MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

ELIHU HARRIS STATE BUILDING

1515 CLAY STREET

AUDITORIUM

OAKLAND, CALIFORNIA

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10:02 A.M.

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Dr. Calvin Hobel

Dr. Kenneth L. Jones

Dr. Carl Keen

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Dr. La Donna White

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Dr. Patricia Sutton, University of California, San Francisco

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Ms. Caroline Silveira, Grocery Manufacturers Association

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Dr. Rochelle W. Tyl, RTI International

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Dr. William C. Hoyle, North American Metal Packaging Alliance(NAMPA)

Ms. Julie Silas, Health Building Network

Mr. Bill Allayaud, Environmental Working Group

Mr. Luis Cabrales, Coalition for Clean Air

Ms. Caroline Cox, Center for Environmental Health

Ms. Pamela Palitz, Environment California

Ms. Janet Nudelman, Breast Cancer Fund

Ms. Anita Sarah Jackson, MomsRising.org

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Ms. Elisa Batista, MomsRising.org

Ms. Sophie Noero, Worksafe

Ms. Andria Ventura, Clean Water Action

Dr. Joseph H. Guth, Science & Environmental Health Network

Ms. Nancy Bellen

Ms. Alissa Shaw, Planned Parenthood

Dr. Sarah Janssen, Natural Resources Defense Council

Ms. Gretchen Lee Salter, Breast Cancer Fund

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PROCEEDINGS

DIRECTOR DENTON: Good morning, everyone. Can you hear me? I'm not getting a lot of feedback.

Good. The microphone is on. My name is Joan Denton, and I'm the director of OEHHA. And I would like to welcome all of you in the audience as well as the panel members and those in the audience on the webcast to the Proposition 65 Developmental and Reproductive Toxicant Identification Committee meeting.

Today, we have one large item on the agenda and that's the consideration of Bisphenol A for identification.

I have a few -- I want to make a couple of -- I just want to make some introductions and then we have some housekeeping rules that I need to tell you about and then I'm going to turn it over to Dr. Burk who's the chair of the Committee.

So let me do my introductions first. On my right is Dr. Linda Roberts and she's a senior toxicologist at the Chevron Research and Technology Company.

And then next to Dr. Roberts is Dr. Kenneth Jones, who is professor of the Department of Pediatrics at UC San Diego.

And then on my far right is Dr. La Donna White. And she is a clinical faculty physician at the Mercy

Family Practice Residency Program.

On my immediate left is Dr. Dorothy Burk who is an associate professor at Department of Anatomy at the University of the Pacific, School of Dentistry. Next to Dr. Burk is Dr. Carl Keen, who is a professor at UC Davis in the Department of Nutrition. Then Dr. Ellen Gold who is a professor at the Department of Public Health Services at UC Davis. And then on my far left is Dr. Calvin Hobel who is a vice chair in Obstetrics and Gynecology at Cedars-Sinai Medical Center.

So we appreciate all of the panel members being here today. Dr. Hillary Klonoff-Cohen who, as you know, is another member of the Committee, our other member of -- last member of the Committee is unable to attend.

Then just brief introductions. The individuals, the OEHHA staff at the staff table Dr. Jim Donald, Dr. Mari Golub, Dr. Lily Wu, Dr. Lauren Zeise, Dr. George Alexeeff and Carol Monahan-Cummings who is our counsel.

So with that, I just want to give you a few housekeeping items. As is required, if we need to evacuate, there are exits up in the back and they're also in the front in the way that you came in. And then you can exit out the building.

The next one is very, very important as is the first, but the second is immediate. Would you please turn

off your cell phones and your PDAs. Maybe we could take make a moment and everyone could get their cell phones and turn them off. The reason is that the meeting is being audiocast. And even the presence of your cell phones being on will interfere with the audio recording equipment. So we appreciate it. And we know that it's probably the most difficult thing we will need to do today, but we need to make sure that everyone can hear clearly the proceedings of this meeting.

If you're not aware already, the bathrooms are outside and on your right as you go out the doors, they're on the right not very far down.

And also as you experience the security in this building is fairly tight. That is if you exit back out again, then you'll have to go through security to get back into the auditorium.

This meeting is being recorded and it's audiocast on the Internet, as I mentioned. So when you speak, please be sure that you speak clearly into the microphones and then just to let the panel know that the microphones do not have an on/off switch. Therefore, all of our microphones are on all the time. So just a word there.

(Laughter.)

DIRECTOR DENTON: Word to the wise.

So now it's my pleasure to turn the meeting over

to Dr. Dotty Burk who will conduct the Prop 65 Developmental and Reproductive Toxicant Identification Committee meeting today.

CHAIRPERSON BURK: Good morning, everyone. And thank you very much, Joan.

I'm pleased to see so many people here. And although we only have one chemical to consider today, I think it's going to be potentially long, but definitely interesting meeting. So I thank you all ahead of time for your contributions. A large amount of work went into preparing this by the staff, by the public comment, commenters and by the Committee members.

So according to our agenda, we will begin with the consideration of a chemical that's known to the State to cause reproductive toxicity and that is Bisphenol A. And the first up will be the staff presentations. And I think Dr. Jim Donald is going to start that off, is that correct?

DR. ALEXEEFF: Dr. Burk, I'll start. This is George Alexeeff, Deputy Director for OEHHA. And I thought I'd just make a couple of comments. Actually, a fairly comprehensive presentation today. We have six staff members presenting within their own areas of expertise on this chemical.

As you know, there's lots of information. And I

thought I'd just give a little bit of why we are bringing this chemical to you today. So as you probably recall, in December of 2004, we adopted a new prioritization process for identifying chemicals to bring before the DART IC as well as the CIC. And in September of 2007, we completed a screening process for prioritization, and BPA was identified as a candidate DART IC.

We brought that to the panel in December of 2007. And at that time, the panel recommended that we prepare hazard identification materials for BPA.

At the same time, you'll probably know the NTP, the CERHR was also looking at BPA. And there was no date certain as to when they would be completed with their process, so we continued with our process.

We requested additional information from the public in January of 2008, which closed in March of 2008. And then we began preparing the document or the materials.

So in September of 2008 the NTP had completed its process. But by that time, we were already pretty far along in preparing the materials for this -- the hazard identification materials for this committee. So we felt we should go ahead and complete our material preparation and proceed with the meeting, it had already been on our schedule and such.

So that's the reason we brought it before you.

And I think you'll find the presentations to be of great interest to you.

(Thereupon an overhead presentation was Presented as follows.)

DR. DONALD: Good morning. My name is Jim Donald and I'm going to give a brief overview of general information of Bisphenol A. And then the primary authors of the sections on developmental, female and male reproductive toxicity and on the endocrine activity of BPA will make brief presentations.

In the interests of time, we will keep the presentations short and general in nature. Please note that the data are diverse and that many endpoints presented were reported to be affected in some studies, but not affected in others.

We do not have time to discuss the specifics of the studies, but we will be happy to answer any questions the Committee members may have at the end of the presentation.

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DR. DONALD: Bisphenol A is an organic compound with two phenol functional groups. At ambient temperature, it is a white solid with a mild phenolic odor and it is soluble in water at room temperature.

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DR. DONALD: BPA is produced in very large quantities and is used primarily in the production of polycarbonate plastics and epoxy resins. Polycarbonate plastics are used for a variety of purposes, such as food and drink packaging, including water bottles and baby bottles. Uses of epoxy resins include coatings for food cans and bottle tops, and in dental restorative materials and sealants.

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DR. DONALD: The most common route of BPA exposure in humans is oral. BPA is known to leach from dental composites as well as food containers, such as cans and polycarbonate plastic water bottles. Detectable levels of BPA have been found in the general population.

BPA measured as urinary BPA in the 2003/2004 National Health and Nutrition Examination Survey, or NHANES, was detected in 92.6 percent of persons greater than or equal to six years of age. Total concentrations range from .4 micrograms per liter to 149 micrograms per liter, with a geometric mean of 2.6 micrograms per liter.

Children had significantly higher concentrations than adolescents, who had significantly higher concentrations than adults. In a recent study of 54 premature infants in neonatal intensive care units, mean total urinary concentration of free and conjugated BPA was

28.6 micrograms per liter, almost ten times higher than concentrations in 6 to 11 year old children measured in NHANES 2003/2004.

