was Darrow.

When we're trying to do a weight of the evidence, we do have to look at ones. Now, granted if the exposure was very minimal, like the Brauer, so low that you wouldn't be able to find anything, then you can't give that much weight either way.

COMMITTEE MEMBER GOLD: So if you're asking about the Darrow study, that sort have -- I ranked it sort of in the medium category. And the findings were essentially negative. So again, you know, the ones that I think I would rank the quality as highest were the -- there were only two of them in my view and one was -- had positive findings and one had negative.

Then I had in my second category, I had five studies that were sort of medium quality and four of them

were positive. And then I had three studies that I thought the quality -- again, we could disagree about this ranking -- that I thought the quality was not great. And all three of them had positive findings. So to me, there was an inverse relationship between having a positive finding and the quality of the study.

COMMITTEE MEMBER KLONOFF-COHEN: I'm not sure you'd say it's an inverse relationship. I think what you're saying is that high quality studies as well as poor quality studies came up with the same finding. So the question is what does that mean?

COMMITTEE MEMBER GOLD: I'm not sure I would say that exactly.

COMMITTEE MEMBER KLONOFF-COHEN: I wouldn't say it was an inverse relationship.

COMMITTEE MEMBER GOLD: I was just looking proportionally. And granted, the number of studies is too small for this to have any, you know, statistical meaning at all. It's --

COMMITTEE MEMBER KLONOFF-COHEN: Did you give like a point system for things. So in other words, like if they had confounders that you thought were appropriate, then you would give them X number of points. And, I mean, how did you actually do that?

COMMITTEE MEMBER GOLD: That would be a more

sophisticated system than what I did.

(Laughter.)

COMMITTEE MEMBER KLONOFF-COHEN: So that's why I'm a little uncomfortable. So you're saying like an inverse relationship, unless there was like a -- do you know what I mean, like you subjectively ranked them in other words?

COMMITTEE MEMBER GOLD: Right, of course, it was subjective, but what I was thinking about in my mind was --

COMMITTEE MEMBER KLONOFF-COHEN: All of the important qualities of an epidemiology -- right.

COMMITTEE MEMBER GOLD: The study design, right.

CHAIRPERSON BURK: Well, I don't know. My issues are a little different. It's probably more about what the possible mechanism is and the timing and all of that.

But we're kind of at the limit of our court reporter's wits here. And so I think we probably will break for lunch, and -- is that okay? And we will begin again at one o'clock.

See you then.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just to remind the Committee members, that when you go to lunch please don't discuss the issues that are in front of you today among yourselves, particularly because you are the quorum,

so please talk about the weather or something else.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON BURK: Good afternoon, everyone. We'll begin the meeting again. The plan right now is to work up until 1:30 on sulfur dioxide at the latest. But at that point, we will then continue with the agenda item on the listing mechanisms. And so what we've decided is to ask for the staff presentation on female reproductive toxicity, and then we'll finish our discussion.

(Thereupon an overhead presentation was Presented as follows.)

DR. KIM: Good afternoon.

I'm going to talk about female reproductive toxicity. One epidemiologic study and one animal study examined female reproductive toxicity, not including pregnancy loss as I mentioned earlier. A study by Legro et al., in the mid-Atlantic region, examined women undergoing their first cycle of in vitro fertilization, or IVF. Air pollution concentrations at various stages of the IVF process were considered.

SO2 exposure was consistently, but not significantly, associated with decreased odds of live birth. However, associations with other pollutants were stronger than those for SO2. Only NO2 and O3 were included in multi-pollutant models.

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DR. KIM: In one study, rats were exposed to SO2 by inhalation at about 1,500 parts per billion. Effects were seen on estrous cycle length and F0 and F1 offspring, pregnancy frequency and duration, and offspring growth. No changes were observed at 57 parts per billion. However, the study was not well reported providing no data or statistics.

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DR. KIM: Now, I'm going to talk about related studies. One study examined effects of sodium sulfite on oocytes of sheep, cows, and mice. In vitro exposure of sheep or cow oocytes resulted in fragmentation of chromosomes with or without rearrangement.

No effects were seen in a mouse oocytes exposed either in vitro or in vivo.

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DR. KIM: In summary, for female reproductive toxicity, there is some evidence from an animal study for an effect on the estrous cycle and data on fragmentation of chromosomes in sheep or cows.

Any questions?

CHAIRPERSON BURK: I see none.

Opportunity for public comment?

Please come forward.

Again, limit to three minutes. State your name

and affiliation. Thank you.

MR. HEWITT: Thank you, Madam Chair, Committee members. John Hewitt on behalf of the Grocery Manufacturers Association. GMA is a national trade organization representing food, beverage, and consumer care products companies.

My comments are relative to the broader issue of sulfur dioxide, not specific to any of the three components of it. It's our opinion that, you know, if a determination to list sulfur dioxide is made, that the listing should be limited to inhalation exposure. And a listing beyond that is not supported by the evidence in the staff documents and reports.

For example, the February 2011 report involves inhalation exposure. Also, just draw the Committee's attention to page 20 of OEHHA's report acknowledging that the quote, "Data pertaining to absorption of sulfur dioxide by the oral and dermal routes appear to be lacking", end quote.

So again, on behalf of the Grocer Manufacturer's Association, we don't take a position relative to the listing of sulfur dioxide. But to the extent that this body does decide to do it, we would ask that you consider limiting it to inhalation exposure only. Thank you very much.

CHAIRPERSON BURK: Thank you. Are there any other public comments?

All right. I guess we'll get back to our Committee discussion. Does anyone want to say anything for or against the endpoint of female reproductive toxicity?

COMMITTEE MEMBER KEEN: I mean, I guess I would say there's insufficient evidence to judge it one way or the other.

CHAIRPERSON BURK: I agree. I just wanted to put it on the record there. All right. So I think we're back to preterm birth, and particularly to the fetal growth issues. So do we have any continuation to the preterm growth epidemiologist debate here?

I guess you'll agree to disagree kind of thing.

Okay. All right. Let's move on then to -- actually, I want to make sure that we actually talked about all the other ones. And I think there's insufficient evidence for animal social behavior, the childhood asthma limited to prenatal exposure.

The congenital malformations, you know, there was a ton of data, but it seemed very inconsistent to me and not particularly plausible. Any comment on that, Carl?

COMMITTEE MEMBER KEEN: Well, I would concur. I'm not seeing a specific pattern. And if anything, it

seems to further support the idea that when looking at the inhalation data, if indeed there's a modulating influence, sulfur dioxide, it could be modulated by the other pollutants, which also happen to be there. And that would explain why you see a different spectrum potentially of malformations.

The experimental animal data I find very unconvincing. And it does seem to be complicated by the fact that there are at least acute periods of food removal and some general systemic toxicity, which, in the past, this Committee has urged caution in overinterpreting, because by definition once you get to that point, you're going to start seeing effects on minor ossification sites, low birth weights, et cetera, at least in the experimental animal model.

So I find overall the lack of any sense of a pattern, as well -- in terms of the human side, and any real biological criteria. Just -- I use whole criteria and I don't see it.

CHAIRPERSON BURK: Agreement there.

Also, even OEHHA staff does not find support for pregnancy loss or spontaneous abortions. So I don't think we need to discuss that one.

So I think we'll talk about fetal growth, where there were quite a number of studies. And perhaps we'll

let Dr. Gold start first on this one, get your rating system for the studies.

COMMITTEE MEMBER GOLD: I did use the same subjective rating system.

So here though, it did seem to me that even some of the better designed studies did have positive findings. Again, though, I would just caution that the effects appear to be modest. And so there is still the possibility of uncontrolled confounding.

But on the whole, I would say the findings here are a bit more consistent than what we've seen with preterm birth, I would argue, or some of the other outcomes. So maybe I'll just keep it to that.

CHAIRPERSON BURK: Dr. Klonoff-Cohen, do you concur?

COMMITTEE MEMBER KLONOFF-COHEN: Yes.

CHAIRPERSON BURK: All right. And one other issue, since it was just brought up, I think we should talk about before we vote, would be whether we would consider listing it by inhalation only. To my mind, the vast majority of the studies are by inhalation. I didn't -- I don't know what the difference would be, truthfully. I mean, I don't know what the mechanism is, so I don't know what difference it would make if you ingest it. But the sulfite studies mostly were negative,

so -- and that would be the main food way, wouldn't it?

COMMITTEE MEMBER KEEN: Yeah, again, I'm not sure if that's within the realm of what we can do if we could. I, for one, would feel much more comfortable. One of the things that I find worrisome is again this very large difference between the concentrations that are used in experimental animal studies and very modest -- we're not talking a factor of 10, we're talking in excess of a hundred.

But one potential explanation, which one could get some satisfaction with, is that it is acting as -- in concert with other pollutants. So then it becomes quite defensible to say it makes sense to go ahead and say well, we're looking at the environmental concentrations, because they don't work in isolation.

But every study that I looked at, where it's done in isolation, you get a completely -- a very different answer. Either, you get no effect or you have something of several orders of magnitude difference. But whether that's even doable, I don't recall us dealing with this before.

CHAIRPERSON BURK: Well, we'll ask for a legal opinion.

CHIEF COUNSEL MONAHAN-CUMMINGS: In terms of past practice, the Committee has, from time to time, put in a

parenthetical on a particular chemical. We have one where the Committee used a phrase of airborne particles of respirable size. I'm not sure whether that would be appropriate in this case. That would be up to you.

You know, generally speaking, we don't, even from our listing, limit listings by route, because, you know, if there's an assumption that if it causes, you know, an effect by inhalation, it most likely will cause the effect from something else.

However, if you choose to do that, I don't think that you'd necessarily be challenged on that, at this point. And we could also bring the chemical back to you in the event there are studies that show maybe a dermal or ingestion kind of scenario actually occurs and that it has a similar result. I don't know if the staff is aware that any of that is coming, but we could monitor those and bring it back at that point.

I mean, our office has recently put a parenthetical on a listing, but it's that airborne particles of respirable size type thing. And I don't know if that fits this, because of the type of effects you're talking about.

CHAIRPERSON BURK: Well, maybe the staff could comment. Just generally in this case --

ACTING DIRECTOR ALEXEEFF: Can I make a comment.

CHAIRPERSON BURK: Okay. Sorry.

ACTING DIRECTOR ALEXEEFF: Yeah. Maybe either Lauren or Cindy remember, but I think we have the formaldehyde listing as parenthetical gas.

DR. ZEISE: Formaldehyde gas, yes.

ACTING DIRECTOR ALEXEEFF: So possibly that might be more suitable, or you could say if you'd prefer -- well, if you said by inhalation, then that talks about an exposure route. It doesn't really describe the compound. So gas might be better.

CHAIRPERSON BURK: So we could say as a gas or would we say in air pollution?

ACTING DIRECTOR ALEXEEFF: Well, the formaldehyde listing just has formaldehyde parenthesis gas. The other --

CHAIRPERSON BURK: Okay. Sulfur dioxide is a gas, so I mean that's kind of --

ACTING DIRECTOR ALEXEEFF: That seemed to convey the correct information. And the one that Carol was referring to had to do with when we're talking about particulate matter and clarifying what kind of particulate matter, what size of particulate matter, which doesn't pertain in this case.

CHAIRPERSON BURK: I'm not exactly sure what the answer is, but gas sounds good. It's suitably vague

though. I mean -- but I think that does imply by inhalation, would you think?

I don't know. Certainly, we don't want to do anything that's not in our purview, so it may just be an advisory note we'll be still voting on sulfur dioxide, but --

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, you know, the Committee has, in the past, done a number of things where they are limiting a chemical. Some of them we're not that comfortable with, and others that -- you know, like George said, you know, putting it in terms of a gas, you know, would be -- then you're not talking specifically about a route of exposure. That kind of can come later in terms of what kinds of exposures a person might, you know, have.

So I think George's comment is something to consider. But like I said, I don't believe that there would be -- it doesn't say that we couldn't get sued on something, but the likelihood is pretty low given the -- you know, the evidence that you guys are looking at, and the fact that there, as far as I could tell, maybe there was one -- something that related to dermal or you were saying that it could be absorbed or something?

I mean, there's just not anything really to base a general listing on, other than this presumption that,

you know, could cause it by another route.

CHAIRPERSON BURK: Yeah. Well, that's the part that's kind of confusing me, because we don't usually have this discussion, and we've had numbers of other chemicals that could have multiple routes. It just seems like all the studies we looked at were inhalation, so I'm comfortable saying that.

COMMITTEE MEMBER KEEN: Yeah. Again, I think it's important to note, it's not just that they were inhalation versus other routes of exposure. It's inhalation accompanied by other pollutants. I mean, that's where I think the rub is. And it's quite different than any other compounds we've looked at in the past.

CHAIRPERSON BURK: Right. Well, then what about SO2 as part of air pollution?

COMMITTEE MEMBER WHITE-PORTER: Yes, that makes more sense.

CHAIRPERSON BURK: I mean, to my mind, that's what we're talking about. You think that would fly. I don't want to do anything that gets us sued.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, again, that has been done -- that particular parenthetical has been done in a different context, in terms of alcoholic beverages, and --

CHAIRPERSON BURK: I remember that one well.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- associated with alcohol abuse, for example.

But, you know, given that you're looking specifically at this chemical and not necessarily its interaction with other chemicals. You know it is a mixture. There's, you know, other chemicals that you've listed as a mixture, like environmental tobacco smoke, or at least one of the Committees did, and things like that, where it wasn't -- it wasn't even limited to a gas, but it, you know, kind of implies that.

But my own preference would be that you'd talk about a gas, because that's the -- that is the chemical you're looking at. You're not listing, you know, general air pollution based on one chemical that may be in the air pollution.

CHAIRPERSON BURK: Comments.

COMMITTEE MEMBER GOLD: Yeah. I'm a little uncomfortable with adding the air pollution thing, because the animal studies were not done that way. And most of them were inhalation studies, so I'd be a little bit more come with that. Saying it's a gas --

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Gold, we can't hear you. Sorry. Just pull the whole thing closer to you now.

COMMITTEE MEMBER GOLD: I was just saying that

the animal studies were not air pollution studies, they were actually administering the one compound. So I would be uncomfortable with adding the air pollution caveat to this. And adding the gas caveat to me just seems redundant. So I would consider inhalation, because most of the studies were done that way.

CHAIRPERSON BURK: All right. Are we ready to take our vote?

Any further comments, questions?

My understanding is and I'll read this endpoint by endpoint, that five yes votes are required to add a chemical to the list.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

CHAIRPERSON BURK: Okay. So first -- and I don't know, when I read this do I say has sulfur dioxide by inhalation or can we just add that on later?

CHIEF COUNSEL MONAHAN-CUMMINGS: Are you talking about by inhalation or is, you know, a gas or --

CHAIRPERSON BURK: A gas. Well, I don't know. We haven't really decided on that yet. I guess --

CHIEF COUNSEL MONAHAN-CUMMINGS: You need to do that first before you ask.

CHAIRPERSON BURK: Perhaps we should do the voting and then go back to the addition? No.

Or do we have to vote on exactly what we're going

to say.

ACTING DIRECTOR ALEXEEFF: Yeah, I think you have to vote on exactly what you're going to say. But you could say sulfur dioxide see what the vote is. And you could say sulfur dioxide gas, or sulfur dioxide by inhalation. And, you know, have essentially three votes on that to see what the consensus is, in terms of if there's a parenthetical that the group agrees upon. Or you could ask by a show of hands, I guess, which -- if they prefer to add a parenthetical, just right up front, and decide on the parenthetical and then vote with the parenthetical in the ballot.

COMMITTEE MEMBER WHITE-PORTER: I think the parenthetical just decreases any confusion. We may not be confused. We know sulfur dioxide is a gas, but I think because there is some discussion about it, and we did have a public comment that forced us to think about how to consider it. I think having the parenthetical as a gas may not be a bad idea.

DR. DONALD: If I could just raise a couple of issues for your consideration. One is that in the epidemiologic studies of course, even though the exposure is going to be predominantly from inhalation, there will be dermal exposure concurrent with it, and we don't really know what contribution each of those routes would make.

The other point is that in consideration of developmental toxicity, the exposure of the fetus, which is what we're concerned about, is going to be the same, irrespective of what route of exposure occurred in the mother.

CHAIRPERSON BURK: Very good points. I think we may just be back to sulfur dioxide.

(Laughter.)

COMMITTEE MEMBER WHITE-PORTER: Right.

CHAIRPERSON BURK: Really, I'm afraid it might complicate things by trying to -- I don't know. Do we have agreement on that? Should we vote on that part, first?

COMMITTEE MEMBER WHITE-PORTER: Sulfur dioxide as it is.

CHAIRPERSON BURK: Okay. So I hear sulfur dioxide as it is, as it is, as it is. Okay. Well, I think that's probably wise in this case.

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

(Hands raised.)

(Laughter.)

CHAIRPERSON BURK: Okay. Well, no, it's tough.

It's tough when we all -- when it has to be unanimous, so we don't even have anybody can dissent.

So we have five voting yes on developmental toxicity.

All right. Has sulfur dioxide been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity?

All those voting yes, please raise your hand.

(No hands raised.)

CHAIRPERSON BURK: Zero.

All those voting no, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Five. Okay. And finally, has sulfur dioxide been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity.

All those voting yes, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: I'll vote for male. Three, okay. All those voting no, please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Two.

So the result is that sulfur dioxide will be added to the State list for developmental toxicity.

All right. So we can move. Yes, we'll bring Linda Roberts back in, so that we'll have six of us up here for the next portion.

The next agenda item will be, and we'll stall a little, but it will be Agenda Item number 3, Proposition 65 listing mechanisms an informational item.

And this will entail staff presentations and an opportunity for public comments and Committee discussion. But again, there's no vote on this particular issue.

CHIEF COUNSEL MONAHAN-CUMMINGS: I think we'll wait for Dr. Roberts.

(Thereupon an overhead presentation was Presented as follows.)

CHAIRPERSON BURK: All right. Linda Roberts has rejoined us. And I'll turn it over to whoever is going to present.

Carol Monahan-Cummings.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. We're actually going to split this presentation between myself and Dr. Donald.

Just for in terms of context for this discussion, if you recall at the last meeting of this Committee, there was some discussion about wanting to understand better what -- how the other listing mechanisms under Prop 65 work, and how they may affect each other. And so we put

this on the agenda as an informational item, but we have allowed some time for public -- you know, limited time for public comments on these issues.

Again, as I mentioned this morning, in terms of making -- or having you understand what these mechanisms do, you don't have to make any legal determinations about what the statute says or what the regulation says or what it means. That is up to your legal counsel, including the Attorney General's office.

And so you may here comments on that, because no doubt, I mean, we're going to have some attorneys presenting. It's hard to stay off of that when you're an attorney. But in terms of, you know, basically it's a -- so you can understand our process, how we've interpreted the statute and the regulations and how we implement those.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So in terms of what we're going the present to you today, we're going to give you a general overview of the four different listing mechanisms under Prop 65. You're probably pretty familiar with the one you use, that we'll also briefly talk about that.

We'll talk about the authority for each of those

mechanisms, what the procedures is for implementing each of them, and we'll give you some -- an example of a recent listing for each of those mechanisms.

And then, of course, we'll have time for questions from the Committee and also public comments.

Next slide, please.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the four mechanisms that are listed in the statute for identifying chemicals that are known to cause reproductive toxicity are the identification by the State's qualified experts. So that would be your group. Identification via a reference in the California Labor Code that actually kind of goes back to federal regulations, mostly OSHA regulations, and some listings by IARC and NTP that affect carcinogens.

There's another provision where we would list chemicals based on a formal requirement that the chemical be labeled or identified by California or the federal government as causing reproductive toxicity. Generally, that applies to prescriptions. Most of the listings under that heading have been prescription drugs.

And then lastly, there's the formally identified by an authoritative body regulation, which is the primary subject of the meeting this afternoon. And will go into

that in some detail.

One thing I wanted to mention, in terms of these four mechanisms is that the statute uses the word "or" and doesn't provide a hierarchy between the four mechanisms. So essentially, none of them trump the others in terms of decision making. And I know that's been an argument for BPA and maybe some other chemicals where, you know, your Committee has made a decision, but we also are required to look at chemicals under the other provisions, as well.

EPA -- the time frame is a little tighter than we have had on some of the other chemicals, but there's no, you know, if you make a decision, that doesn't mean we can never look at the chemicals under the other mechanisms.

We've had --

ACTING DIRECTOR ALEXEEFF: Carol, why don't you move your mic just a little bit closer.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Sorry.

We've had a few court decisions over the years concerning both the authoritative body and Labor Code listing processes. And both have determined -- these cases determined that we have to list both the animal and human carcinogens. And actually that applies to this group as well as all the other listing mechanisms.

So we don't determine whether or not chemicals are, in fact, human carcinogens. We just -- we can rely

on the fact that they are animal carcinogens.

Your group or the predecessors to your group -- I don't know if you were all around then -- identified authoritative bodies. And once they're identified, we can determine whether or not the chemicals meet our criteria in the statute or the regulations. We actually don't have regulations related to Labor Code listings.

There was an early case -- fairly early case in 2000 that clarified that we have the responsibility and the ability to look at the entire record of a particular decision by an authoritative body, and make a determination.

And it is up to our office, not the authoritative body, to make the specific finding that a chemical has been identified and that there's sufficient scientific evidence to meet our regulation. That was a more recent decision in 2009.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: In terms of the listings for developmental or reproductive toxins, you can see here that there are a total of 302 listings for DART effects, and the primary endpoint has been developmental only. And then there's some -- you can see the numbers here for the other types of endpoints.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The other thing I'd point out is that although when some of our regulations were adopted, which for the most part they were adopted very early in the process for implementing Prop 65. Most of them were done in 1987 through about 1990. At that time, the agency was under the impression that the State's qualified experts would be doing the primary listing processes.

As you can see here, that hasn't been the case in terms of the formally required and the authoritative body listings there have been more of those than the State qualified experts. There's a couple reasons for that.

And one of them is that the -- really, the reason that the authoritative body provision is in the law is so that the -- this group can consider chemicals that haven't been fully discussed, all of the evidence hasn't been considered, and nobody has essentially made a finding on those chemicals. And where they have, and they are chemicals that -- or they are found by authoritative bodies that you all have identified, there's no reason for us to bring those to the Committee. And particularly in the formally required area and Labor Code, it's essentially an automatic listing if they meet the minimal

requirements in the statute or regulations.

There's also obviously been resource issues in greater complexity for the chemicals that were brought to this Committee than there were maybe early on in terms of listings. And so, as you see, like today, you've looked at one chemical. Whereas, during the year, we can look at any number of chemicals under these other authorities, and move through those much more quickly.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So we're not going to go in much detail in terms of your -- did you do the next slide?

There you go.

And in terms of your process, because we've already talked about that today, and you've applied that today. But your group has this -- the clearly shown standard that's used. And you have to make the finding that, in fact, the chemical has been clearly shown to cause developmental or reproductive toxicity. That language comes directly from the statute. It's not just in the regulation.

The next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The procedure

that we use in terms of providing you with information on chemicals, you're aware that we have a -- we do screen chemicals based on the prioritization procedure that we established in 2004 with input from this Committee, as well as the Carcinogen Committee. You provide advice on the priority of chemicals, in terms of which ones you'd like to see in what order. And then depending on our situation resource-wise and, you know, that sort of thing, we choose which chemicals to provide to you, the HID information so that you can consider them.

And then, of course, you are required to apply the clearly shown standard to the information that you're provided at the meeting or prior.

The Committee did adopt criteria, as I mentioned this morning, in 1993, that essentially explains what clearly shown means in terms of a scientific discussion.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So we've got an example here a recent listing that your Committee did, and that's chromium hexavalent compounds. And that was -- well, I don't want to read through all of this, but that one was listed by your Committee as a developmental male and female -- for the developmental female and male endpoints.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The Labor Code mechanism that I mentioned earlier is an interesting one to me, because we had to go through and fair amount of litigation on this particular listing method. But we recently got a decision that -- from the court of appeal that, in fact, we're required to list these chemicals. It's a ministerial act. And so we are required to do that, and we will continue to do it.

As I mentioned for the Labor Code provision, we have not adopted regulations that describe the procedures that we use to identify those. It's pretty straightforward, if -- sometimes. Pretty straightforward if you follow this little process. You look at the California Labor Code, which refers to the federal hazard communication standard for occupational exposures. And there's certain chemicals and places where you would find those in the federal regulations.

So we have, in the past, looked at adopting a regulation for that, and we may well do it, but it is not required to adopt regulations for these -- any of these mechanisms, but we have done so for the other three.

So I just mentioned in terms of procedure, we monitor publications that identified chemicals that may be

covered by the Labor Code provisions. If we identify any of those chemicals, we publish a notice of intent to list the chemical in the CRNR and we provide a 30-day public comment period. We consider the comments submitted and determine whether or not the chemicals meet the statutory requirements, and then decide whether to list or not list.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Some examples of recent listings under the Labor Code that have to do with DART endpoints are these two chemicals. I'm not going to try and pronounce the first one, but we did list that particular chemical for developmental effects based on a ACGIH finding that the threshold limit value for the chemical was based in part on embryo fetal damage.

And so what we do is we look for the basis for a threshold limit value. And if it's, in part -- in full or in part based on a developmental or repro endpoint, then we'll go ahead and list the chemical.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. I mentioned earlier that a formally required process is also very ministerial, in that there's not a lot of process that we follow. The statute just says that if an agency

of the State or federal government has required the chemical to be labeled or identified as causing reproductive toxicity, it has to be listed.

And so we do look at package inserts, for example, in prescriptions. And if there's information in there where they're providing essentially a warning or identifying the chemical as causing reproductive or developmental effects, we will go ahead and follow -- propose the chemical for listing.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So in terms of procedure, this is very much like the Labor Code listings. The chemicals, we look at their labels or other identification of a chemical by a State or federal agency to see if they've been identified as causing reproductive toxicity. We publish a 30-day notice that we intend to list the chemical. We review any public comments that are submitted, and then we look at whether or not the chemical meets the statutory requirements; and if so, the chemical is listed.

If it doesn't meet the statutory requirements under this procedure, we will also review the same chemical for listing under the other mechanisms.

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CHIEF COUNSEL MONAHAN-CUMMINGS: This is an example of a listing that we made based on an FDA package insert for a drug. And the package insert described potential developmental effects associated with the use of the drug. And that was sufficient for us to identify the chemical as causing developmental toxicity and it was listed.

Something of interest, kind of a side note, is that we also have a regulation that essentially says if you're giving informed consent to your patients in terms of these drugs in particular, a separate warning under Prop 65 is not required.

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CHIEF COUNSEL MONAHAN-CUMMINGS: And you can see here -- where is that -- okay. You can see here the actual language that was used by the -- what was required by the FDA to be included in the package inserts for this particular drug.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. In terms of the authoritative body listing process, this again is established in the statute, and there's a piece of this

that this Committee is involved in, which is actually at issue this afternoon. And that is that you have identified particular agencies or groups that are authoritative, in terms of identifying chemicals that cause reproductive toxicity. And then if a chemical has -- we think that a chemical has been identified by that group, and if it meets our regulatory criteria, then we'll proceed with a listing of the chemical.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Currently, the agencies or groups that are named in the statute or in the regulation are IARC, NIOSH, NTP, U.S. EPA and U.S. FDA. There is a caveat in terms of the NTP identification that says that the -- it's solely those final reports of NTP's -- the Center for the Evaluation of Risk to Human Reproduction or CERHR.

There's also a limitation in terms of IARC. And that is that it's -- the items that we can identify under their documents are only those that identify transplacental carcinogenicity. And that limitation was put on in 1998.

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CHIEF COUNSEL MONAHAN-CUMMINGS: And again, the

process that we use is the DART, your group, designates authoritative bodies. The last time the authoritative bodies list was updated was in 2002. We also provide notices to each of you each time we are proposing a chemical for listing under this authority, and you have the opportunity as individuals or as a Committee to comment on those proposed listings. Although, I'm not aware that any of you have done that, at least in the recent past.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The specific procedures that we use in terms of authoritative body listings are in our regulations. And what we do in this case is, again, we monitor the publications, reports and documents that are published by the authoritative bodies, and look at them to see if they appear to meet the regulatory criteria in the regulation.

If so, then we publish a request for relevant information in the CRNR. We give 60 days for the public to comment, and provide any additional information that may not have been considered by the authoritative body.