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DR. DONALD: BPA is considered to be a chemical of low general toxicity. The limited data available indicate LD50s in excess of 2,000 milligrams per kilogram in laboratory species. One study of inhalation exposure found only slight and transient damage to nasal tract epithelium after six hours of exposure to 170 milligrams per cubic meter, the highest concentration attainable.

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DR. DONALD: The pharmacokinetics of BPA is an important consideration for overall risk assessment, but is relevant to hazard identification, only to the extent that qualitative rather than quantitative differences between experimental animals and humans in relevant parameters can be clearly demonstrated.

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DR. DONALD: BPA is well absorbed after oral exposures, the primary route by which humans are exposed, as well as by intraperitoneal or subcutaneous injection. Many experimental studies have used routes of exposure other than the oral route. A study in rats and non-human primates indicated that BPA is less bioavailable via oral

exposure than by subcutaneous, with oral administration of BPA resulting in a lower area under the serum concentration curve than subcutaneous administration. However, a study in three day old CD-1 mice conducted at lower doses reported similar bioavailability of BPA by both subcutaneous and oral routes.

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DR. DONALD: A simplified scheme of Bisphenol A metabolism is depicted in this slide. BPA is predominantly glucuronidated by uridine diphosphate glucuronyl transferase, and BPA glucuronide is the major metabolite. Glucuronidation occurs primarily in the liver, but glucuronyl transferase is also present in numerous other tissues. BPA-glucuronide can also deconjugate back to -- excuse me. BPA-glucuronide can also be deconjugated back to BPA by beta-glucuronidase. Metabolism by cytasolic sulfotransferases in the liver also occurs, resulting in the formation of BPA sulfate. Other minor metabolites of BPA, such as BPA diglucuronide and 5-hydroxy BPA have also been reported.

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DR. DONALD: In rats, most orally administered BPA circulates in plasma as BPA-glucuronide. After subcutaneous administration, most BPA is absorbed into the systemic circulation without being metabolized in the

subcutaneous tissue. BPA distributes widely in the body and easily crosses the placenta, resulting in fetal exposures. Although, BPA glucuronide has been reported to cross the placenta less easily. BPA has also been detected in human breast milk.

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DR. DONALD: In humans, BPA-glucuronide is rapidly excreted in urine. A half life of less than six hours has been reported, although recent data suggests it may be longer.

BPA-sulfate has been reported as a minor urinary metabolite in humans. Unlike humans, the BPA-glucuronide formed in rats undergoes enterohepatic recirculation so is excreted from the liver via bile into the gastrointestinal tract, cleaved back to BPA and reabsorbed into the blood.

This results in slower elimination of BPA and its conjugates compared with humans. Terminal elimination half-lives in rodents are between 20 and 80 hours. The enterohepatic cycling and decreased first pass metabolism of BPA in rats results in higher plasma levels of unconjugated BPA in rats, compared to humans given the same dose.

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DR. DONALD: The influence of route of exposure in BPA has already been covered. Age dependant maturation

of glucuronyl transferases affects the metabolism of BPA. Neonatal rats showed higher plasma concentrations of BPA at earlier times post-dosing than adults dosed at the same level, with the neonates also showing differences in the BPA metabolite profiles from the adults.

A study in premature human infants found free BPA, but more than 90 percent was in a conjugated form, such as glucuronide or sulfate. The authors concluded that conjugated species were the primary urinary metabolites of BPA, suggesting that the premature infants have some capacity to metabolize BPA. The quantitative capacity of the young to metabolize BPA remains unknown. Glucuronidation is less mature at birth than in adults, and is likely even more so in utero, while sulfotransferase has greater activity in the fetus than in the neonate.

That completes the introduction, and now Dr. Golub will present an overview of developmental toxicity.

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DR. GOLUB: My name is Mari Golub, and I'll be presenting the information on developmental toxicity.

Studies relevant to developmental toxicology, include just two in human populations but a larger number in laboratory rodents.

Some animal studies are based on the guidelines

of regulatory agencies. Additionally, Bisphenol A has attracted the interest of many scientists all over the world with expertise in a variety of areas, leading to a large number of investigator-initiated studies.

The dose range studied -- the doses reached from the low microgram per kilogram range in connection with concern about endocrine disruption to the gram per kilogram range, the highest range used in toxicology studies. For reference, the picture illustrates 100 milligram per kilogram dose. A teaspoon of Bisphenol A, 6,000 milligrams ingested by 132 pound, 60 kilogram woman would be 100 milligram per kilogram dose in the higher end of the range used in toxicology studies.

Thus, the lowest dose study would be less than 1/100,000 of a teaspoon administered to a person.

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DR. GOLUB: Two recent human studies published in 2008 looked at the association between maternal Bisphenol A exposure and pregnancy outcome.

One was a cross-sectional study with 40 women and the other a prospective study with 404 women. The primary outcomes were gestational age, weight, length, and head circumference at birth. No significant associations were found.

The studies are limited in the first case by a

small sample number, and in the second by a low exposure relative to population norms. So the remainder of the presentation will be on studies in rodents.

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DR. GOLUB: In rats and mice, several studies of pregnancy outcome found Bisphenol A effects on offspring viability in the higher dose ranges, as reflected in measures like fetal loss, decreased litter size, and decreased live pups per litter.

Offspring weight at term was also lower than controls in some studies. Pregnancy outcome will also be discussed later under female and male reproductive toxicity.

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DR. GOLUB: Gene expression studies asked whether factors controlling gene transcription in the embryo and fetus were affected by Bisphenol A exposure. Most of these studies gave Bisphenol A to the pregnant dam and about half of them used oral dosing.

They looked at retinoic acid receptor, aryl hydrocarbon receptor, homeobox genes, all important regulators of development, as well as chromosome abnormalities and epigenetic effects.

As is the case for most of the studies I am describing, these studies had multiple endpoints, and at

least one effect of Bisphenol A was reported in each of them.

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DR. GOLUB: Bisphenol A like estrogen can influence food intake and weight gain. Studies in this area are currently a focus in the biomedical literature. Five developmental studies found decreased postnatal weights using a higher dose range, with weight mostly measured in the fetal and neonatal period.

Four studies found a weight increase in the lower dose range and they usually used a later weight -- age at weighing.

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DR. GOLUB: Of these studies, four involved Bisphenol A administration only during pregnancy. As is the case for most of the studies I am describing, Bisphenol A is commonly administered throughout prenatal and postnatal stages of development to examine its toxicological effect. The other five studies used this approach.

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DR. GOLUB: Postnatal immune function there are four studies in the lower dose range all in mice, all with oral administration. This is a recent area of interest in the literature. In immune challenge experiments,

Bisphenol A increased the immune response, according to several measures such as inflammation, cytokine production, cell proliferation, and antibody production.

In two studies, Bisphenol A led to decreased suppressor T-cells, which is consistent with the enhanced immune response. These effects are similar to those of estrogen and to Bisphenol A on the immune response in adult mice.

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DR. GOLUB: These studies looked at brain and behavioral endpoints known to be influenced by developmental estrogen exposure. The size and number and types of neurons in different brain regions, that are sexually differentiated, showed selective Bisphenol A effects. As regards behavior, some aspects of mating behavior and juvenile social interaction were influenced by developmental Bisphenol A., and there was a more general depression of maternal behavior.

Some measures of sex-differentiated non-social behaviors also showed effects, generally those reflecting affective and exploratory behavior. Spatial learning and memory, a sex-differentiated behavior in humans as well as in rodents was affected in one study.

This graphic, over to the side, illustrates that lack of sex differentiation can be -- can have several

forms in experiments. This bar graph shows a situation with sex differentiation, with the males in blue having higher values than the females. A lack of sex differentiation could be seen in a study where either the male values were decreased, the female values were increased or both the male and female values were intermediate from their original values in the control group.

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DR. GOLUB: So in summary, there were no associations between Bisphenol A exposure and birth weight or gestation length in two recent human studies. In rodents, effects on offspring viability were reported in the higher dose range, also postnatal growth effects, possibly depending on dose range and the time of evaluation. Immune hypersensitivity was affected and there were changes in aspects of sex differentiation of brain and behavior.