After that, if we decide that the regulatory criteria are not met, then the chemical goes back into our tracking database, and will be also evaluated for any

other listing procedure.

If the chemical does meet our criteria in our opinion, then we'll publish a notice of intent to list the chemical in the CRNR, and we give an additional public comment period of 30 days.

After reviewing the public comments, we will then decide whether or not the regulations have been -- the regulatory criteria have been met. And if so, then we'll publish a notice of listing that advises the public that the chemical has been listed and starts the one-year clock for deciding whether or not a warning is required or a discharge is prohibited.

If we think, after looking at all the information that we have received, that the criteria are not met for a chemical where we previously thought it had been, then we refer the chemical to your group, give you all of the data available, not just from the authoritative body, and have you look at that and determine whether or not it should be listed.

I should note also that the data call-in period in that request is not actually required by the regulation. The regulation actually starts with the notice of intent to list.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: There are two sets of criteria in the regulation. And Dr. Donald is going to talk about that. But there is a -- one part has to do with whether or not a chemical has been formally identified. And the other part has to do with the scientific criteria that needs to be applied by OEHHA to determine whether or not a chemical should be listed under Prop 65.

It's important to note that, again, there have been legal challenges to our authority to determine these two -- whether or not a chemical meets these two criteria. And a very recent decision has upheld our authority to do that. It's pretty expressed in the regulations. It says, "The lead agency shall determine whether it's been identified...", and, "The lead agency shall determine whether or not there's sufficient scientific evidence".

So at this point, if you -- unless you have specific questions about what I've covered, then we'll have Dr. Donald go over some examples and other information on the authoritative body listing process.

CHAIRPERSON BURK: I don't see any questions, so you may continue.

DR. DONALD: Thank you, Carol.

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DR. DONALD: This slide shows the criteria applied by OEHHA in determining whether formal identification of a chemical as causing reproductive toxicity has occurred.

The three criteria on the left establish that the authoritative body has made a statement or taken an action that identifies the chemical as causing reproductive toxicity. The criteria on the right ensure that only appropriate documents released by the authoritative body are used for this purpose.

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DR. DONALD: So once it's been established that formal identification has occurred, OEHHA staff then review the scientific data relied upon by the authoritative body in making that identification. OEHHA does this only up to the point where it is clear that the authoritative body relied upon sufficient relevant data to support the identification.

While OEHHA is not permitted to substitute its judgment for that of the authoritative body in interpreting relevant data, data that are clearly established to be scientifically invalid are not considered further. Also, in some cases, data that are relevant to the authoritative body's purpose may not be

relevant to Proposition 65, such as developmental toxicity, resulting entirely from postnatal exposures.

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DR. DONALD: And this slide just briefly summarizes the listings that have occurred via the authoritative body's mechanism, since the current set of authoritative bodies was established in 2002.

As you can see, IARC has not been used at all and NTP CERHR has been used quite extensively.

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DR. DONALD: I'm now going to give a couple of examples of recent listings that have occurred via this mechanism. The first is acrylamide, which was listed in February of this year as known to cause developmental and male reproductive toxicity.

The listing was based on two documents from the National Institute for Occupational Safety and Health, and a more recent document from the National Toxicology Program.

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DR. DONALD: And this graphic is taken from the final report from NTP CERHR, and shows the weight of

evidence that acrylamide causes adverse developmental or reproductive effects in animals. Formal identification is provided by this weight of evidence conclusion by NTP.

And as Carol has said, it was established by litigation in the early days of Proposition 65 that animal data alone can provide a basis for listing.

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DR. DONALD: In addition to that graphic representation, the NTP CERHR document also has a narrative conclusion that would in itself provide formal identification. This states the data are sufficient to conclude that acrylamide is a developmental toxicant in rats. It also states the data are sufficient to conclude that acrylamide is a reproductive toxicant in male rats. And data are sufficient to conclude that acrylamide is a reproductive toxicant in male mice.

And as Carol pointed out, although it's not required that the authoritative body take a position on biological plausibility in humans, it happens that, in this case, NTP also stated that the rat and mouse data are assumed relevant to the assessment of potential effects in humans.

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DR. DONALD: It should be noted that the level of concern about the possibility that human developmental or -- development or reproduction could be adversely affected by exposure to acrylamide is not what provides formal identification of developmental or reproductive toxicity.

That conclusion is based both on hazard and exposure data as shown in the bottom line of the table. Regarding the conclusion about negligible concern for adverse developmental or reproductive effects in the general population, the NTP CER doc -- excuse me, the NTP CERHR document states, "This conclusion is based on the low levels of estimated exposure to acrylamide in the general population".

Identification of a developmental or reproductive hazard does not need to be the sole or final purpose of an authoritative body document used in this listing mechanism. Most, if not all, of the documents we have used from all authoritative bodies had other purposes.

All that is needed for this part of the process is that the document provide a formal identification of developmental or reproductive toxicity that meets the criteria specified in regulations.

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DR. DONALD: So applying the criteria for what constitutes as causing reproductive toxicity, OEHHA simply confirmed that NTP CERHR had considered sufficient data to support a conclusion that acrylamide causes developmental and male reproductive toxicity. This slide briefly summarizes the data cited by NTP.

As I already mentioned, OEHHA is not permitted to substitute its judgment for that of the authoritative body in identifying developmental or reproductive toxicity, but is required by regulation to determine that the criteria for us causing reproductive toxicity have been met.

In practice, this means determining that the authoritative body made its identification of developmental or reproductive toxicity on the basis of a sufficient quantity of relevant data. Studies that do not meet the specified criteria are not considered supportive of the identification.

In addition, because Proposition 65 does not take into account developmental toxicity resulting from postnatal exposure, effects that result entirely or predominantly from postnatal exposure are not considered.

In the case of acrylamide, although some developmental toxicity might have occurred from postnatal exposure, the cited effects shown in this slide were incontrovertibly the result of prenatal exposure and were

clearly sufficient to support identification of developmental toxicity.

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DR. DONALD: Formal identification of acrylamide as causing developmental and male reproductive toxicity was also provided by NIOSH in two older documents. And this slide shows the relevant statements that constituted formal identification by NIOSH.

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DR. DONALD: As with NTP, OEHHA confirmed that NIOSH had considered sufficient data to support a conclusion that acrylamide causes developmental and male reproductive toxicity. And this slide briefly summarizes the relevant data cited by NIOSH.

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DR. DONALD: Another recent authoritative body listing was of avermectin B1 in December of 2010. Avermectin B1 is a pesticide that was listed for developmental toxicity on the basis of formal identification by the U.S. Environmental Protection Agency.

As with acrylamide, identification of a

reproductive hazard was not the final purpose of the documents issued by U.S. EPA. Rather, consideration of whether such a hazard existed was a unnecessary precursor to the final action being taken by the agency.

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DR. DONALD: In this case, the documents issued by the authoritative body met two of the criteria explained earlier. Not only did U.S. EPA conclude that avermectin B1 causes developmental toxicity, it also otherwise formally identified it as causing developmental toxicity by using developmental toxicity as the basis for several reference doses for human exposures.

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DR. DONALD: Much of the early data on avermectin B1 were generated using the CF1 strain of mouse, a strain that U.S. EPA later decided was not suitable for use in human health risk assessment, because of that strange lack of a particular transporter protein involved in detoxification of the chemical.

However, even after discontinuing consideration of data from the CF1 mouse, U.S. EPA continued to identify avermectin B1 as causing developmental toxicity, based on data from three species, including another mouse strain

that has the transporter protein.

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DR. DONALD: And with that, we'd be happy to take any questions you may have.

CHAIRPERSON BURK: All right. I don't know. Does anyone have any questions?

It seems fairly clear. Shall I ask for public comments at this point in time?

So does anyone wish to speak?

Three minutes.

MR. LANDFAIR: Thank you, Dr. Burk, and Panel members. My name is Stanley Landfair. I'm from the law firm of McKenna, Long, and Aldridge. And I represent the American Chemistry Council on a matter you're going to be hearing later.

With Carol's introduction that, you know, legal matters are generally to be issued here, I agree with that, but sometimes we just have to eat our peas, as the President would say. And there are some things we need to understand for context.

And you know we're coming up to an issue that involves the role of the authoritative body's process in this. So, you know, one of the things we have to understand, there are -- sometimes some false issues are

raised. And a false issue, in my mind, is whether or not is there a hierarchy among these different listing mechanisms.

It's accurate to say there's not. But nevertheless, there is a purpose for the authoritative bodies process. And as Carol said, it was intended primarily to save your time and resources. But that's not to say that it was to just cast our lot with the wind either.

And when the Panel first designated its first authoritative bodies, it expressed great concern that in choosing them, we're not -- we didn't want to have unrestrained listings. We wanted to have listings that would reflect the criteria that the Panel applies also. And that's memorialized very clearly in the statement of reasons that adopts the regulations.

And just a few random quotes that reinforce that. "We condition the designation upon application of certain controls to listing of chemicals pursuant to that designation, and ask the agency to draft rules embodying those controls." The controls were intended to make sure that the authoritative body's listing mechanisms would be about the same as you would say, so we wouldn't have questions about whether or not there's a hierarchy.

I got my one minute sign, so if I could ask you

to refer back to Dr. Donald's Slide 21. On the left-hand panel he identified some identification criteria. Accurate, of course, and there are three. The chemical is, ellipsis, either on an authoritative body issued list. Well, it's very clear if an authoritative body issues a list, whether the chemical appears on the list.

The next is the subject of a published authoritative bodies report that concludes that a chemical causes reproductive toxicity. When an authoritative body so concludes in a report, that's generally fairly clear.

And where we run into controversy is Item 3, is whether it's not on a list, the report doesn't conclude it, but we want to say that somehow the agency, the authoritative body, otherwise identified the chemical.

And that is where we are in the context for which our petition is going to be considered. That's really where the controversy arises, and we think it's important as you understand that. And frankly, I've just got to throw in an editorial comment. Sometimes the process for determining whether or not the agency believes that a chemical has been otherwise identified is just completely opaque.

CHAIRPERSON BURK: Okay. Thank you. Do you want to respond to that or -- you're keeping it opaque.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: One thing I'd like to respond to, however, is that it's my understanding that the document at issue this afternoon and the next presentation will -- we actually identified it under number 2 on that list. It wasn't otherwise identified.

In the examples that Dr. Donald showed you, there's a couple of different ways that we can determine whether or not CERHR has identified a chemical. One is in the little graphic that they put in there, in terms of the actual does it cause an effect. And the other one is the actual language used in the report. So we're not talking about an otherwise identified chemical.

CHAIRPERSON BURK: Right. Do I understand you're saying that the issue with the CERHR, that generally falls under number two?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right.

CHAIRPERSON BURK: So does anyone know an example of number three?

DR. DONALD: Could we go back to slide 31, I think -- 32. Sorry. Slide 32.

Yes.

I'll confess to being a little confused by the term opaque. When we have used this third provision of the criteria, we have always expressed as clearly as we were able, the basis for our conclusion that the

authoritative body had otherwise identified the chemical as causing reproductive toxicity. In this case, U.S. EPA based its regulatory levels explicitly on developmental toxicity that occurred in a developmental toxicity study in rabbits.

CHIEF COUNSEL MONAHAN-CUMMINGS: Also, as I mentioned, when I did my part of the presentation, we provide a number of opportunities for public comment, and we provide quite an extensive documentation generally for each one of the chemicals we propose, and identify exactly the phrases that we're relying on in that document so that people are clear what the basis for the proposed listing is.

CHAIRPERSON BURK: Any other questions or comments on this presentation?

Renee Sharp.

MS. SHARP: Thank you for a really informative presentation. I think it was really helpful for all of us to hear. I have one comment and then a question. My comment is actually in response to the previous commenter where he mentioned this concern about unrestrained listings. And I just went back and did a little bit of quick math.

And so this whole process has been around for about 20 years. And according to the slide we just say,

they've listed amongst all of the different listing mechanisms, 302 chemicals. So that works out to about 15 chemicals per year through all the different listing mechanisms. And for this particular listing mechanism, this DART Committee listed about 32 chemicals, if my memory serves me correctly. So that's about 1.5 chemicals per year. And considering that we have, you know, approximately 80,000 chemicals in commerce, I don't think that we're really getting anywhere near unrestrained listings, so I don't think that you should be very concerned with that. That's my comment.

My question is something that I think has confused a number of us in the advocacy community for a number of years. And that is this question of it's a little bit of a tangent, but I think it's relevant just to ask, just for my own clarification, this question of prenatal and postnatal and when you can look at what.

And a specific little subset to that question is was this in the original law or how did this come about? Because it's a little -- it's just a little weird. I mean, development doesn't end with birth obviously, so you can have an exposure that could clearly affect your development postnatal.

So that's my question. I'll take it off the air. Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Renee, we're going to have to tag team on that question too. The basis for looking at prenatal versus postnatal began by looking at the preamble to the proposition and the language in there that talks about birth defects and other reproductive harms.

So our interpretation of that has been that we aren't really looking at chemicals that cause postnatal -- are caused by postnatal exposures.

MR. ROBERTS: Can you speak up, please.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. I don't know how far back I need to go back. But in terms of the preamble, you're looking at about page 53 of that. And it specifically says that California -- the people of California have declared their right to be informed in order to protect themselves and the water they drink against chemicals that cause cancer, birth defects, or other reproductive harm.

It again says to be informed of that exposures to chemicals that cause cancer, birth defects, and other reproductive harms.

So our interpretation of that has been that we are looking at prenatal exposures that may cause, you know, developmental effects after birth, but we're not looking at exposures after birth that may cause effects

later.

I don't know if Dr. Donald wants to add to that or not.

DR. DONALD: Well, I'll leave the legal part alone and just talk about the science.

With regard to how we interpret data on developmental toxicity, bearing in mind that legal interpretation, we do apply a certain amount of judgment. Now, as I pointed out earlier, we're prohibited by the regulation from substituting our judgment for that of the authoritative body. But in this case, we're making a judgment on an issue that the authoritative bodies do not deal with at all. They don't differentiate between pre and postnatal exposures, and identifying developmental toxicity.

So the position that we've taken is that if developmental effects clearly occur as the result of postnatal exposures, they're not relevant. They're not currently considered relevant to Prop 65.

There are some -- obviously, there's some gray area. If an effect is manifested postnatally, and there has been both pre and postnatal exposure, we will look at whatever data are available to help us determine what the sensitive period for that effect was. If it's clearly prenatal, then we use the data. If it's ambiguous, then

we use sort of a weight of evidence approach. If it seems that it's most likely -- that it's predominantly the result of prenatal exposure, then we may use those data but it's looked at carefully on a case-by-case basis.

Another caveat is that in some instances, effects that result from a postnatal exposure in an animal model, for example, a neurobehavioral effect in a rodent model may actually be relevant to a prenatal exposure in humans. So our interpretation is that since that could be construed as a potential birth defect in humans, then those data are relevant.

CHAIRPERSON BURK: Very good. Thanks. I believe we should take a 10-minute break now and be back ready for our phone conversation with NTP at, you know, 25 after, let's say.

(Thereupon a recess was taken.)

CHAIRPERSON BURK: I'd like to call the meeting back to order. We're now on Agenda Item 4, consideration of the designation of the National Toxicology Program, NTP, as an authoritative body.

And I think Carol Monahan-Cummings is going to start out this item.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. I'm going to put this microphone way close to my mouth, and I hope I'm not doing that "puh" thing.

Okay. So I just want to give you a little bit of context for this particular item. And then, of course, we've got the individuals from NTP on the phone. Actually, I think they're on right now, so they can see this part. And, George, will introduce them in a couple minutes.

So if we can get my slides up.

(Thereupon an overhead presentation was Presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So let's just jump to the next slide.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So in terms of the issues in front of you today, there's really kind of two. At the last meeting, we had mentioned to you that there was a petition that was filed by the American Chemistry Council regarding de-designating or rescinding the designation of NTP CERHR as an authoritative body for purposes of developmental reproductive identifications.

Since that time, there's been some changes at NTP that we wanted to make you aware of. And so we've kind of expanded the item to include both of those issues. So I wanted to just cover a couple of general items, so you can have some context for the discussion we're going to have

today.

There is -- there have been some statements already from myself and others about the State's qualified experts versus -- or compared to the authoritative body listing mechanisms. And I just wanted to remind you that both are required by the statute. And by statute and regulation, the State's qualified experts, which is your group, identify the authoritative bodies.

Once that's done, we make the presumption that having -- you having identified the organization, you're comfortable with the way that they develop their documents and the criteria that they use to make their conclusions. And they may or may not, most likely they don't, use the actual language out of the statute about clearly shown and all that.

But the regulations that we have adopted for the authoritative body identification is -- they were based on input from this Committee, and they were also based generally on some U.S. EPA guidance that was available at that time. They were adopted back in about 1987.

And I also mentioned previously that courts have looked at the regulations and OEHHA's interpretation of the regulations, including OEHHA's authority to determine whether a given chemical has been identified by the authoritative body and whether or not the authoritative

body relied on sufficient scientific data to meet our regulation.

Obviously, these authoritative bodies are not developing their reports or their lists or whatever in order to comply with Proposition 65. They may or may not even be aware that we have this law. And so they have their own requirements and their own mandates to develop documents.

And when this regulation was adopted, it was clear that the -- we made it broad enough with the consent of the Committee to where we could kind of look at some of these documents. We're aware that the language is a little different from one to another. And so that's why it was allowed for us to look at it in order to see if it meets the criteria in our regulation.

So in terms of -- let me look and see -- there was also a comment earlier that the listing mechanisms must be exactly the same between the State qualified experts and the authoritative body process. And that is not the case. We don't have to have a statement from a committee or one of the designated authoritative bodies that says the chemical has been clearly shown by scientifically valid evidence to -- you know, the finding that you all make.

Again, it's a language that is specific to the

statute, and it's a general finding that this group makes based on the evidence. It's not one that a authoritative body is likely to have made, and so we are looking at an analogous finding, but it may well not be in terms of the findings that you all make.

And that was made clear in the Statement of Reasons when it was adopted.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Just to let you know, the current designation of the National Toxicology Program that is in the regulations, it doesn't have a parenthetical. I think we were talking about it that way. But it says exactly what is up on this slide.

So it says that there is -- they can be considered an authoritative body solely as to the final reports of the CERHR. So it's not all of NTP. It's not any other office within NTP at this point. And if you want to change that, you can certainly do that today, and I'll show you what the criteria for that is. But we would have to adopt a change to the regulation in order to implement that, if you do so.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Also, I'm sure

you don't want to read through this whole regulation, but we've put in the -- and highlighted the language that may be most useful to you, this section about allowing you both to identify an authoritative body and to rescind the identification of an authoritative body.

This Committee has done both. They've identified and in the past rescinded the identification of an authoritative body. And actually that was NTP that was rescinded and then it was added back in with an additional caveat.

Again, I'd remind you that the legal interpretation of this particular provision of the regulation is up to OEHHA, and ultimately the courts. And so there's no need for the Committee to engage in a process of trying to interpret what this means, other than, you know, it says that you have the expertise -- you have the authority to revoke or rescind a designation if you find that the body no longer has the expertise that it did at the time that you designate it previously.

Another point I'd want to make is that you are not required to make any change to the existing designation, simply because the ACC or anyone else has requested it. And so you're comfortable with what's in their right now or you want to wait until there's some other information, you know, you want to wait till you see

some of the documents that would be later coming out from NTP, that's fine. So you don't need to feel like you have to make an affirmative decision on that today. Other than, you know, you can say we just want to leave it.

If you do decide to make a change, we will want you to state on the record the grounds for that change. We'll need that in terms of the documents that we'll have to use with the Office of Administrative Law to adopt the change to the regulation, and it will also be helpful in the event that there's a legal challenge to that decision.

Okay. Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Just to review briefly. This is a slide that I believe Dr. Donald used in his presentation. And that is that in terms of the NTP CERHR currently, we look at their findings concerning the evidence of an adverse effect. We don't consider their findings in terms of their level of concern for human exposures to the chemicals.

And so we just want to make that clear that we can -- we do look at both the human and animal evidence that's in the record in front of this group, as well as any of the other authoritative bodies, and determine whether or not they have actually identified a chemical. So this is really the hazard identification stage, not

the -- you know, the subsequent decision whether or not there's a risk to human health at this time.

So I would encourage you to feel free to ask questions as you go along the -- we're not necessarily sure that the NTP folks will be able to stay for the whole discussion. And so particularly if you have follow-up questions for them, you should ask that during or after their presentation. And, of course, I'm here to answer questions and the technical staff as well.

So any questions at this point?

Okay. I'll go to George.

ACTING DIRECTOR ALEXEEFF: This is George Alexeeff. I just have one more comment to make regarding this as to why we're taking this item. This issue of NTP has been pending, in large part because of a petition to the panel. And while it's been pending, there have been some changes at the National Toxicology Program. So it seemed appropriate for you to hear about those changes, in terms of considering any changes in the designation of NTP.

So we contacted NTP, and they had indicated -- you know, we had already set the date. They'd indicated they'd be able to participate by phone, because they were at a retreat, and they're participating after their full day of work.

So I'd like to introduce -- the advantage of this is we get to have the Associate Director of NTP speak to us and answer questions.

So I'll introduce him a little bit. His name is Dr. John Bucher. Many of you may know him. He's the Associate Director of the National Toxicology Program. He joined NTP as a toxicologist in '83. And he's played a major role in a lot of -- shaping the program's research and policies.

And he's an internationally recognized expert in the design and interpretation of cancer bioassays. He's authored a number of important publications examining critical issues in dose selection for toxicology and cancer studies. He has Doctorate in Pharmacology from the University of Iowa, a Master's of Science in Biochemistry from the University of North Carolina at Chapel Hill, and a Bachelor's of Arts and Biology from Knox College in Galesburg, Illinois.

So, Dr. Bucher, I hope you're on the phone. I hope you can hear me. And if so, if you can take over.

DR. BUCHER: Thanks very much, George.

Can you hear me?

ACTING DIRECTOR ALEXEEFF: Yes, we hear you well.

DR. BUCHER: Good.

(Thereupon an overhead presentation was

Presented as follows.)

DR. BUCHER: Can you see my slides. You should in a second?

ACTING DIRECTOR ALEXEEFF: Yes, we see your slides.

DR. BUCHER: Okay. They should be full screen now, right?

ACTING DIRECTOR ALEXEEFF: Correct, full print.

DR. BUCHER: Okay. Thanks very much for the opportunity to talk to you this afternoon. And I will remind you it is after a full day of work.

So what I'd like to do today is give you a short introduction to the National Toxicology Program; talk to you a little bit about the Center for the Evaluation of Risks to Human Reproduction; the kind of conclusion that they come to, the process that they used for conducting their evaluations. Then I'd like to talk a little bit about the Office of Health Assessment and Translation, which is the new incarnation of the CERHR; compare them a little bit with the CERHR and the process, go over some of the details about the process that they're going to be using to conduct their evaluations as well.

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DR. BUCHER: So the NTP was an interagency program. It was established in 1978. It was

headquartered administratively at the NIEHS. And the Director of NTP is also the Director of NIEHS. That's currently Linda Birnbaum.

The mission, "To evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology".

We have a lot of information available on our website. And I'd encourage you to look at that for data, meetings, workshop reports, et cetera.

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DR. BUCHER: The National Toxicology Program, as I mentioned, was an -- is an interagency program. We report directly to the Assistant Secretary of Health. We have primary components at NIEHS, also a component at the Food and Drug Administration. Principally the National Center for Toxicological Research and the NIOSH of CDC are the three primary legs of the NTP.

We have policy oversight from a number of health, regulatory, and research agencies in the government. We have science oversight by an external NTP Board of Scientific Counselors. And we also receive input on our alternatives to animal testing programs through a scientific advisory committee on alternative toxicological methods.

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DR. BUCHER: NTP carries out really two types of major activities. We have a very large research and testing program where we've looked at literally thousands of substances that have been evaluated through the years. Most of our studies, at least the comprehensive toxicology studies are carried out in rodents and rats and mice. Although, we have -- we are developing and are conducting studies on many, many chemicals in high and medium throughput screening assays.

For the chemicals that undergo comprehensive toxicology studies, the scope and the types of the studies are dictated by the data needs for the specific substances. We also carry out some analysis activities. We have a Congressional mandate to produce the Report on Carcinogens, which I'll talk about in a second.

The non-cancer health endpoints that we evaluate include those that are -- traditionally have been done by the CERHR in reproduction and development.

And we also -- as I said, we have a program in developing and validating alternative animal test methods.

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DR. BUCHER: We communicate through a number of different vehicles. You can see way up on the left, we have an information document that's available on our website. The next one is the 12th Report on Carcinogens.

We have reports that come out of our alternative animals theories. The CERHR report is in the center -- this was the methanol document.

And then on the right-hand side are examples of the technical report series that we have to report the findings of our cancer studies, our general toxicology studies, our studies in genetically modified models for cancer. And we also have two new series that we are beginning.

Reports for our immune system function studies, as well as reproduction and developmental reports. And these two we have not yet put out any reports, but I'll talk a little bit about that in a second.

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DR. BUCHER: So the NTP reports for the identification of cancer hazards, as I mentioned, they include the Report on Carcinogens. And this is a Congressionally mandated document that the agents that are either known or reasonably anticipated to be human carcinogens. We use specific criteria for listing that have been approved by the Secretary of the Department of Human Health and Services. There's a multi-step review process with public comment and peer review. And I'll emphasize here that we're looking at the entire body of relevant literature, human studies, animal studies,

mechanistic studies, anything that relates to potential listing for cancer hazards.

As I mentioned earlier, we have our NTP technical report series on toxicology and carcinogenicity studies. This is a longstanding series. We've studied over 600 agents for chronic toxicity and carcinogenicity. They're usually conducted in rats and mice, males and females. We have a five tiered hierarchy for establishing the levels of evidence for carcinogenic activity of a particular substance.

And the draft reports are peer reviewed in public meetings with opportunities for public comment.

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DR. BUCHER: With respect to identification of reproductive and developmental hazards, I mentioned we're in the process of developing a new report series, which will outline and evaluate the findings from the National Toxicology Program studies that are done on reproduction and development.

We have again developed a five-tiered hierarchy to classify the outcomes of these studies. And they're consistent in many respects with the criteria that we use for the cancer studies, but they are specific for reproductive and developmental endpoints. And the actual levels of evidence and how one would reach one of those

levels of evidence are outlined in the URL that's given there.

When these reports come -- when they actually come out, we will be having these reports reviewed in public sessions with public comment for peer review.

And then the other aspect of the repro and developmental hazards evaluation, of course, is the NTP CERHR monographs, which I'll go into a little more detail here.

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DR. BUCHER: So the Center for the Evaluation of Risks to Human Reproduction was in operation in from 1998 to 2010.

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DR. BUCHER: The name has been changed in 2011, and I'll talk about that in a second.

CERHR evaluated selected chemicals, agents, mixtures, or exposure circumstances based on production volume, the potential for human exposure and the extent of public concern, and the extent of available literature with data that were applicable to an evaluation of reproductive and developmental hazard.

These have been published as NTP CERHR monographs that assess the evidence, whether the environmental substance causes adverse effects on reproduction and

development, which as you heard earlier, is the Phase 1, the hazard identification phase of the document.

And secondly, the second phase is to provide an opinion on whether these substances may be of concern, given what is known about current human exposure levels. And these are the levels of concern statements that are developed.

So far, there have been 19 monographs that have been published through CERHR on industrial chemicals, drugs, a number of different phthalates, and Bisphenol A.

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DR. BUCHER: As you saw in one of the slides previously, the hazard identification portion of this used a seven point hazard identification scale, weighing the evidence from both human and experimental animal data. And these were considered independently. And then the conclusions are reached on a case-by-case basis.

And you can see that the language used in these descriptors ranges from clear evidence of adverse effects, some evidence, limited evidence, all the way down to clear evidence of no adverse effects.

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DR. BUCHER: Once these evaluations were completed and there was a decision made on the hazard identification portion of the data, then the level of

concern conclusions were reached, using a five category scale, plus one category for insufficient data.

And what this was was an integration of the weight of evidence from the adverse developmental and reproductive effects in humans and experimental animals. With what we knew about the extent of current human exposure, and taking into consideration other factors that might influence this evaluation, such as comparative pharmacokinetics in animals and humans, and reaching then a conclusion on the potential for adverse effects on human reproduction or development.