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DR. GOLUB: After we completed our review document, a study of developmental toxicity in non-human primates was published. The 2009 study is from a research group that previously published work on comparative pharmacokinetics of Bisphenol A and effects of Bisphenol A on behavior in rats.

Here, pregnant cynomolgous monkeys were exposed to Bisphenol A via an implant that released ten micrograms per kilogram per day equivalent to an oral dose of five milligrams per kilogram per day to rats, based on the investigator's previous pharmacokinetic work.

The exposure continued from the first trimester to the estimated time of birth. After birth, videotapes were made of the mother-infant behavior prior to weaning. In statistical analysis of the coded videotapes, Bisphenol A was found to affect clinging to the dam and social exploration, categories of behavior that were both decreased in male Bisphenol A-treated infants and also outward looking, a sex-differentiated variable, which was increased in male Bisphenol A-treated infants.

That concludes my part of the presentation.

Female reproductive toxicity is next.

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DR. WU: Good morning. My name is Lily Wu. I will present a brief outline of the available data on female reproductive toxicity of Bisphenol A.

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DR. WU: There were seven human studies of female reproductive outcomes, including six cross-sectional studies and one case-control study. Three cross-sectional studies are presented in this slide.

The findings include higher levels of Bisphenol A in men than women. Women with polycystic ovarian syndrome had higher Bisphenol A levels than obese healthy women. Positive correlations were seen with certain hormone levels, such as testosterone and androstenedione. And no association was seen between Bisphenol A levels and endocrine-related disorders.

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DR. WU: In the remaining three cross-sectional studies, findings included:

Lower Bisphenol A levels in women with endometrial cancer or complex endometrial hyperplasia; no association between Bisphenol A levels and endometriosis; and no association with pubertal status.

Lastly, a case-control study reported higher levels of Bisphenol A in women with recurrent miscarriages. Factors limiting the usefulness of these studies in assessing causal association between Bisphenol A and reproductive toxicity include the cross-sectional study design, small sample sizes, single measures of exposure, and lack of consideration of potential confounders.

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DR. WU: Twenty-seven laboratory animal studies were identified that examined uterine parameters after

Bisphenol A treatment. Fourteen of these studies were conducted in rats and 13 in mice. These studies used oral dosing or subcutaneous injection as routes of exposure. The effective doses used in these studies ranged from 250 nanograms per kilogram per day to 800 milligrams per kilogram per day.

Females were dosed with Bisphenol A at various stages of life, including prenatal, perinatal, and adult stages, also during pregnancy.

Commonly reported effects of Bisphenol A on the uterus are presented. The numbers in parentheses represent the number of studies that identified changes in these parameters. Not all studies that examined these parameters reported effects.

Parentheses located next to the parameters on subsequent slides will continue to represent the number of studies that identify effects.

Uterine weight increased in females that were treated with approximately 1.2 to 800 milligrams per kilogram per day, at approximately three weeks of age and older.

Uterine weight decreased in females dosed with .1 to four milligrams per kilogram per day prenatally and perinatally. Changes in uterine cell morphology, such as height and volume, were noted with Bisphenol A doses of

250 nanograms per kilogram per day to 50 milligrams per kilogram per day. And, altered uterine gene and protein expression were noted in females treated with .5 to 600 milligrams per kilogram per day.

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DR. WU: Six studies were identified that examined the ovary. Two of these studies were conducted in rats and four in mice. Bisphenol A was administered orally or by subcutaneous injection. The effective doses used in these studies, ranged from 1/1000 to approximately 700 milligrams per kilogram per day.

Asterisks on this and subsequent slides indicate values that OEHHA calculated to maintain unit consistency In this case, zero to nine day old rat pups were given up to four milligrams Bisphenol A per pup per day, which was calculated to be approximately 700 milligrams per kilogram per day.

Females were dosed with Bisphenol A at various stages of life, including prenatal, perinatal and adult stages, also during pregnancy.

The effects of Bisphenol A treatment on the ovary, included histological alteration, such as cystic ovaries, and neoplastic lesions, when 1/1000 to approximately 700 milligrams per kilogram per day. An increase in ovarian weight was seen when rodents were

exposed to .1 milligram per kilogram per day for 28 days as adults and reductions in ovarian weight were seen when rats were exposed to .2 micrograms per kilogram per day to approximately 700 milligrams per kilogram per day, prenatally and perinatally.

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DR. WU: Oocytes are contained within ovarian follicles. The cells of an ovarian follicle include the Oocyte, granulosa cells, and the cells of the internal and external theca layers. Bi-directional communication between the granulosa cells and an oocyte is necessary for oocyte maturation. Granulosa cells regulate the progression of meiosis, while the oocyte orchestrates granulosa cell proliferation, differentiation, and function.

Eleven studies were identified that examined the follicle or oocyte. One of these studies was conducted in rats and 10 in mice. Of the 11 studies, six were in vivo studies. Rats and mice were treated with Bisphenol A by oral dosing, subcutaneous injection, or subcutaneous implant. The effective doses examined ranged from 2/100 to approximately 700 milligrams per kilogram per day. Asterisks indicate unit conversions by OEHHA to maintain unit consistency.

Some observed effects of in vivo Bisphenol A

exposure on the follicle and oocyte include perturbation of the meiotic cycle at a dose of .13 milligrams per kilogram per day for seven weeks, increased polyploidy and chromosome misalignment at doses of .04 to .5 milligrams per kilogram per day, cystic follicles at doses of approximately 180 to 700 milligrams per kilogram per day, and disruption of early oogenesis in female offspring, also known as the grandmaternal effect, which can be more specifically described as an exposure of a pregnant female, which affects the oocytes of female offspring from an exposed dam.

All of these effects add to a growing body of evidence that exposure to Bisphenol A has the potential to impact at least three different stages of oocyte development. Those three stages of oocyte development, include meiotic initiation in the fetal ovary; follicle formation in the perinatal period; and oocyte growth and maturation in the adult.

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DR. WU: Five studies were identified that examined the in vitro effects of Bisphenol A on the follicle or oocyte. The in vitro dose range examined was 100 picomolar to 43.8 millimolar. Cells were cultured for various lengths of time from 0 to 12 days. In vitro effects of Bisphenol A included disruption of the oocyte

meiotic cell cycle with exposure concentrations of 10 micromolar to 43.8 millimolar Bisphenol A. Increased chromosomal misalignment was evident with a dose of -- with a concentration of 43.8 millimolar. Significantly more irregular calcium oscillation patterns were seen in oocytes exposed at 100 micromolar concentration of Bisphenol A compared with controls.

Although, oocytes tended to show a frequency of more irregular calcium oscillation patterns in concentrations of Bisphenol A, as low as ten nanomolar. And, decreased granulosa cell viability was seen with Bisphenol A concentrations of 100 picomolar to 100 micromolar.

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DR. WU: Eleven laboratory rodent studies were identified that examined estrous cyclicity. Eight of these studies were conducted in rats and three in mice. These studies used oral dosing or subcutaneous injection as routes of exposure. The effective doses used in these studies range from 0.2 micrograms per kilogram per day to approximately 700 milligrams per kilogram per day, which the asterisk indicates was calculated by OEHHA. Females were dosed with Bisphenol A at various stages of life, including in utero, perinatal, and postnatal periods.

Alterations to estrous cycles attributed to

Bisphenol A exposure during the perinatal period, included an extended diestrus phase or estrus phase. Cumulatively, this resulted in an altered estrus pattern, with exposures of 20 micrograms per kilogram per day to approximately 700 milligrams per kilogram per day.

Estrous cycle lengths were also altered by 50 to 100 milligrams per kilogram per day exposure. The cycle lengths tended to be longer. Finally, exposure of dams to 20 micrograms per kilogram per day resulted in female offspring having an earlier onset or being a younger age at the first estrus cycle compared to controls.

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DR. WU: Fertility is a parameter that is an indicator of reproductive performance. Some multi-generation and continuous breeding studies report effects on fertility. The studies of this nature reviewed by OEHHA showed general trends of reduced female fertility as a result of Bisphenol A treatment. The primary route of Bisphenol A exposure in these studies was by diet. Most rodents were exposed during pre-breeding, mating, gestation, lactation, weaning and post-weaning periods. A reduced trend in the number of total pups per litter was observed in two and three multi-generation studies.

A reduction in the live birth index was also seen in the two-generation CD-1 mouse study, and a reduced

trend in the number of live pups per litter in a three-generation Sprague-Dawley rate study.

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DR. WU: Sixteen studies were identified that examined the vagina after exposure to Bisphenol A. Nine of these studies were conducted in rats, and seven in mice. These studies used oral dosing, subcutaneous injection or implant or intraperitoneal injection as routes of exposures. The effective doses used in these studies ranged from 250 nanograms per kilogram per day to 800 milligrams per kilogram per day. Females were dosed with Bisphenol A at various stages of life, including prenatal, perinatal, and postnatal stages.

Effects on the vagina included alterations in vaginal epithelial cell morphological differentiation, stratification, and cornification, as well as an increase in the number of epithelial cell layers. Age at vaginal opening, which is generally accepted as a signal of the onset of puberty in rodents, was also affected. Female rats exposed to 2/100 to 800 milligrams per kilogram per day prenatally and perinatally, via subcutaneous injection or subcutaneous implant, exhibited vaginal opening at a younger age compared with control rats.

Pregnant rats exposed to 1/10 to 500 milligrams per kilogram per day via oral gavage had female offspring

that exhibited vaginal opening at a older age compared with control rats. Vaginal weight was also reduced among female offspring who were exposed to 250 nanograms per kilogram per day from Gestation Day 9 to Postnatal Day 4.

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DR. WU: Eleven studies were identified that examined the mammary gland after exposure to Bisphenol A. Four of these studies were conducted in rats and seven in mice. These studies used oral dosing, subcutaneous injection or subcutaneous implants as routes of exposure. The effective doses used in these studies ranged from 250 nanograms per kilogram per day to 54 milligrams per kilogram per day. Females were dosed with Bisphenol A at various stages of life, including prenatal, perinatal, and juvenile stages.

The effects of Bisphenol A treatment on the mammary gland included acceleration of the epithelial cell cycle. Cell cycle alteration in the mammary gland is typically associated with carcinogenesis. In female mice treated with 250 nanograms per kilogram prenatally and perinatally, the number of terminal end buds significantly increased, compared with controls. Exposure of CD-1 mice to 25 nanograms per kilogram on Gestation Day 8 to 18 promoted maturation of cells comprising the fat pad and altered localization of collagen.

Lastly, mouse dams given one percent Bisphenol A in rodent chow, which the authors state is equivalent to 1,000 milligrams per kilogram per day, had reduced prolactin levels, and offspring from these dams also weighed significantly less compared with controls.

Prolactin is a hormone known to positively regulate the secretion of breast milk. These two endpoints taken today indicate insufficient milk was produced for the mouse pups of these dams.

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DR. WU: Details of the effects of Bisphenol A on certain maternal endpoints upon were discussed in the developmental section. However, some endpoints are relevant to female reproductive endpoints as well, such as behavior and maternal fetal transfer.

Bisphenol A appears to affect maternal behavior, specifically a reduced duration of frequency and frequency of licking and grooming, anogenital licking and the arched-back posture. There is also reduced nursing behavior among Bisphenol A exposed dams. Evidence from pharmacokinetic studies also suggest Bisphenol A is readily transferred to the fetus via the follicular fluid, placenta, amniotic fluid, and milk.

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DR. WU: In closing, limited data on reproductive

effects of Bisphenol A in women were identified. The recurrence of miscarriage in women is possibly consistent with the perturbation of the meiotic cell cycle and the chromosome misalignment in oocytes noted in laboratory animals. Numerous female animal studies showed effects on the female reproductive system from Bisphenol A. Alterations to the uterus, ovary, follicles and oocytes, estrous cycle, vagina and mammary gland were notable.

Dr. Li will now present the male data.

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DR. LI: Good morning. My name is Ling-Hong Li. I will present a brief outline of the data available on the male reproductive toxicity of Bisphenol A.

Next.

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DR. LI: This slide reminds all of us the important milestones in the development of the male reproductive system. Development of major male reproductive organs begins in the fetus. In rodents, formation of testis takes place around Gestational Day 10 to 12, but the prostate only begins to grow and differentiate after birth.

Therefore, different organs at different developmental windows may respond to a toxic insult differently. It is important to keep in mind that the

development and the function of the male reproductive system rely heavily on the balanced actions of many hormones, such as androgens and estrogens, in an organ-, cell type-, time-, and duration-dependent manner.

Alterations in one hormonal function may cause changes in one organ at a specific time, but it may have no effect at all to a different organ or to the same organ at a different time.

Therefore, evaluation of the data on the male reproductive effects of chemicals require careful consideration of each organ's developmental stages and biological characteristics. With that in mind, I will turn to the human data on the male reproductive effects of BPA.

Next.

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DR. LI: There are only two occupational studies in humans available; both of them are cross-sectional in study design. One study found lower follicle stimulating hormone levels in workers exposed to BADGE with no difference in LH or free testosterone. While the other study found higher LH with no difference in testosterone or FSH.

Turning to the animal data.

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DR. LI: There are a total of about 100 studies in laboratory animals, including studies that used the whole animals in vivo studies and studies that used the in vitro models. Because of the time limit, I will not go through all the numbers on this slide, but would like to point out a few features of this data set.

For the studies in in vivo, almost all of them were conducted in rodents, rats or mice. Different studies treated the animals at different stages of the development, that include prenatal, neonatal, perinatal, pubertal, in the adulthood or through a lifetime, such as either RACB studies or multi-gen studies.

Almost all the studies focused on one or some of the following organs or endpoints: Reproductive performance, testis, epididymis, seminal vesicles, prostate, sexual maturation and hormonal levels or functions. Except in two multi-generational reproductive studies, not all of the studies assessed all the organs or endpoints.

It should be noted that the findings from the studies that treated the animals prenatally should be considered as evidence on the developmental toxicity of BPA under the Proposition 65 program.

Next slide.

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DR. LI: There are eight studies evaluated the reproductive performance in animals exposed to BPA as either neonatally or through a lifetime.

Two studies that treated the neonatal rats by s.c. injection found no apparent effect on the reproductive performance in the treated animals when they grew into the adulthood. The number of live pups per litter was one of the parameters that were commonly used in other studies. Reduction in the number of live pups was observed in three RACB studies, and the cross-over mating trial study in RACB study found that this effect was at least partly mediated through the male repro effects.

One dietary two-generation study found increased still birth, but the increase was not statistically significant when analyzed by the study authors using the pairwise comparison method.

The three-generation study found apparent reductions in the number of live pups per litter in F1 and F3 generation, but not in the F2 generation. The reduction was only significant at high doses.

Next slide.

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DR. LI: Turn to the BPA effects on the testis. There are more than 60 studies investigated the BPA

effects on the testis. The endpoints used in these studies can be largely put into six categories.

Organ weight: Among the 48 studies that weighed the testis, nine reported significant reduction, roughly by ten percent, as compared to the concurrent controls. The lowest observed effective doses identified in these nine studies ranged from .002 milligram per kilogram per day in a prenatal study to 600 milligrams per kilogram per day in a two-generation repro study in mice.

There are 28 studies included histopathological evaluation, using the method that are routinely used in most GLP or standardized testing studies. Only one study found degenerative changes in the testis with a LOEL of 600 milligrams per kilogram per day.

Sperm parameters include testicular spermatid head counts, and analysis of epididymal sperms. Among the 26 studies that evaluated the sperm, ten reported either reductions in sperm count or sperm motility or both. The LOELs found in these studies ranged from .02 to 875 milligrams per kilogram per day. As you can see from this slide, the results on these three categories of endpoints from different studies vary largely.

Some of the studies on this slide were conducted in GLP labs. Others were from academic research labs. All of them had been already published in peer-reviewed

scientific journals.

Next.

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DR. LI: There are also many studies examined the endpoints that were not routinely used in GLP or guideline studies. There are 12 studies that conducted quantitative histopathology or ultrastructural evaluation of the testicular tissue. Ten of these 12 studies found abnormal changes in the testis.

Similarly, six studies evaluated the testis by immunostaining for structural or functional proteins, and five of them reported BPA-induced changes that were not seen in the concurrent controls.