And I will mention here that there could be, and have been in the past, evaluations that differed, insofar as conclusions of risk or hazard for different life stages for different levels of exposure.

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DR. BUCHER: So let me take you then through the Process that the CERHR used for evaluating substances and reaching their conclusions.

This is a three-part process, consisting of a phase of nomination and selection of candidate substances; scientific evaluation of the data around the candidate substance; the development of a NTP brief or an opinion on the information that had been developed to that stage; and a peer review of that document. The final step is the

release of the NTP CERHR monograph, which contained what we called the NTP brief, which was the NTP's opinion on that substance, plus the expert panel report and information with respect to public comment.

The NTP monograph again outlined the information that comprised the hazard identification steps, as well as the levels of concern steps.

Each one of these phases, the candidate nomination phase, the evaluation phase, and the peer review of the NTP brief and monographs included an opportunity for expert outside opinion, either through our NTP Board of Scientific Counselors, through an expert panel that we would convene to look at the information compiled under the direction of the National Toxicology Program with respect to the body of literature that was relevant for making a decision.

And then the NTP Board of Scientific Counselors was then again used with, in some cases, ad hoc group experts to review the NTP brief, which again included the NTP's overall opinion on both the hazard identification and level of concern statement.

As you can see, there are a number of places in this process where we have received public comment, starting initially at the initial designation of substances for consideration for the review, also

soliciting public comment on the background materials that were put together for the expert panels to evaluate, and also at the stage of the issuance of the draft NTP brief before the NTP peer review by the Board of Scientific Counselors.

The final again aspect of this is the release of the NTP CERHR monograph.

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DR. BUCHER: As an example, just to show you the kinds of information that might comprise the hazard identification and the level of concern steps, this is an example from DEHP published in 2006, where the weight of evidence for developmental and reproductive toxicity was evaluated in laboratory animals, and in humans. The data in laboratory animals was considered to comprise clear evidence of adverse effects. And there were few studies in human on which to make a decision, so this was considered insufficient evidence for a conclusion.

When one then calculates the information with respect to human exposures, there is one highly -- potentially highly exposed group, which would be neonates and infants undergoing extensive medical procedures with plastic tubing that contained DEHP. Fairly high levels of exposure. And in this situation, for critically ill male infants, there was a serious level of concern expressed

based on the findings from the laboratory animal studies and the information on human exposure.

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DR. BUCHER: So other monographs that have indicated in their hazard identification phase that there was clear evidence for reproductive or developmental hazards were in the monographs on the -- that you can see on the slide, acrylamide, BPA, bromopropane, and a number of the phthalates, genistein and methanol.

Genistein is an example of one where the hazard call in the animal studies did not relate to a particularly high level of concern in human studies or for human risk.

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DR. BUCHER: So let me now switch to the Office of Health Assessment and Translation, which is the new name for the CERHR group. And I will say it comprises the same people as were in CERHR at this point.

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DR. BUCHER: So let me compare these. The CERHR, the scope of the evaluations is primarily on reproduction and development. And under the new system, the scope remains primarily reproduction and development, but we're expanding it to other endpoints. And this reflects the institutional emphasis that we've developed on

understanding the full range of outcomes that could result from early life exposures.

So we're not just looking at reproductive and developmental endpoints anymore. We're looking at diabetes, obesity, a variety of other conditions that could result from early life exposure.

The end product under the CERHR program was a monograph including an NTP brief, which contained our opinion and the expert panel report. And the end product of the new process will also be an NTP monograph, which will include the NTP brief, our opinions, and the literature review component, whatever form that might actually take.

There's a set evaluation process using -- under the CERHR process there was a -- we always used an expert panel, and we always collected public comment. Under the new process, we will always collect public comment and input, and we're going to have a more flexible way of gathering outside expert opinions, and as we develop these background documents and as we develop the NTP conclusion.

However, the evaluation under both the old system and the new system continues to have two phases, both the hazard identification phase and the level of concern phase.

Under the new process, the hazard identification

phase has not yet completely established the descriptors that we'll be using, but they will be similar to those that were used in the old system. And we've, at this point, decided to continue forward with the level of concern five tier hierarchy as we have used in the past.

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DR. BUCHER: So under the new system, I will take you through this fairly quickly. Again, we have a three-part process, the nomination and selection of substances; the middle part is the review process; and the peer review and release of the NTP monograph.

Again, the monograph as I mentioned, will have hazard identification and level of concern components to it. We will have again input from three -- or from outside experts, and at least three phases of this process, the Board of Scientific Counselors will be used as it was in the past to vet the proposed substances that we would be reviewing, and they would also be reviewing the NTP brief, which includes the NTP opinion.

Where we differ a little bit is that we would add flexibility in the middle portion, which is the scientific evaluation of the body of literature that was compiled under the direction of the National Toxicology Program. This could comprise again utilization of an expert panel. We could also simply convene technical experts to provide

advice or have public listening sessions for a variety of different types of ways to provide a little more flexibility and provide us with the opportunity of providing these documents in a more timely manner.

Again, public comment and public input is paramount in this process at every phase. And we would end up with the peer review of the NTP draft and the release of the NTP monograph.

To give you some idea of how we would decide how to design this public input phase during the evaluation, it would depend partly on the topic. We would like at the nature and the extent of the literature. We'd look at the degree of scientific complexity of the problem that we're looking at, and we'd also take into consideration the amount of public interest that we perceive that would surround this particular evaluation.

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DR. BUCHER: So in summary, the NTP is an interagency program with the mission to evaluate agents of public health concern. We carry out a number of research testing and analysis activities that I've gone over.

We identify chemical hazards using set classification schemes. We produce high quality scientific reports for use in public health decision making. And we always follow formal processes to prepare

the reports that include external peer review and, as you can tell, several opportunities for public comment.

I think that concludes my remarks and I'd be happy to take questions from the Panel.

CHAIRPERSON BURK: Thank you very much, Dr. Bucher. This is Dotty Burk, Chair of the Committee. I'll open it up to questions. I think -- does anybody want to chime in. I have a couple. I'll start out just because -- when do you think the first publication will be ready in your new series of reports?

DR. BUCHER: Well, I think it's hard to say at this point, because we are still in the process of designing this activity. I would guess that it would be late 2012 or early '13.

CHAIRPERSON BURK: So in other words, you haven't actually started one of those yet.

DR. BUCHER: Well, we've -- no, not really. I mean, we've done a lot of the literature evaluation phases, but we're still designing the processes and putting into final place the pieces for the entire evaluation.

CHAIRPERSON BURK: Great. And are there any chemicals still being written up in monographs with the CERHR program?

DR. BUCHER: I think there is one that we are

just about to publish on soy infant formula. And I believe that that's the last one in the old series.

CHAIRPERSON BURK: Does anyone else have any questions.

Linda Roberts.

COMMITTEE MEMBER ROBERTS: Good evening, Doctor.

Can you hear me all right?

DR. BUCHER: Yes.

COMMITTEE MEMBER ROBERTS: All right. Does the -- will the OHAT also incorporate any of the more modern or the, say, the ToxCast 21st Century types of methods?

DR. BUCHER: Well, that's really the genesis or part of the reason for expanding the scope, is that we want to also use this process to integrate the new -- where we can, new areas of toxicology and bring those to bear on problems where we have a large traditional database in human and animal data. So, yeah, it's a place where we think very exciting advances can be made in that area.

COMMITTEE MEMBER ROBERTS: Do you foresee any final reports that would be based upon these alternative methods that are in development and validation that would identify hazards on the basis of the hierarchical scheme that you have.

DR. BUCHER: I think not at this point. I think what we're doing, at this point, is actually using the strength of the animal and human data that are developed to then go back and look at the high throughput screening output and see what we're missing, and see how we can design better high throughput screening assays that would allow us to generate the kind of data that would be, you know, ultimately used to be able to make those kind of decisions in the reverse order, if you know what I mean.

COMMITTEE MEMBER ROBERTS: Okay. So they have been more supplemental to the rat-mouse data that you -- the non-clinical types of tests that NTP currently conducts.

DR. BUCHER: That's correct, yes.

COMMITTEE MEMBER ROBERTS: Okay. One of the questions that's come up about the hierarchical statements that come in at least the CERHR reports, at least it's come up in my questions, is when it comes to clearly adverse or adverse or whatever, there is no commentary in that statement on something like maternal toxicity. And compromise of the adult animal is something that is of concern in reproductive and developmental toxicity.

Would there be any change in those -- your reports on that point?

DR. BUCHER: I think when the literature are

initially valuated by the expert panel and by the NTP, we take into consideration maternal toxicity, in essence weighing the influence that the outcome would have on the overall determination. So I don't think that we have a statement anywhere that specifies exactly how one would utilize information with maternal toxicity but is taken into consideration.

COMMITTEE MEMBER ROBERTS: Okay. The reason I raise the question is a couple of years ago, we looked at a very well written CERHR document that indicated that what was referred to at high dose, that there was a clear evidence of developmental toxicity. And I believe nobody on this DART Identification Committee disagreed with that perception. But it occurred in the presence of maternal toxicity.

And there was a statement under the hierarchical scheme that there was clear evidence. And it's my understanding that that statement partly drove a listing, and it was not voted to be listed on at that meeting.

So that's why I'm posing the question, would there be potentially any change to that type of statement that appears in an OHAT type of document.

DR. BUCHER: Well, I don't exactly know the situation that you're referring to, but I'm sympathetic with the problems that maternal toxicity presents in

interpreting these studies. And all I can say is that we recognize this. When we designed the evaluation criteria for our own NTP developmental and reproductive toxicity studies, we have, in fact, taken into consideration how maternal toxicity might figure into an overall evaluation.

So as we go forward and utilize more of the NTP studies that have the evaluations carried out, using the criteria what we've developed, I think this will be clearer.

COMMITTEE MEMBER ROBERTS: Okay. Thank you.

ACTING DIRECTOR ALEXEEFF: This George Alexeeff. I just wanted to follow up to Dr. Roberts question.

I'm not sure, Dr. Bucher, if you have any another -- if you're able to answer this question or get back to us. But I was just wondering on the previous CERHR documents when you made a -- when a determination of clear evidence was made, was that irregardless of maternal toxicity or was that taken into account, that basically that it was a inclusion of the Panel and NTP that the chemical was causing it as opposed -- directly or as opposed to through maternal toxicity or was it not really a consideration to try to delineate those two?

DR. BUCHER: Well, I can't answer for the entire set of documents that have found clear evidence in the hazard identification phase. But my recollection is that

the topic is always one of the principle issues that's discussed by expert panels and by the internal NTP staff as they're evaluating any of the particular studies that go into an evaluation.

So I would be very surprised if maternal toxicity was a primary driver in more than perhaps the one case that was just mentioned. And I'll have to look back and find out what that case was.

CHAIRPERSON BURK: Dr. Carl Keen.

COMMITTEE MEMBER KEEN: Yeah, I appreciated the preview you gave us of this. And I just want to make sure I'm understanding what I think might be happening. And again, I appreciate it's in the future. But when you talked about obesity and, say, diabetes, then you're reflecting on looking epigenetic changes. In many cases, it's not that it's the direct causative agent necessarily of that obesity or diabetes, but rather it's acting as a more permissive window for other completely separate insults. There is enhanced probability of seeing some of these chronic diseases of aging.

And that kind of changes the way that we might look at reproductive insults or toxicants. Do you envisage that you're going to separate those in a different category or would that simply, indeed, we view a developmental insult or a new risk or a teratogen as

something which just increases the probability opportunistically for another insult much later.

DR. BUCHER: Well, that's a very difficult question. I think though that if you consider that in most cases we're looking at a convergence of information from animal studies where you wouldn't necessarily have that second influence with -- other than perhaps the genetics of a particular species and strain you're looking at, and then correlating that with human information where hopefully if the epidemiology studies have been done in a way that allows one to eliminate and control for biases and confounding properly, that the answer would be that there might be some -- well, that wouldn't necessarily be the case.

CHAIRPERSON BURK: Are there any other questions? George.

ACTING DIRECTOR ALEXEEFF: Yeah. This is George Alexeeff again. So this is just sort of a -- not to test you on each one of the documents, but just sort of the general overall approach just to be clear of the CERHR program was an integrative approach of all available information, is that correct, as opposed to focusing simply on humans or simply on animals, but the purpose of that was to look at all the information that might be available about the chemical and make a determination, is

that correct?

DR. BUCHER: With respect to the level of concern, yes, I think that's correct. But we do -- as I indicated, we made individual assessments of the human date and the animal data with respect to hazard identification.

CHAIRPERSON BURK: Are there any other questions, staff or public?

We'll have a discussion later, but I want to make sure we have a chance to ask questions right now and then I can thank Dr. Bucher. And if he wants to stick around he can -- okay. One more from Lauren Zeise.

DR. ZEISE: Well, I wonder if Dr. Bucher would be able to stay on the line while we have public comments, in case something comes up in the public comments, that would be great.

DR. BUCHER: Sure, I can do that.

DR. ZEISE: Thanks.

CHAIRPERSON BURK: All right. That's exactly what I wanted to know. So I think perhaps we go to the public comments at this point. Again, for this particular part, we're not on the petition yet. So just three-minute comments about designating NTP as an authoritative body, just in the general sense.

MR. LIVINGSTON: Dr. Burk, members of the

Committee, I'm Gene Livingston, with the law firm Greenberg Traurig. And I'm here today without a client. I'm here in my 25th year of being involved with the implementation of Proposition 65, and as an advocate for rational science-based decisions in this whole process. And hopefully all of you got the letter that Michèle Corash, Trent Norris and I sent to you expressing our concerns.

Having just heard the presentation, I guess I would urge you not to take any action today on designating NTP and the OHAT body. You heard that nothing is going to happen until 2012 -- late 2012 at the earliest, maybe even 2013. There's still a number of issues that they're still working on, including the hierarchical descriptors. This issue of maternal toxicity seems to me to be very indefinite yet, and I know that there's been concern about that in the past.

And what your predecessor did, and some of you I think were around in 1999 and 2002, some of you very young people, but you waited three years for CERHR to come out with a number of final reports to see if you were comfortable with how that body handled these issues. And that approach seems to me to be appropriate here, and particularly since there is no reason to make a decision today.

CHAIRPERSON BURK: Thank you. And Renee Sharp.