Using biochemical analysis including gene expression analysis, six out of seven studies reported abnormal changes resulting from BPA exposure. As you can see from this slide, most of these studies consistently reported abnormal changes after BPA treatment at doses as low as .02 milligrams per kilogram per day. It should be noted that most of these studies were conducted in academic research labs, but all of them have been published in peer-reviewed journals.

Next.

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DR. LI: In addition to the studies in vivo,

there are also nine in vitro studies, including four on Sertoli cells and five on Leydig cells. Except for one study that found no apparent effects of BPA on cultured Leydig cells, all other studies reported alterations in cell viability, cellular function, or expression of certain genes in cultured Sertoli cells or Leydig cells.

Next slide.

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DR. LI: Turn to data available on the prostate. There are a total of 33 in vivo studies, 24 in rats and nine in mice. The animals were treated at different stages of development by oral administration, s.c. injection, or s.c. implants. The doses ranged from .002 milligrams per kilogram per day to 1,750 milligrams per kilogram per day.

Most studies measured the prostate weights. Some weighed the whole prostate, which consists of three lobes: dorsal, lateral and ventral. Other studies only measured the ventral prostate, as you can see from the slide.

A few studies also included histopathological evaluation of the prostate.

Next slide.

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DR. LI: Among the 31 studies that weighed the prostate, six studies treated the animals in utero and

examined the prostate of the male pups at different ages. Only one study found increased prostate weight. None of the 11 studies that treated the animals neonatally or perinatally reported changes in the prostate weight.

On the other hand four of 13 studies that treated the animals in the adulthood or through lifetime in the RACB or multi-gen studies found reduced prostate weight by BPA at relatively high doses, usually in the milligram per kilogram dose ranges.

Seven studies included histopathological evaluation using the methods that are routinely used in the guideline studies. None of them reported any abnormal changes in the prostate.

On the other hand, all of the five studies that evaluated the prostate with quantitative histopathology or immunostaining found either increased proliferated activities or abnormal differentiation by BPA at doses -- rather ten micrograms per kilogram per day or higher.

Next slide.

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DR. LI: In addition to the in vivo studies, there are also at least six studies on the prostate cells using the in vitro models. All six studies reported BPA-induced alterations in proliferation, differentiation, gene expression, or cell's response to androgen

stimulation, depending on the endpoints used in the study.

Next.

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DR. LI: This slide shows an overall picture of the studies that examined the BPA effects on other organs or endpoints. For the epididymis and seminal vesicles, most studies only reported the organ weights with no data on the histopathology.

There are 15 studies that evaluated the effects of BPA on sexual maturation, using AGD, age of preputial separation, or nipple retention as endpoints. In addition, there are 22 studies measured blood levels of sex hormones. In general, the studies that found effects on these endpoints also reported effects on the testis or prostate in the same studies. Major findings from many studies on these endpoints are all summarized in the HIM.

Next slide.

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DR. LI: To summarize, there is very limited data in humans, but numerous studies in lab animals.

With regard to the BPA effects on reproductive performance, the RACB and mutli-gen studies reported reduced number of live pups per litter.

On the testis, results on the testis weight, sperm parameters, and routine histopathology from

different studies varied from no effect to significant effects.

Majority of the studies that used the quantitative pathology or molecular approaches consistently reported BPA-induced effects on the testis.

All but one in vitro study reported BPA-induced changes in cultured Sertoli cells or Leydig cells.

Next.

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DR. LI: On the prostate: Results on the prostate weight from different studies varied from no effect, increase, or reduction, depending on the doses and exposure time or duration.

Histopathological evaluation of the prostate with routine method found no effect.

Studies that used the quantitative pathology or immunostaining evaluation consistently reported BPA-induced effects. All in vitro studies reported BPA-induced in the cultured prostate cells.

On the other organs or endpoints:

Results from different studies varied. Effects on these endpoints are often associated with testicular or prostate effects in the same study.

That concludes my presentation. Thank you for your attention.

Dr. Moran will report on endocrine activity effects next.

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DR. MORAN: Good morning. My name is Francisco Moran and I will be presenting the endocrine activity of BPA.

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DR. MORAN: I would like to start by reviewing with you the hypothalamic-pituitary-gonad axis. Here is a cartoon that summarizes the endocrinology of reproduction.

First we have the players: The hypothalamus, the pituitary, and the gonads. The endocrine system is controlled in part by the nervous system through hypothalamic neurons. These neurons produce gonadotropin releasing hormone, gnRH in our slide, that stimulate the anterior pituitary to release gonadotropins: luteinizing hormone, LH, on follicle stimulating hormone, FSH.

Gonadotropins stimulate the gonads to produce the gametes and hormones, such as the steroids, progesterone, estradiol, and testosterone.

These hormones could finally reach target organs and close the loop by feedback to the superior centers.

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DR. MORAN: The principal mechanism of action of BPA is through disturbing the endocrine system. There is

evidence that BPA is an endocrine disrupting chemical, from now on, EDC.

OEHHA identified 35 articles that address one or more of the proposed mechanisms for endocrine disruption of BPA.

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DR. MORAN: This diagram summarizes the general mechanism of hormone action and how an endocrine disrupting chemical could interact with it.

Here, we have a generic hormone, delineated by H, outside the cells. The intracellular space is defined by the plasma membrane, pm. Depending on the chemical structure, the hormone could find its receptor, HR, either in the plasma membrane or the intracellular compartment.

This interaction of the hormone with the hormone receptor leads to a signal transduction that could be:

One, the production of second messengers for a final cytosolic event or;

Two, regulation of gene expression.

Now, and EDC, that usually mimics the chemical structure of the endogenous hormone may interfere at least at four points marked in the slide.

There is some action here.

The circulating hormone, one; two, the interaction between the hormone and its hormone receptor,

either as plasma membrane or cytosolic; three, the production of cytosolic events, and; four, the regulation of gene expression.

In the following slides, I will present a summary of the available data on BPA as an endocrine disrupting chemical.

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DR. MORAN: First, interaction with the estrogen receptor, ER.

There were 11 in vitro studies demonstrating that BPA not only binds but also is able to activate the estrogen receptor.

There are eight studies using the human estrogen receptor in various cell lines, and three studies on the rat estrogen receptor in both primary culture of anterior pituitary and cell lines.

The EC50 of either the reported gene or prolactin production for the pituitary cells is in the low micromolar range, on the right column on the slide.

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DR. MORAN: Second. Interaction with the androgen receptor. Three studies were identified showing that BPA can interact and inhibit the androgen receptor. These studies used cell lines cotransfected with the androgen receptor and a reporter gene. BPA inhibits

androgen receptor activity with an IC50 in the low micromolar range, from 1 to 7 micromolars.

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DR. MORAN: Third. Effects on sex hormone binding proteins. Three studies reported interaction of BPA with plasma carrier proteins. One study on human sex hormone-binding globulin showed no competition with dihydrotestosterone, an important androgen.

A second study on human sex hormone-binding globulin showed an IC50 or 51 micromolars for testosterone and 13.6 micromolars for estradiol. A third study showed no competition between BPA an estradiol for binding to rat alpha-fetoprotein that is equivalent of the hormone-binding globulin in rodents.

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DR. MORAN: Fourth. Effect of BPA on estrogen receptor-alpha expression.

There were four in vivo studies that investigated the effects of BPA on ER-alpha expression. Three of them had oral exposure at various times and one was with a subcutaneous injection.

There was an increase in females and a decrease in males at medium and high doses -- or in the estrogen receptor expression.

When looking at the hypothalamic nuclei, we have

results from no effect to decrease or increase in the estrogen receptor expression, depending on the region of the brain study.

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DR. MORAN: Fifth. The effects of BPA on progesterone receptor.

Two in vivo studies in rodents were identified on the effect of BPA on the progesterone receptor. Rats were treated with oral dose from .02 to 800 milligrams per kilogram per day for three days. As a result, we found that BPA increased the progesterone expression and in one of the studies BPA decreased the estradiol stimulated progesterone receptor gene expression.

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DR. MORAN: Sixth. Effects of BPA on steroid production. Three in vitro studies were identified that reported the effects of BPA on progesterone and estradiol production.

One, first in pig granulosa cells treated with .01 to 100 micromolars BPA for 72 hours, it was found that progesterone increased at the low dose and decreased at the high dose. BPA also decreased the FSH-stimulated estradiol production.