MS. SHARP: I just wanted to make a really quick comment. Renee Sharp from Environmental Working Group again. And that is a number of the points that were made and questions by the Panel, even really the -- in some ways, the presentation by Dr. Bucher, in my opinion, actually more -- has more relevance for actually the use by the DART Committee of the forthcoming reports than necessarily actually its designation as an authoritative body, or rather to the point that's coming up, of rescinding NTP's designation as an authoritative body.

Because as we heard Carol Monahan-Cummings speak, and you saw the slide up there that actually highlighted what the legal grounds can actually be used for rescinding authoritative body status, and that was a change in the expertise of NTP. And as we heard Dr. Bucher say, that certainly hasn't changed. In fact, it's the same people. And I think that it would be hard to question the expertise of the National Toxicology Program irrespective of that. So that's my single comment.

Thank you.

MS. HUGHES: Good afternoon. Trudi Hughes of the California League of Food Processors. I'd just like to echo what Gene Livingston had to say. We'd encourage you not to take action today, to give us a chance to really

review the changes and digest them and have a more deliberative process moving forward, so we would hope that you would heed the words of Mr. Livingston and put this on hold for a little while and give us a chance to really digest.

Thank you.

MR. LANDFAIR: Hello. Stan Landfair previously introduced.

I'd like to speak to one -- make one particular point clear with respect to our petition in ACC, is that we do not see these issues as connected. And I tried in my letter to you of last Friday to explain that the issue of whether to designate NTP or to the NTP OHAT or something other than NTP CERHR, which no longer exists as an authoritative body, is a prospective decision only.

And our petition, in contrast, is retrospective with respect to monographs that were published by the previously existing NTP CERHR. I just wanted to make sure that those issues aren't confused in your consideration.

And then more generally speaking, we, as you would expect, agree that it would be prudent to wait until we've seen some reports, but also until other opportunities -- members of the regulated community and the advocacy community on the other side get a chance to see some of the briefs, and so you can see some of the

briefs, because, from our view, there's absolutely no hurry. It won't make any difference if we do this today -- well, you get my point.

Thank you very much.

MS. COLEMAN: Good afternoon. Brenda Coleman here on behalf of the California Chamber of Commerce.

And I'd just like to associate my comments with those of the previous commentators and simply add that as the committee president has demonstrated thoughtful and careful deliberation is needed upon designation of an authoritative body. So in keeping that in mind, we ask that you hold off on taking any action at this time, until the issue is thoroughly vetted by the Committee and until the public is afforded the opportunity to provide extensive public commentary, so -- in order to ensure a transparency before a decision is reached.

So for those reasons, we ask that you hold off on taking any actions at this time.

Thank you.

DR. JANSSEN: Good afternoon. I'm Dr. Sarah Janssen with the Natural Resources Defense Council. I'll also keep my comments brief. I just would like to reiterate that we fully support the expertise in developmental and reproductive toxicity of the National Toxicology Program. This Committee has relied on them for

the past 12 years. They have, as you heard earlier today, done 19 monographs, many of those, including five phthalates, have resulted in Prop 65 listing. Those are well established developmental and reproductive toxicants.

They had the same levels of evidence, the clear evidence of adverse effects for developmental and reproductive toxicity that Bisphenol A had in their report. And I have to say that I think that Bisphenol A has really driven much of this discussion. But that aside, the National Toxicology Program really does have the expertise that this Committee and OEHHA has relied upon. They have a clear set of scientific criteria. They have external and internal peer review process, and they have adequate public comment periods.

In addition, the staff outlined earlier today the authoritative body criteria that are called for under Prop 65. And NTP clearly meets those as well.

So I would urge you not to remove them as an authoritative body, but rather -- one more point that I wanted to make was that the NTP reports are not written specifically for Prop 65, as you also heard earlier today. However, staff have been able to use those reports to gather the information they need in support of a listing. And there's no reason to think that that information is going to change in the new process. In fact, probably

it's only going to get stronger with more definitive criteria.

So based on all that, I would urge you to continue to use the National Toxicology Program as an authoritative body.

Thank you.

MR. HEWITT: Madam Chair, Committee Members, John Hewitt on behalf of the Grocery Manufacturers.

Just a procedural point of order or question, a little bit of confusion as to -- as I look at the agenda and then with some of the speakers, as to what is in front of the Committee at this point. If we could get the Committee Chair to clarify that, I think that would help us all immensely.

CHAIRPERSON BURK: Yes. I wanted to have questions for Dr. Bucher while he was here. I believe we should proceed to the petition very shortly, and then we will hear comments specifically on that. Does that make sense?

But we actually have two issues in this agenda item. One is the petition that we're going to hear about de-designating CERHR. The other is this new OHAT. Do we want to change our designation of NTP to now include the OHAT, because the CERHR is no longer in existence? So does that make sense? There's sort of two things here.

MR. HEWITT: Yeah. Madam Chair, at the risk of putting words in your mouth, if I could just reiterate, so I make sure I understand it. There are two distinct issues before the Committee here today, and that they will be voted on and heard separately?

CHAIRPERSON BURK: Um-hmm.

MR. HEWITT: Okay. Thank you.

MS. COX: My name is Caroline Cox, and I'm with the Center for Environmental Health in Oakland.

And I just wanted to remark that, you know, I was really impressed by the presentation from the National Toxicology Program. And, of course, I expected it would be impressive. But it seems clear to me that what they are doing is continuing to do what they've been doing very successfully. There's a name change, which is not surprising. Agencies do name changes on a regular basis. But the process and the expertise and the thoroughness and all of those things that we've come to expect from the National Toxicology Program have not changed at all.

And I would recommend that this Committee recognize that by continuing to make use of this really valuable resource, which you all have available to you.

CHAIRPERSON BURK: Thank you. I think that's the end of the public comments.

And again, I'd like to thank Dr. Bucher. I don't

know if he needs to stick around for all of the discussion, but again that's totally up to him.

I would propose that we have a little discussion among the Committee right now about specifically the OHAT program, and whether we want to designate that.

Comment, Linda.

COMMITTEE MEMBER ROBERTS: Dr. Bucher, this is Linda Roberts again on the Panel. One last question for you. For Prop 65 when we use it, what we'd need to use is something -- in terms of developmental toxicity, something that is equivalent to human prenatal exposure. And, of course, for U.S. EPA and NTP developmental toxicity has a different meaning. It can be prenatal and postnatal exposure. Do you foresee your documents clarifying that when you come to your hierarchical classification of adverse or concern levels?

DR. BUCHER: Well, I think that the documents clarify that in the sense that we cite the specific studies that support the findings, and in the NTP brief, and we would outline the exposure situations that led to that conclusion. So if there was a study that included prenatal and perinatal exposure, then that would be made very clear.

CHAIRPERSON BURK: One last call for questions?

Okay.

I want to ask the Committee how they want to proceed at this point. We have the petition to hear, and I think perhaps we should hear that now before we have our kind of total discussion on this whole matter. So is that okay with everyone?

You can say so -- oh, okay, so apparently we have to vote to decide if we want to hear it. Although --

DR. BUCHER: If there's NOTHING else from me --

CHAIRPERSON BURK: Yeah. No, there isn't. And thank you again very much. Much appreciated.

DR. BUCHER: Thanks for the opportunity. Bye.

CHAIRPERSON BURK: Bye

I'd like to know where they were on their retreat. I hope it's somewhere nice.

(Laughter.)

CHAIRPERSON BURK: Okay. So as I understand it, we need to vote on whether we want to hear the petition, is that what you're saying?

ACTING DIRECTOR ALEXEEFF: We could ask Carol, but I believe the case you've been presented a petition as to whether or not you want to consider the petition. I think that's part of it. Maybe Carol could explain.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. What I had mentioned earlier is that you -- you don't have to take any action at all today based on, you know, our

recommendations or anyone else's request regarding the designation that currently exists.

And so I guess what you'd need to determine is whether or not you want to consider the removal of CERHR from the current designation. And then if you do, then we need to have the folks that are requesting that come and talk to you about it, which is the public commenters.

CHAIRPERSON BURK: Right. I'm just asking since it was on the agenda, I sort of assumed we were going to hear it, so I just want to know if we need to actually vote to hear it? Is there some --

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, I guess it would be easiest --

CHAIRPERSON BURK: Okay. All right.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- for us if you voted, rather than just kind of acclamation or something. But, you know, I just wanted to make it clear, you don't have to consider it just because you got a petition.

CHAIRPERSON BURK: Okay. So I guess I'll ask, would we like to hear the petition? By a show of hands, who's agreeable to that?

(Hands raised.)

CHAIRPERSON BURK: Okay. Well, I think it's only fair. And I had previously told Mr. Landfair that we would limit the time for the presentation to five minutes

per speaker. And I understand you have three speakers.

And then, of course, there will be time after that for other comments from anyone else that wants to speak, again limited to the five minutes per with no ceding.

So if you're ready to begin.

MR. LANDFAIR: Thank you again, Dr. Burk.

Can you hear me now?

Thank you again, Dr. Burk, and thank you members of the Committee. Thank you for allowing us to be heard, and thank you all for voting to consider our petition.

Let me identify our speakers. I've introduced myself. You'll also be hearing from Dr. Jay Murray whom you know, and also from Dr. Steven Hentges, who is from the American Chemistry Council.

We would really encourage your questions, and that's why we insisted so hard that we be allowed to speak to you. We think, you know, dialogue is productive. We'll take your questions and answer them to the best of our can. Again, I'm just the lawyer, so you if asked me any scientific questions, I'm certainly going to defer to the other two.

So let me try to explain, as simply as I can, what our petition asks you to do, what it doesn't ask you to do. And I raise these issues in the spirit of some of

the commentary that came from OEHHA, and also from the Panel during our last meeting on October 21st, 2010.

So what does our petition ask you to do?

In plain terms, all we're asking you to do is revoke or rescind the designation of NTP CERHR as an authoritative body. Now, you saw that regulation and how it's framed. It's only the NTP CERHR that presently is the authoritative body. It's not NTP or any other division of NTP. And it's only their NTP CERHR monographs. We're asking you to undo that.

What would be the effect?

You've heard a presentation differentiating between the authoritative bodies mechanism and the State's qualified experts mechanism. The State's qualified experts are you. Presently, the NTP CERHR monographs can serve as the basis for an authoritative body's listing. They may also serve as the basis for State's qualified expert listing.

If you grant our petition, one thing will change. It will mean that the -- of the remaining three NTP CERHR monographs, of which we're unaware that have not been acted upon, those will not only -- will no longer be eligible for consideration for authoritative bodies listings. They still will be eligible for consideration by you.

So there's no change to the chemicals that will be listed or to the monographs that can be considered. It only means it will be considered by you through the State's qualified expert mechanism. And we think that's good. We think it's appropriate.

Which leads to why did we file the petition?

We filed the petition because of the anomaly that came to our attention after the BPA decision two years ago. And as you recall, your Committee voted 7 to nothing, unanimously on all three toxicity endpoints to determine that BPA should not be listed as a reproductive toxin.

That very day a petition was submitted asking the chemical to be listed versus the authoritative bodies mechanism. And now I don't know how much you are kept abreast of what's going on in other -- now, the agency is actively considering listing the same chemical under the authoritative bodies mechanism on the basis of the same document that you reviewed so carefully and so thoroughly, with days of testimony talking in person to the people who conducted those studies, to determine whether or not the document, on its face, either concludes that BPA is a developmental toxicant or that it otherwise identifies the chemical as a reproductive toxicant.

We think -- I mean, that means if those two

things can happen on the same day and on the basis of the same document, something is seriously wrong. It's not -- that's no insult to the staff and their expertise. It's no insult to you and your expertise. It's no insult to NTP and its expertise, but it's a question of how this document can be used productively and whether it can be used productively, consistently, and authoritatively to be served as the authoritative bodies listing, or conversely, maybe whether it's not, and instead it should be considered by you in a forum where you have the freedom to delve down into the data and make a decision based on the data.

Always conscious of time, so there's one point that I need to take out of order here just to make sure we're absolutely clear. There is no question whatsoever that you have authority to grant this petition.

Now, you read a regulation that speaks to your authority. And it appears to be the position of the agency that that somehow limits your authority. I am -- and counsel's comment was that the agency gets to interpret the regulation. The agency already has interpreted the regulation.

I'm holding in my hands what's called the Statement of Reasons. That's a document published by the State of California, and specifically to the lead agency

for Prop 65, that contains and explains its reasons for regulations and its interpretation of the law.

And it says, "Implicit in the power to designate authoritative bodies is the power to revoke or rescind". The Lord giveth, the Lord taketh away. And you're the Lord.

It goes on to address this regulation and says why it was passed.

MS. SHARP: Five minutes.

MR. LANDFAIR: Thank you for being so kind.

It said we're going to make explicit that it has this authority. And then it at the end it says, "Subsection (b) further provides that this regulation shall not be construed to limit or otherwise interfere with the authority to revoke or rescind an authoritative body designation". That is the law.

CHAIRPERSON BURK: Okay. Thank you.

Next, Dr. Jay Murray.

DR. MURRAY: Thank you, Dr. Burk and Committee members. I'm Jay Murray.

This is about reports. It's about documents. It's not about expertise or qualifications. I agree with Renee Sharp that NTP has the scientific expertise to evaluate developmental and reproductive toxicity of chemicals. That's not what's at issue here. If it were

that simple, the organizations that you all work for, the universities, the hospital, the company, they all have the scientific expertise to evaluate as well.

But what is important is the documents and the reports, whether they can be used to formally identify a substance as causing developmental and reproductive toxicity.

And it's also not just about BPA. I'm going to use BPA as an example, because it's near and dear to my heart these days. But you heard that there are two others, methanol and you heard Dr. Bucher talk about soy -- infant soy formula. Those are the -- that and BPA are the three that are outstanding at this point.

And the issues are all similar. And the question for you is do you really want to put these three on autopilot, which is essentially what the authoritative body process is, given the importance and given the complexity of the issues. Because there's some issues with these three that didn't exist with the early CERHR reports in the examples you were given.

So it's also not you versus NTP CERHR. People, you know, have positioned this as, oh, you all voted not to list and NTP CERHR, you know, says it is a developmental toxicant.

Not that simple. And I don't think there is a

meaningful difference in their evaluation and your evaluation of BPA.

And also, hopefully you all have the attachment to the letter that I sent you a couple of weeks ago with the yellow highlighted things. And I'm going to draw your attention to a couple of things there real quick.

One is, and you heard this from Dr. Bucher, the monograph is two reports, the expert panel report and the NTP brief. In the attachment I sent you, if you look at page eight, that's page eight of the brief. And you'll see Figure 2B, where unlike the acrylamide and the DEHP examples that you were shown earlier, there's some real differences.

One of those differences is that those compounds had two or three authoritative bodies that had addressed those substances. But here, if you look at Figure 2B, you'll see two arrows, one for high dose developmental toxicity, another for low dose developmental toxicity.

You'll see Footnote 1 on high dose developmental toxicity, and it refers to the same studies that you looked at and said those studies clearly showed effects. That's when you considered the issue of maternal toxicity and made your determination.

And I saw Mike Shelby a couple weeks ago at the Teratology Society meeting. And I asked him how does

CERHR deal with maternal toxicity? How did they deal with maternal toxicity in the old monographs, not where they're going -- what they're going to do going forward. He said it was -- we left it up to each expert panel. He said some of them handled it one way, some of them handled it a different way, but we did not provide any guidance on that topic.

Also, it's important for you to know -- if you look through the rest of my attachment, page 38 is the NTP conclusions and the brief. That's followed by the expert panel report. And you can see their conclusions starting on page 381. There's a section that starts on page 382 called "Overall Conclusions" and continues on the next page.

And then there's a one-page document behind this. Okay. And this is not one of the two monograph documents. This is the NTP Board of Scientific Counselors. This was the peer review that Dr. Bucher was referring to. And take a look at what they peer reviewed. Okay. Look at what they were addressing. It's the level of concern.

If you go back to page eight in the NTP brief, where you see clear evidence and Footnote 1, that was not peer reviewed. That was Mike Shelby writing that figure in the NTP brief. That wasn't peer reviewed. You won't find that in the expert panel report, because the expert

panel never made that statement. And you won't find it in the peer review by the NTP Board of Scientific Counselors.

So, you know, the important thing is that these documents --

MS. SHARP: Five minutes.

DR. MURRAY: Oh, I'm sorry. I didn't see it go up.

CHAIRPERSON BURK: I'll give you one more minute.

MS. SHARP: Apparently, no one else is.

DR. MURRAY: I'll do it in 20 seconds here, because -- yeah, the primary conclusions are levels of concerns, both in the brief and in the expert report. And my recommendation is that -- my opinion is that the last three NTP CERHR reports are ill-suited for purposes of Proposition 65 authoritative body listings.

And I would not allow those last three reports to proceed on autopilot.

Thank you very much.

DR. HENTGES: Dr. Burk, members of the Committee, thank you for the time today. I'm Dr. Steve Hentges of ACC.

I'm going to start my comments off with a quote that is taken from a recent editorial written by NTP's leaders, including Dr. John Bucher. What they stated is this, "To our knowledge, CERHR was the only resource of

its kind producing evaluations that considered toxicity findings in the context of current human exposures to derive level of concern conclusions. This qualitative integration step is what distinguished CERHR documents from more traditional hazard evaluations prepared by other agencies".

My first point comes directly from that quote. CERHR clearly is focused on risk in the form of level of concern conclusions. That's what they're trying to derive. On the other hand, as you well know, Proposition 65 is focused only on hazard. Under Prop 65, exposure and risk cannot be considered at all. So at the outset, what we see is that what NTP CERHR did is different from what Prop 65 requires.

My second point has to do with the hazard evaluations. Of course, to reach any kind of a risk-based collusion, hazards must be evaluated. And as you've heard, NTP CERHR does that. They did that.

However, what they did, the standard that they used, the way they evaluated hazards is different from what is required under Prop 65. And I'll illustrate that point using BPA as the example, not because the points are specific to BPA, just that I happen to know that database better.

For high dose developmental toxicity, NTP looked

at eight studies that had relevant data. One of those studies involved only postnatal exposure. That's clearly not relevant for Prop 65. Four of the studies involved both pre and postnatal exposure. Those studies may or may not be applicable to Prop 65. Only three of the studies involved only prenatal exposure. Presumably, those studies are relevant.

NTP's overall characterization of hazard then is based collectively on those eight studies. And that characterization may or may not apply to a subset of studies, for example, the three studies that focused only on prenatal exposure. That characterization may or may not apply to specific aspects of studies, for example, the prenatal component of the studies that involved pre and postnatal exposure.

The only way to know for sure is to analyze the studies in detail and reach a conclusion that's directly relevant for Prop 65. While OEHHA may evaluate studies, they may not -- they are not permitted to substitute their opinion -- their opinion or judgment for the judgment of the authoritative body.

DART IC, your committee on the other hand, can and does evaluate studies to reach conclusions that are appropriate for Prop 65. And in that regard, NTP CERHR reports are an excellent resource for your use for your

deliberations, but they're not directly applicable as an authoritative body for Prop 65 purposes.

A similar issue comes up with maternal toxicity, as we heard briefly before, which may or may not be analyzed in detail by NTP -- in NTP CERHR reports. However, as you know, maternal tox must be considered under Prop 65.

For NTP, the nature and extent of that evaluation really depends on the circumstances. And here I'm going to give you another quote. This is one sentence from the report on BPA. "In regard to those high dose developmental studies, these effects were seen at the same dose levels that also produced some weight loss in pregnant animals". That it. That's the entire extent to which maternal tox is discussed in the NTP report.

Clearly, that's not a thorough analysis. And, in fact, it's not even a complete statement, because in those eight studies, other high dose maternal toxicity effects were reported. NTP didn't need to analyze maternal tox in detail though. The reason is that the dose levels used in those eight studies was so high, compared to human exposure, that those effects led to a negligible concern conclusion, the lowest level. So that's a great approach for NTP. It's not adequate though for Prop 65.

The third point has to do with peer review under

Prop 65. Authoritative body reports must be reviewed by an advisory committee. And for NTP that's the Board of Scientific Counselors.

In the case of BPA the Board of Scientific Counselors formally voted only on the seven level of concern conclusions. They did not formally vote, for example, on the whole report, or on any individual -- any other individual components of the report, for example, the hazard evaluation component, which is of most importance here. Again, that's a fine approach for NTP CERHR. It's not adequate for Proposition 65 purposes.

So in conclusion, I would encourage you to carefully consider what NTP CERHR did in comparison to what Prop 65 requires. They are different. And again, NTP reports are a great resource. For your purposes, they're not directly applicable as an authoritative body under Prop 65.

Thank you.

CHAIRPERSON BURK: Thank you. Does the Committee have any questions for the petitioners?

Lauren.

DR. ZEISE: Yeah. I just have a point of clarification on a comment that Dr. Murray made with respect to the three NTP reports. I think he mentioned soy infant formula. If you turn -- I just pulled up soy

infant formula report on the screen. And the NTP found it to have insufficient evidence. So just to clarify that point, it wouldn't be something that would drive a listing.

CHAIRPERSON BURK: Yes. I'll allow another comment.

DR. MURRAY: May I clarify that?

You might ask Dr. Zeise what the arrow points to for clear evidence of adverse effects? It's genistein, which is one of the components of soy infant formula. So that's what makes that one so complicated is you've got two arrows. One for one of the ingredients that says clear evidence, and one for the substance itself, which says, I think, insufficient evidence. Do I have it right?

DR. ZEISE: And that was on Dr. Bucher's -- in Dr. Bucher's talk.

DR. MURRAY: Okay.

CHAIRPERSON BURK: So what are the three that are pending? The soy formula, but genistein is part of it?

ACTING DIRECTOR ALEXEEFF: No, there's three documents pending. One is Bisphenol A, genistein, and methanol.

DR. DONALD: There actually maybe a fourth. It wasn't in Dr. Bucher's slide. But the NTP report on ethylene glycol found clear evidence of developmental

toxicity at high levels of exposure.

ACTING DIRECTOR ALEXEEFF: Thanks.

CHAIRPERSON BURK: So BPA is still pending from CERHR? I thought we read it two years ago.

ACTING DIRECTOR ALEXEEFF: No. Just to clarify. The reports -- the four reports we just mentioned are reports that CERHR has completed, but OEHHA has not taken any action on them.

CHAIRPERSON BURK: Oh. And so when you said --

ACTING DIRECTOR ALEXEEFF: Instead of not taking any action, has not completed any action on them. Maybe that's a better way of saying it.

CHAIRPERSON BURK: All right. But when I heard stop the last three, I thought that meant the ones that aren't in the pipeline already.

Okay. So what you're asking is a retroactive?

MR. LANDFAIR: Could you please clarify that they are actively considering BPA now pursuant to a request for relevant information. You said they're not considering or...

ACTING DIRECTOR ALEXEEFF: Yeah, I can clarify it further. So basically there's the four documents genistein, methanol, Bisphenol A, and ethylene glycol. And in terms of Bisphenol A, just in terms of clarifying the comment Stan had made in terms of the quote actively

considering. We had received a petition to consider it under the authoritative bodies mechanism, and we have submitted -- we submitted a request for relevant information, which is our pre-regulatory step for information. And we are now looking at all the information to see if we will propose a notice of intent to list, which actually starts the formal process.

So we actually haven't started any formal process at this point, but we are reviewing all of the information.

CHAIRPERSON BURK: I still have some questions about that, but perhaps we should hear if there are any comments also from the public on this issue, and then we'll start our final discussion.

MS. SHARP: Again, it's Renee Sharp with EWG. I have to say this whole process regarding the petition has been -- the word I would use is a bit surreal for a number of reasons.

Number one, the advocacy community over the years has petitioned the DART Committee on occasion, and actually no petitions have actually been heard, much less given 15 minutes to speak about it. So that's kind of one reason why it's surreal and one of the reasons why some of us, me really, were pointing out when they were going over time.

Number two is that this is actually kind of a pattern, because if you remember back 12 years ago -- you probably you don't -- the industry also actually petitioned to remove EPA as an authoritative body, when essentially they didn't like the fact that certain chemicals that the industry found kind of priority chemicals for them may be listed under the authoritative body mechanism.

So that's just kind of interesting we've seen this kind of pattern before. This is also kind of surreal, because there's nothing that's changed actually since the Committee actually designated CERHR as an authoritative body. And so if they decided to rescind that designation, it would be somewhat arbitrary.

Also, this is also pretty surreal, because we hear a lot from industry about how they really want to see risk-based assessments. And, you know, here's the situation, they're basically saying, well, you know, the NTP is doing risk-based assessments, but Prop 65 is a hazard-based program. So, in fact, those are not actually very relevant. So that was -- it's just odd.

And then the final reason why it was really surreal is, again, the only legal reason that the DART Committee can rescind authoritative body status is based on expertise. And that's really not what either petition

was really talking about or the commenters were talking about.

So I would urge you to not take any action to delists. And since I didn't say it before, I would also urge you to list OHAT as an authoritative body.

Thank you.

COMMITTEE MEMBER ROBERTS: Just a quick comment. Mike Shelby who was the head of CERHR was at the teratology meeting. This was actually the first time I'd heard of OHAT. I didn't even know it existed. I did ask him what it was going to do, and his comment was he had no idea. I think he may have said, "No dam idea", but I'm -- the bottom line is that he was not clear that it was going to be a continuation of what CERHR did. He had actually commented to me back when the first discussions had come up, when I called him, that he didn't feel CERHR or NTP should be considered an authoritative body, because their purposes were different. That was just him stating his opinion.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, just to clarify that. A number of people that are associated with authoritative bodies or Labor Code provision or any other have opined that we shouldn't use their documents for purposes of Prop 65. And it's really not their call. I mean, it is a California law that's very specific. You

all have identified these people. And we have regulations under that particular law that allow us to consider these documents.

And so really it doesn't matter whether or nobody somebody thinks we should use the documents or not. And you just heard from Dr. Bucher, who is, you know, the head of this group what they are going to be doing. And so it may well be that Steve was not informed of that at that time. It seems like it's a pretty recent decision. So just to clarify.

DR. JANSSEN: Dr. Sarah Janssen with the Natural Resources Defense Council.

My points are very similar to what Renee just said, but I think they're very important, so I'm going to repeat some of them. First is we're not here to debate the BPA report. You are designating the body, not blessing individual reports. The only issue here is whether NTP is an authoritative body. It's been considered an authoritative body for the past 12 years. I don't know what has changed that would make you remove it as an authoritative body at this point.

You do have the authority to rescind their authoritative body status, but you have to have a substantive reason, and you have to be able to explain that rationally. Otherwise, it's an arbitrary and

capricious decision.

Thanks.

MS. COX: Caroline Cox, Center for Environmental Health.

We've heard discussion here today about the deliberative and fairly lengthy process that this Committee went through in 2002 to designate NTP and CERHR as an authoritative body. And I haven't heard anything definitive that's changed since then that would make, you know, a reasonable basis for changing that designation.

It seems perhaps what's changed is, you know, some of the politics of the situation, but the science and the expertise has not changed. And so it seems that the most deliberative thing to do would be to retain that decision that was made before.

I believe -- I was not present at that meeting when those decisions were made. But my understanding is that, at that time, ACC supported the designation of NTP CERHR as an authoritative body. And like I said, I don't think that a lot has changed. Although, that organization seems to have changed their interpretation.

But in terms of what NTP does and how they do it seems to be the same. And I would recommend that this Committee recognize that continuity and stability.

CHAIRPERSON BURK: Were there any further public

comments?

Do you need a break? Tell me -- I think probably we should take 10 minutes now for your sake and then we'll finish this up. Back at 4:15.

(Thereupon a recess was taken.)

ACTING DIRECTOR ALEXEEFF: Let's get back together here.

I have a request. So we have some informational binders that are usually back there. And apparently two have been borrowed. So if someone has borrowed them and can just return them to us, we'd appreciate that.

Okay. So there are two binders that it was just for reference. So we'd appreciate them returned.

Thank you.

CHAIRPERSON BURK: Okay. Cough them up.

All right. Before we start discussion, Carol Monahan-Cummings has asked to speak again.

CHIEF COUNSEL MONAHAN-CUMMINGS: I promise that tomorrow I won't speak nearly as much.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: A couple of things I wanted to reiterated from some of the comments I had made earlier are that -- and you know a lot of the comments we've heard from the public have to do with OEHHA's process, in terms of implementing the

authoritative body provisions. And there is -- and there have been challenges to that -- our work on that. And that was one of the cases I mentioned earlier that was ExxonMobil, you know, sued us for identifying a chemical that was important to them.