In human granulosa cell lines treated with 20 to 100 micromolars BPA for 48 hours, it was asserted that BPA

decreased the FSH-stimulated estradiol production.

In Sprague-Dawley rats, it was found that BPA at .01 to 1 micromolar for 48 hours increased the progesterone production in theca cells, but close treatment had no effect on the rat granulosa cells.

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DR. MORAN: Seventh. One cytosolic event... Aromatase activity. Three in vitro studies using human cell line, human placenta microsomes and equine purified enzyme treated with BPA from 10 to 1,000 micromolars for 15 minutes or 48 hours. In all of the studies it was observed that BPA decreased aromatase activity.

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DR. MORAN: Eight. Other endocrine related BPA effects. BPA alter enzymes and transporter proteins involved in estradiol metabolism; reduce mean concentration, and pulse amplitude and frequency of luteinizing hormone in treated lambs; increase production of prolactin in F344 rats, but not in Sprague-Dawley rats; decrease glucose and increase insulin production in mice associated to estrogen receptor; increase insulin production in mice and mice pancreatic beta-cells associated to a plasma membrane and independent of ER-alpha; antagonize the thyroid hormone receptor from the Sprague-Dawley rat liver; and decrease thyroid

hormone-induce activity in an amphibian bioassay.

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DR. MORAN: As a summary, we have that BPA binds and interacts with estrogen receptor, androgen receptor, and sex hormone binding proteins; BPA modulates expression of estrogen and progesterone receptor; BPA increases progesterone and decreases FSH-stimulated estradiol production; Decrease aromatase enzyme expression and alter enzymes and transporter proteins involved in estradiol metabolism; reduce luteinizing hormone concentration; increase production of prolactin; decrease glucose and increase insulin production in mice in dependent and independent to the estrogen receptor; and finally, antagonize the thyroid hormone activity.

Thank you.

DR. DONALD: That concludes our presentation summarizing the extensive data on the toxicity of BPA, and on a potential mechanism of action. We'd be happy to respond to any questions or if the Committee would like us to expand on any of the information presented, we'd be happy to do so either now or during the course of discussion.

Thank you.

CHAIRPERSON BURK: Thank you very much. I'll open it to questions from the Committee.

None yet.

Dr. Jones.

COMMITTEE MEMBER JONES: Dr. Li, I'd like to ask just a couple questions of. You didn't mention the in vitro studies in humans, at least I don't think you did, in your discussion.

Can you comment about them I'd be particularly interested.

Well, maybe you could just comment on those in vitro studies.

DR. LI: Just in answer to your question, I'll comment on the human studies -- using humans. In vitro studies in using human tissues. In our literature search we did not find any in vitro studies -- let me go back. There's one study using the human sperm, there are two studies. I think it was summarized in the HIM, but because of a time limit, I did not present it in a slide.

COMMITTEE MEMBER JONES: What I'm particularly interested in is this study that relate -- this in vitro study that relates to sperm. It's a study that -- and I got it through your evaluation here in the report. It says that there's no effect on calcium response to 17 beta-estradiol or progesterone in spermatozoa from healthy donors, suggesting that BPA does not interact with membrane receptors for either of these compounds.

And I'm just interested in that as it relates to the animal data that does show, according to, again, your report, that sperm are decreased in the animal model.

DR. LI: I will have to clarify it. It's the human data. Also, Dr. Farla Kaufman was the leading person in evaluating the human data. I was focusing on the animal data, that's one.

Number two, the animal studies, I'm not aware of in vitro studies that use the animal sperm, you know, comparable to the human study. If you think about to link the two studies together, you've got to have one study using human sperm and another study using animal sperm, right. I'm not aware of any study that used the animal sperm to look at the similar effects.

COMMITTEE MEMBER JONES: So you're saying that they're all in vivo studies in the animals.

DR. LI: Right. The in vitro studies I presented were cells, the Sertoli cells or the Leydig cells in the testis, not the sperm.

COMMITTEE MEMBER JONES: Okay.

DR. LI: I hope I answered your question.

COMMITTEE MEMBER JONES: I have one other question.

In the studies -- in the reproductive studies, again I'm talking about in the male reproductive studies,

it's unclear to me if these studies were looking -- whether most of these studies were looking at male or female reproduction when it came under the male reproductive section in your study?

In other words, it looked to me as though it was unclear whether they were males or females that were, in fact, responsible as far as the reproductive outcome.

DR. LI: So you're asking the reproductive performance endpoint. Basically, there are eight studies, the neonatal ones the males were treated. They were treated pups neonatally, then let the pups grow up in to adulthood, then assess the reproductive fertility or, you know, the reproductive performance. Those studies were clearly male mediated.

COMMITTEE MEMBER JONES: They're clearly male mediated.

DR. LI: Yeah. Now you have the IECB studies. There's one NTB sponsored IECB study. In that IECB study design, you have a section -- you have Task 3. That's a cross-over mating trial. Basically, you have three groups, control versus control, and a second group is mating the treated male to a control female. Then another group treated female mated to untreated male. So that reduction in number of live pups per litter was observed in the second group, when the males were treated mated to

the control female. So that implies at least the reduction is partly mediated through the male repro effect.

Now if you go to the multi-gen studies. Both males and the females are treated. It's difficult to say it's a male or it's a female.

COMMITTEE MEMBER JONES: Okay. Thank you.

CHAIRPERSON BURK: Are there any other questions at this time?

I know you'll all be available when we get to our final discussion. So maybe we'll save questions till then.

The next thing on the agenda is the public comments. And I don't have any cards yet. Yeah, why don't we take a two, three minute pause for us to review the public commenters and try to come up with a plan for how we're going to approach this.

CHIEF COUNSEL MONAHAN-CUMMINGS: Can we make it longer so that the court reporter can have a break.

CHAIRPERSON BURK: Okay. Why don't we make it -- would you take ten minutes?

THE COURT REPORTER: That's great.

Okay, ten minutes for the court reporter

(Thereupon a recess was taken.)

DIRECTOR DENTON: If everyone would take their

seat, we're getting ready to go.

Once again, if everyone would take their seats, we have quite a few individuals who want to comment on this issue, so we'd like to get started.

CHAIRPERSON BURK: Okay. A reminder, please. I've been asked to ask again for those that maybe came late, please turn off your cell phones. Any cell phone will interfere with the microphone systems and we've had a bit of trouble.

Okay, as you heard, we have many blue cards, people who have asked to speak. And we want to be fair to all. I think we had told you previously that we would have ten minutes maximum per person. Although, we have some groups. And within the groups, we would allow you to cede time to each other if that works better, so you could have a total time, but we're going to stick to ten minutes per person maximum.

We have a little warning system here to make that work so Lauren has a color-coded system. Anyway, if the green is up, it means you can keep going. When the yellow comes up, it means there are ten minutes, this is for a group. Orange will be five minutes. And red will mean stop.

So we have one group first. And I would like to call them up and hope maybe they'd come near the front, so

they can use their time more effectively. And in that group is Susan Forsyth, RN, Gina Solomon, M.D., Patrice Sutton, also from UCSF, Lahfat Apatira, I think, Fred vom Saal, Tracy Woodruff. Six people, that means one hour total. And we're hopping to complete that one hour before we take our lunch break.

So again, please speak into the microphone and please introduce yourself when you speak.

Thank you.

DR. SOLOMON: I promise we won't take the full hour. My name is Gina Solomon. I'm a senior scientist at the Natural Resources Defense Council. I'm also an Associate Clinical Professor of Medicine at UCSF in the Division Of Occupational and Environmental Medicine.

And I just wanted to express my appreciation for the very difficult complicated decision you're facing today for reading through all of the extensive materials in preparation for this meeting. And I'm certainly sure that there's going to be a fair amount of muddying that's going to be happening one way or another with all the public comment from both sides.

But rather than sort of getting into that muddying, what I just wanted to do at the beginning was point out one key sort of backstop that I feel like there is in this decision. And that is that the NTP's Center

for the Evaluation of Risk to Human Reproduction looked at the evidence of developmental reproductive toxicity for Bisphenol A. That report was finalized actually after this panel had already decided to prioritize BPA and bring it here. Their final report came out nearly a year ago, and their review took place a couple years ago, so obviously there was some new science, I think you'll be hearing about from our next major speaker Dr. Fred vom Saal. But during the interim, the science on BPA has actually become stronger not weaker.

CERHR found that there is quote "clear evidence of adverse effects"... -- sorry, we're trying to get, I guess, the slides set up.

CERHR found that there's "Clear evidence of adverse effects with high doses of BPA in guideline studies in looking at five developmental outcomes: Fetal death in rats, decreased litter size in rats, decreased number of live pups per litter in rats and mice, reduced growth in rats and mice, and delayed puberty in male and female rats and in male mice."

The NTP cited eight studies showing these effects. And there was quite a bit of consistency in the findings. And you heard about many of these studies again today and additional studies as well.

The effects were found at fairly high dose

levels, but CERHR and also re-reviewed by OEHHA staff, the conclusion was that they're not simply secondary to maternal toxicity. And I actually looked back at the original studies and I was initially confused, because I noticed that many of these studies, and most of the ones we're talking about are the Research Triangle Institute studies by Tyl et al., the study abstracts when you just read those and the conclusions seem to indicate that the developmental effects are only in the setting of maternal toxicity, might not represent true developmental toxicity.

And then when you actually go through and you look at the data in the reports, it's actually quite clear that there are effects in the setting of minimal, if any, maternal toxicity in most of those studies. And that's what the CERHR panel based their conclusion of clear evidence of adverse effects on.

And so I won't get into the details of why that -- you know, that abstracts might not be totally consistent with the results in the tables or in the studies. But these are -- one of the issues with these high-dose studies is that the estradiol control actually -- so their positive control actually only showed an effect at quite high levels 100 micrograms per kilogram per day of estradiol, which means that the animal model was probably relatively estrogen insensitive. And since

Bisphenol A is about a thousands times less Potent than estradiol, you'd sort of predict that the level at which you would have seen effects in these studies based on the positive control would have been in the range of 100 milligrams per kilogram per day, which is right where you actually saw the effects.

And so in looking at the positive controls in these different studies that actually helps give a sense of whether you'd expect to see an effect at the dose levels that were tested, or at what dose levels you might start to see them.

So my basic conclusion here is CERHR looked at these high-dose studies, concluded that there's clear evidence of adverse effects. The language that they use clearly parallels the Prop 65 language, so their criteria were similar to yours. And this panel did recognize CERHR as an authoritative body. So in making your decision, it's just, you know, something that I encourage you to think about. And I very much encourage you to list BPA as a developmental toxicant in its own right, based on the data that's before you and consideration of panels that have come before.

Thanks, and I'll cede whatever is remaining of my time to the rest of the speakers.

Yes.

COMMITTEE MEMBER ROBERTS: You were quoting from the CERHR about the clear evidence?

DR. SOLOMON: Yes.

COMMITTEE MEMBER ROBERTS: If I can ask, I'm looking at their publication. And in their publication Birth Defects Research Part B page 329, what they have under summary and conclusion of developmental hazards, "There are sufficient data to conclude that Bisphenol A does not cause malformations or birth defects in fetuses, exposed during gestation at levels up to 640 milligrams per kilogram per day rather than the 1,000 milligrams per kilogram per day mice. This is consistent with the lack of malformation seen in offspring of multi-gen. There are sufficient data to conclude that Bisphenol A does not alter male or female fertility in rats after gestational exposure."

The next paragraph goes, "There are sufficient data to conclude that Bisphenol A does not change the age of puberty in male or female rats."

Next paragraph, "There are sufficient data to conclude that Bisphenol A exposure during development does not permanently affect prostate weight in adult rats or mice. And then the final paragraph, there are sufficient data to suggest that developmental exposures to Bisphenol A causes neural and behavioral alterations related to

sexual dimorphism in rats and mice.

DR. SOLOMON: Are you -- I'm reading from the final report.

COMMITTEE MEMBER ROBERTS: I'm looking at the peer-reviewed publication.

DR. SOLOMON: Because, yeah, it's the final -- I was reading from the final report where on page -- I assume that's also in the binder, but --

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER ROBERTS: Okay, all right.

DR. SOLOMON: And it says on page seven, "The NTP finds that there's clear evidence of adverse developmental effects at quote 'high doses' of Bisphenol A in the form of fetal death, decreased litter size, or decreased number of live pups per litter in rats greater than or equal to 500 milligrams per kilogram body weight per day, and mice greater than 875 milligrams per kilogram body weight per day...", et cetera. And there's a paragraph that continues with each endpoint, so that's page seven of the final.

There are other -- you know, there's a lot of conclusions as you saw in the CERHR reports on you know, lots of different endpoints. So I was just focusing on the ones where they actually found clear evidence. There were a lot of others where they find either some evidence

or no evidence.

COMMITTEE MEMBER ROBERTS: Okay, that explains it. Thank you.

CHAIRPERSON BURK: Okay, thanks.

DR. SUTTON: Hi. Thank you. My name is Patrice Sutton. And I'm a research scientist with the UCSF Program on Reproductive Health and the Environment. And I support the conclusions that Dr. Solomon just made. And I'm going to cede my time, please, to Dr. vom Saal.

MS. APATIRA: My name is Latifat Apatira. I'm a fourth year medical student at the University of California, San Francisco. I believe the science supports the listing of BPA and I would like to cede the rest of my time to Dr. vom Saal.

DR. vom SAAL: Thank you. It's a pleasure to be here and have an opportunity to present some information about Bisphenol A to you.

(Thereupon an overhead presentation was Presented as follows.)

DR. vom SAAL: This is a chemical that I've been conducting research that's funded by NIE, Nation Institute of Environmental Health Sciences for about 13 years.

Could I have the next slide?

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DR. vom SAAL: The NIEH ran a meeting on

Bisphenol A a few years ago and a group of experts got together. Could I have the next slide.

--o0o--

DR. vom SAAL: And one of the important things that came out of this meeting was that we felt that the data on exposure was really not able to lead to the conclusion that human exposures were primarily, and in particular most people have said virtually all exposure is through food and beverages. We did not feel that the data justified that conclusion, and, in fact, really wondered how many other sources there were.

The other thing that there was consensus about and also the FDA Science Advisory Panel reached consensus on this, that there is a very marked difference between fetuses and infants and adults, in terms of metabolism. We all know babies are not little adults in their metabolic capabilities.

Could I have the next slide.

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DR. vom SAAL: These predictions of where -- you know, that food would not be the only source of human exposure - it certainly is a major source - was really verified in a recent publication from the University of Rochester Stahlhut et al., which they basically found from thousands of data points in the National Health And

Examination Nutrition Study, that fasting time was not predictive of a dramatic decrease in BPA.

And so clearly, in thinking about exposures to this chemical there are eight billion pounds of this made a year. We don't know where it's put, what products it's in. And without that information, we have a very difficult time figuring out where all the BPA that's found in people is coming from.

Next slide.

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DR. vom SAAL: So there are about a dozen studies using a variety of techniques, not the immunoassay or the enzyme link assay, that show that everybody that's looked at has biologically active Bisphenol A in their blood in the part per billion range. And the question is, if it's so rapidly cleared, how can it always be found at reasonably high levels?

These are levels that are substantially, and at least ten fold or greater, higher than levels that are in animals that cause harm.

Next slide.

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DR. vom SAAL: And again, this was mentioned before in the proceeding talks, that we did this study in my lab. If you inject or feed a newborn, it really

doesn't matter. So some of the data I'll present to you is injecting during early development or feeding, because the baby, once it gets into a fetus or a newborn, it really doesn't matter how it got there, because they do not have the metabolic capability of an adult to engage in the more rapid first-pass metabolism.

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DR. vom SAAL: So as was pointed out, this has been known for over 70 years to be a synthetic estrogen with full efficacy of estradiol and it acts similar to DES.

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DR. vom SAAL: And one of the things that we reviewed a couple of years ago is that if you look at the activity in human and animal cells, they, first of all, are very similar to each other, for both estradiol and BPA. And the activity level in cell culture is below the biologically active level of Bisphenol A, that is found in all of the human studies that have been done, blood levels of unconjugated BPA.