So if the issue is how we implement the regulation, that is different than whether or not you are identifying a particular authoritative body as authoritative or not.

And I also wanted to mention that, as I said before, this Committee has a couple of different opportunities to opine when we are considering a authoritative body listing. We do send the notices to you. And we -- the regulation allows you to comment as individuals or as a Committee on our, you know, conclusions.

And in the event that we start the actual regulatory process, and later determine based on the criteria in the regulation, that those criteria haven't been met, you know, that it's either not identified or there isn't sufficient scientific evidence or other issues, the chemical comes to you for consideration. And so you're not excluded from the process. And so I just wanted to make that clear.

CHAIRPERSON BURK: I'm trying to determine the

best way to approach the discussion, because there's multiple things going on. But I think really, first and foremost, we need to consider the petition and make a decision on that. And then depending on that decision, we can move ahead if we wish.

I do want to announce that Linda Roberts has recused herself from this particular discussion, because now that we heard that ethylene glycol is in the works, and that's a product of her company. So that means, again, there will be -- should we vote, there will five of us voting, and we'll need to have five votes in order to make a decision for any kind of change.

All right. So comments from the Committee about whether we would like to consider de-designating NTP CERHR as an authoritative body as requested by the petitioners.

Carl.

COMMITTEE MEMBER KEEN: Yes. Maybe I'm being far too simplistic here, but listening to the discussions that have been going on, reading the materials that were presented to us, I'm struck that the nuance that I think we're struggling with is what happens when this Committee comes to a conclusion based under the rules and regulations that we understand and that we operate under? Whereas another group, which we'll call for this point an authoritative body, comes to a different conclusion

because they're operating under different rules?

Two specific examples. The one would be the maternal toxicity, which has already been alluded to several times. And the second one was actually kind of came up today. When you open the door on epigenetics, which is a field we work in, then there is a very high probability that what committees that consider that will be looking at are secondary triggers that actually cause the pathology that the initial trigger, which we'll call the epigenetic regulator, occurs in vivo.

So in both cases, we have -- they're outside of our confines, because in the second case you're looking at a situation where the insult that's actually causing the disease of interest is clearly postnatal. It's not necessarily prenatal. Prenatal is just merely shifting your frames of sensitivity forward, in the first case being maternal toxicity.

And I think that's what we're struggling with. Because it's not as if though we're questioning the scientific credibility -- I'm not hearing anyone question the scientific credibility of other authoritative bodies, but rather if we operate under different charges, who trumps who?

And I've heard in the past that nobody trumps anybody. That was actually stated in some material, but

we do have this tension. And I just don't know what the correct answer is. Obviously, that what we're trying to do is protect people, society, kids. So you could say well, we want to be as liberal as possible in our interpretation, but that seems to be against what the rules and regulations we operate under Prop 65.

So maybe I'm off base, but I think that's the gist of what we're talking about. It's not a given organization, it's a procedural issue. And perhaps it could be clarified by the legal counsel for Prop 65.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, one thing I wanted to mention is, again, that a lot of these authoritative bodies, in fact all of them, have their own charges and their own guidance and their own procedures for doing what they do to develop their documents.

You heard from Dr. Bucher today about process. And at least from his perspective, maternal toxicity is considered, maybe not discussed to the extent that we'd like to see it.

But when Dr. Donald talked earlier about criteria, we're looking at the criteria in our regulation. Okay. So these folks may come to a conclusion, you know, whatever it may be, that there's, you know, clear evidence or something. That's an identification if it meets the other requirements of the regulation, but we still look at

the basis for that -- the scientific basis for that.

We may exclude some of the studies that were considered. For example, if there was a postnatal study, that wouldn't fit our regulation. And so it's not a matter of us -- I mean, there is a Prop 65 process that is different. It overlaps. But it's much more similar to what your group does.

And it's because when you identify these authoritative bodies, one of the things that is implicit in that is that these folks are doing a similar function as you would do if you were individual -- you know as a group or looking at these chemicals yourself, but with the caveat that they're not going to use specific language like Prop 65 does, or that sort of thing. And that's where our office, our scientists and the legal staff are required to look at was it identified, was it scientifically sufficient under our criteria?

I don't know if that helps. And, you know, if you have questions for Dr. Donald about how that happens, he's got the slides up here again.

DR. DONALD: I'd just like to raise a couple of points for the Committee's consideration, and hopefully clarify some points that have already been raised.

One point I'd like to bring to the Committee's attention, irrespective of their merits, most of the

arguments that have been made today for delist -- de-designating NTP CERHR are equally applicable to all of the authoritative bodies that this Committee has designated.

With regard to consideration of maternal toxicity, which has been raised in the context of Bisphenol A, I would draw your attention to the last line in the slide that's up there, consideration of maternal toxicity, is one of specific criteria that we apply in determining whether the animal studies are supportive of a formal identification by the authoritative body.

The point was made that CERHR doesn't always consider maternal toxicity exactly the same way each time it considers a chemical.

As I'm sure the Committee recalls, your own criteria state that differentiating between the effects of a toxic agent and the conceptus or reproduction and the effects on the conceptus or reproduction that are secondary to the maternal systemic toxic effect is sometimes difficult and may require special attention on a case-by-case basis, which is how we approach it and apparently how CERHR also approaches it.

Could we go back to the previous slide.

And then it perhaps it wasn't entirely apparent from this slide, since we paraphrased the regulation to

make it fit a little better on the slide.

But the criteria on the right-hand side, the formality criteria, where it says, "One of the following has occurred". These are independent criteria. The regulation specifies that it's reviewed by an advisory committee in a public meeting or public review and comment of the document or that the document is published in publications such as the Federal Register and so forth.

Okay. So I'm sorry that was to clarify that even if the hazard identification was not individually considered by the NTP Board of Scientific Counselors on voting on the level of concern, though it is a little difficult to conceptualize how they would vote on the level of concern without considering the level of hazard. That is not, in and of itself, inconsistent with our criteria. That's only one of the criteria that could be met in determining if that formality criteria has been met.

CHAIRPERSON BURK: One thing I can say, Carl, because when we get the announcements of intent to list, I always read them, if they're by authoritative bodies, because I just want to see would we have done the same. And I've found there have been a number of cases over the years where EPA, for example, there will be something that will be listed, but there's definitely maternal toxicity

involved. So I know that you don't necessarily throw it out if that's in there.

What we're hearing is that it's considered. What I see here is two sort of parallel universes, I guess. And we have our guidance and sort of our philosophy, and OEHHA has actual regulations that they use to undertake the process.

So one thing I would say that I heard that was actually informative is that perhaps we should be more involved when these intent to list come out, and if we have some comment to make, we should, I suppose, make it. I'm must say I don't ever do that, but honestly I've kind of figured that that's their particular part of the process.

I hear your concern about how different authoritative bodies work, but I agree it's almost like saying we have to relook at all of them now and make sure that they all are thinking the way we're thinking. And I find that to be a little bit cumbersome.

COMMITTEE MEMBER KEEN: I'm sorry if my comments came across that way. I was more trying to crystallize for myself, if no one else, what we were talking about.

(Laughter.)

COMMITTEE MEMBER KEEN: And that's what I'm coming up with. It's not that anyone is besmirching the

reputation of any authoritative body, but it is slightly different processes. And if we're going to -- that's just a simple fact. There are slightly different processes.

If it turns out that doesn't stand in the way of listing under the authoritative body regulation, according to legal counsel of BPA, I see this as a non-issue. I was just trying to bring it down to two sentences.

COMMITTEE MEMBER KLONOFF-COHEN: I agree. I think what we're trying to figure is whether the information complements what we're looking at or whether it hinders it, I think, to be hones, in terms of -- that's the problem I'm having, in terms of, so the information that NTP provides for us when we look at it. So are we just questioning whether or not we're looking at their written documents?

CHAIRPERSON BURK: No, not at all. What we're questioning -- I mean what we're asked to determine --

COMMITTEE MEMBER KLONOFF-COHEN: Is there going to be an authoritative body?

CHAIRPERSON BURK: They are an authoritative body.

COMMITTEE MEMBER KLONOFF-COHEN: Whether we're going to reconsider --

CHAIRPERSON BURK: What we are asked to is de-designate --

COMMITTEE MEMBER KLONOFF-COHEN: Right.

CHAIRPERSON BURK: -- CERHR as an authoritative body for the remaining monographs.

COMMITTEE MEMBER KLONOFF-COHEN: That's the first part.

CHAIRPERSON BURK: Right. Again, these are not things we're looking at. The only thing that happened with BPA that was a little bit unusual is that OEHHA could have gone with that mechanism authoritative body on their own and not have brought it to us, but it was already sort of in the pipeline, and there was a nice document for us to look at. So we were able to use it.

But normally, we're not the ones using those documents. So one of the things that's asked, I think, is that we de-designate it and then we use the documents and make our own decision.

My personal feeling is we only meet once a year and I think it's much more productive to let professional full-time people work on this second mechanism, and then leave for us other chemicals that we can tackle that haven't already been looked at by an authoritative body. That's my opinion though, but I'm asking for you guys to chime in, if you have a contrary opinion.

So I would like to take this step by step. And the first step would be for us to actually vote on whether

we wish to de-designate the CERHR as an authoritative body, and then we can go on from there, depending on the decision.

So is that acceptable?

So I would ask all of those who would like to revise the designation of NTP CERHR as an authoritative body by removing the portion that -- or -- yeah, removing the portion that mentions CERHR to raise your hand?

(No hands raised.)

CHAIRPERSON BURK: All right. I see no one. So that does not carry.

So if we vote no, which we did, the designation remains unchanged.

The next discussion we can have is whether we want to, at this point, add -- that we want to add the OHAT to the designation of NTP as an authoritative body.

CHAIRPERSON BURK: All right. George, wants us to have a no vote, so we'll go back to just to make it obvious.

So all those voting, no --

MR. LANDFAIR: Madam Chair, can you clarify for us what the motion is on the -- I genuinely do not understand what --

CHAIRPERSON BURK: Yes. So I'm reading -- I'm making the motion specifically that we're voting to

de-designate NTP CERHR as an authoritative body, specifically CERHR. Does that make sense? Not NTP entirely, but what we have now is an authoritative body is NTP CERHR.

So the question is, we are already asked how many people wanted to do that. Now, I'm asking all those voting no that they do not wish to de-designate NTP CERHR as an authoritative body?

(Hands raised.)

CHAIRPERSON BURK: All those voting no.

All right.

Is that clear?

I hope so.

I didn't have it written down in a formal motion, but I think we've got it clear that the -- it was five to zero no not in favor of de-designating CERHR.

So then the next question comes at this time, do you want to consider adding the OHAT to it or would you like to defer that till we see more documents as has been suggested?

COMMITTEE MEMBER KEEN: I would like to formally suggest we defer it. And, in particular, I think it is important under the spirit of Prop 65 to get clarity as to whether or not OHAT will be looking at epigenetic phenomena. And if they do, if there is a way they can

corral that data set in such a fashion that we do not wind up using something which is clearly postnatal exposure, which is, as I understand it, we're not supposed to be doing under Prop 65.

So I think that just needs to be crystal clear, and then they're a great group of people after that.

CHAIRPERSON BURK: Very valid comment.

Any other comments?

DR. ZEISE: I just wonder if we could get some clarity with the kind of data that Dr. Keen was speaking of, if it's -- if he's thinking mostly in terms of in vitro data or other kind of information.

COMMITTEE MEMBER KEEN: No. I see this as in vivo. What was stated as they're now -- they are including looking, for example, perinatal changes at the genome level, which may increase the risk -- actually, what he stated was with respect to obesity and diabetes.

In some cases, that initial pre or perinatal insult by itself will wind up triggering the obesity or diabetes, but that's probably going to be the rare event. What's going to be far more common is it alters the susceptibility to postnatal triggers that induce these diseases.

That's what the whole developmental theory for chronic and degenerative disease are, so it seems to me.

And again I could be wrong, but out of the mandate of what Prop 65 covers. It may be internally that this gets a lot of discussion and it turns out it does fall within the mandate, and that's fine. But it just seems we need clarity on that.

COMMITTEE MEMBER ROBERTS: I'd just like to ask if perhaps when we discuss it again, if we might be able to -- or at least -- or if OEHHA could at least request that somebody from this OHAT group, that's a reproductive toxicologist, be able to address us in the way that Dr. Bucher did primarily more on the carcinogenicity side.

CHAIRPERSON BURK: And I don't know how long we're suggesting deferring, but I would suggest until there's at least one or two reports available for us to look at, which is I think exactly what we did with the CERHR.

Any other comments on that?

Do we have to vote on that decision?

CHIEF COUNSEL MONAHAN-CUMMINGS: It would be best if you did.

CHAIRPERSON BURK: All right. Now, I have to write it.

So all those in favor of waiting for further information before deciding on whether to designate NTP, specifically the Office of -- what does OHAT stand for

again? I know it ends with translation.

DR. DONALD: Office of Health Assessment and Translation.

CHAIRPERSON BURK: -- Office of Health Assessment and Translation before making a decision about whether to designate that particular entity as an authoritative body. Is that a clear motion?

So all those in favor, and I think Linda can vote on this?

COMMITTEE MEMBER ROBERTS: Yeah, they haven't done any reports yet.

(Laughter.)

CHAIRPERSON BURK: Right. We're just voting to defer it. So you have no conflict. So we need five out of six.

So all those in favor of deferring, raise your hand?

(Hands raised.)

CHAIRPERSON BURK: All right I see six.

Do I have to ask opposed when there's nobody left?

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

CHAIRPERSON BURK: All right. I think considering that we have scheduled time to meet at nine o'clock tomorrow morning, that we would begin the rest of

the agenda at that time, which is the prioritization and staff updates and so forth.

So nine o'clock in this same room.

Okay. Meeting adjourned.

CHIEF COUNSEL MONAHAN-CUMMINGS: Again, the reminder not to discuss the stuff that's still on the agenda. Feel free to discuss the stuff that was already on the agenda though.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee recessed at 4:42 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 under my direction, by computer-assisted transcription.

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

IN WITNESS WHEREOF, I have hereunto set my hand this 18th day of July, 2011.

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