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DR. vom SAAL: And one of the important features,

some data on binding to sex hormone-binding globulin was presented. And the binding affinity for SHBG of Bisphenol A is relatively high. So relatively a small amount of it is actually bound. And therefore, a greater amount of it is biologically active and can transport across the placenta. Whereas was pointed out, it's in the classical nuclear receptor family. It binds to estrogen receptors and activates responses. And androgen and thyroid receptors it inhibits them.

And I'll mention a little bit of data showing that not only does it alter gene activity, but it permanently programs gene activity during critical windows.

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DR. vom SAAL: An important point is that the consensus of the people at the NIH meeting was that the very low dose effects in the low part per trillion or sub part per trillion level of BPA concentration were mediated through this newly discovered estrogen receptor associated with the cell membrane that activates enzyme cascades that essentially act as super amplifiers, where you can take a single binding event and amplify that literally hundreds of millions of times, leading to changes in cell function. And in every study that's been done estrogen, estradiol

and BPA have equivalent potency via this receptor system, unlike the nuclear receptor system where at ER-alpha Bisphenol A is about a thousand fold weaker than estradiol.

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DR. vom SAAL: An example of this was published in the Journal of Endocrinology by Zarnosky showing that in terms of stimulating neurons in the cerebellum below a part per trillion, you could see activation of a MAP kinase, one of these enzyme cascade pathways. And you saw that up to through the part per billion range. And then above it -- or part per trillion range, and then above that the effect went away and then started to come back again. You get these very strange non-monotonic functions out of these chemicals at very, very low doses. The low-dose effects are not predicted if you only look at high doses.

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DR. vom SAAL: So I want to cover a little more about neural effects.

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DR. vom SAAL: And again, I just want to bring

back the concept that the rodent is born in a immature state at about 17 to 18 week equivalent of human gestation. And sexual differentiation of the brain and reproductive system is occurring through the first couple of weeks postnatally.

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DR. vom SAAL: So it's equivalent to prenatal for the human. One of the areas of greatest interest in research going on in my lab concerns the locus coeruleus and substantia nigra. These are areas that are ascending adrenergic systems that regulate motor behavior.

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DR. vom SAAL: And also in the hypothalamus. But one of the things you see is structural changes in the brain, as well as an increase in activity due to fetal exposure and -- or the equivalent of the fetal period to Bisphenol A and the animals are hyperactive, and also show learning deficits somewhat like ADHD.

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DR. vom SAAL: And the NTP said there is a high consistency in that Bisphenol A during early fetal life or during fetal life and neonatal life leads to a loss of sex

differences, normal gender differences are lost, both in terms of structural events and functional in terms of behavior.

So in this particular study by Kubo, and they have five or six papers out like this, you see the males are feminized by Bisphenol A and the females are masculinized.

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DR. vom SAAL: In this study, by Beverly Rubin, what they showed is in the area of the brain that controls the preovulatory gonadotropin surge that regulates ovulation, you see a masculinization of this area, in terms of the ability to produce adrenergic neurotransmitters. And so that the females become masculinized and their estrous cycles are disrupted. They also reported that.

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DR. vom SAAL: And here is an example of a stress response system, so it's not just reproductive events, you see changes throughout the brain, where normal gender differences are not seen after very low dose or even moderate dose Bisphenol A exposure during early life.

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DR. vom SAAL: And this is a very recently published paper from monkeys, where the mother was administered just prenatally BPA. And not only did the behavior of the male baby get dramatically changed and feminized, but the behavior of the mother towards the babies also changed.

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DR. vom SAAL: And we had previously reported - these were studies done in my lab - that administering a low dose of Bisphenol A to a pregnant female decreased her maternal behavior towards her babies. So the mother is a factor in these kind of outcomes, but they're also direct effects on babies.

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DR. vom SAAL: And then this is not a developmental study, but it's kind of interesting, because they're data from rats, and then very recently monkeys - this came out after the NTP report - showing that the brains of animals exposed to BPA look like those of senile adults, because the connections between dendrites and axons are reduced by loss of dendritic spines where the connections occur. And this is something that occurs

during senility. This occurs at very low doses.

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DR. vom SAAL: Okay. And now I want to cover just a few female reproductive events.

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DR. vom SAAL: So this group at Tufts has a whole series of papers they published. And fetal exposure to Bisphenol A causes hyperplasia of the ductile system. And in the terminal end buds, where you find cancer formation, you have genetic changes and structural changes that are indicative of cancer.

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DR. vom SAAL: And another group Coral Lamartiniere's at Alabama has now published a couple of papers showing that in rats you've got the same types of outcomes, in terms of structural and genetic changes. And then you also, if you give a cancer-inducing agent, DMBA, you see BPA exposure lactationally or during after-birth, leads to an increased probability of developing tumors.

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DR. vom SAAL: And in addition to effects on the

mammary gland, as was mentioned before, there are effects on puberty. And we first found this back in the nineties and published this in Nature.

This represented a total of about 450 animals in these studies that we did. Some people say they're very small. This certainly was not.

And what is important about this is that in the mouse, a vaginal opening is not an indicator of ovulation, which it is in the rat, by the way, it's more analogous to adrenarche, and is, in fact, under androgen control. And the epidemiological studies on puberty in humans look at the onset adrenarche and then ovulation. And this is, in fact, a very good model for that where we see that the animals are starting puberty at the same time, but ending earlier, if they're ovulating earlier. If they were exposed to an extremely low doses of Bisphenol A just as fetuses through oral feeding of the mother.

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DR. vom SAAL: And then a study just came out that basically replicated this in the rat. They just injected newborn rats on Day 1 and 2 postnatal, and then Bisphenol A at the low dose went into puberty earlier, just the way the positive controls two different, agonists, estradiol benzoate and PPT cause the same thing.

In addition -- and the next slide.

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DR. vom SAAL: -- these animals later on went into early reproductive senescence. They ceased cycling at a very young age. You know, well before they would normally -- animals wouldn't begin to show cessation of cycling till 9 to 10 months.

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DR. vom SAAL: Okay. And then getting into the male.

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DR. vom SAAL: People have talked about the prostate, which develops as buds outgrowing from the urethra, about the 11th week of gestation in human fetus and towards the end of pregnancy in the rodent.

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DR. vom SAAL: And looking at one of these buds. And again not using conventional staining techniques, hematoxylin and eosin, but if you use immunostaining for specific cell types and cell proliferation, you can see that the target of ten microgram per kilogram dose of BPA or also .1 microgram per kilogram dose of either

ethinylestradiol or DES doubled the rate of proliferation of the basal cells, which are implicated in the development of prostate cancer.

And then Ogura showed that in adulthood basically basal cells in these ducts were showing squamous metaplasia. Again, he couldn't reveal that with H&E staining, only with immunostaining for cytokeratins like we did.

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DR. vom SAAL: And now we have seen that a hundred percent of these animals, just like Ho has already published, show early-stage prostate cancer, PIN lesions, prostate intraepithelial neoplasia.

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DR. vom SAAL: And so what you have is very interesting progression. We and Gupta have shown increase in androgen receptors, which means that these cells are hyper-responsive to androgens.

The basal cell, which is the stem cell, is hyperplastic and metaplastic. And then we think is the transition cell into neoplasia.

And Ho clearly demonstrated that there are epigenetic changes associated with cancer transition.

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DR. vom SAAL: And one important thing is that there were two studies that reported no effects on the prostate, both of them were rejected as inadequate by the CERHR panel, due to the fact that they also showed no effect of DES, the positive control. And so the positive controls, as Dr. Solomon pointed out, are really critical to think about, in terms of evaluating whether a study is a valid study or not.

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DR. vom SAAL: Here's an example where Bisphenol A reduces sperm production in vivo in rats. And the question that asked about direct effects on sperm versus in vivo, remember the sperm are connected with cytoplasmic bridges to Sertoli cells and are really under the control of Sertoli cells. So when you take sperm out of that nurse situation, you really see very, very different things.

And so, what is interesting about this study is that Ashby tried to do a follow up to it. And I think you can see that what happened in his lab is his control animals were abnormal. And this really suggests that the laboratory was contaminated because the only difference

between the two experiments was not in the treated animals but a failed control.

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DR. vom SAAL: And many of the negative studies that exist were conducted with a kind of strange rat-bred selectively bred over 50 years by Charles River, called the CD(SD) rat. Jimmy Spearow from the California EPA wrote a White Paper on this or a commentary for the U.S. EPA on this. And virtually all the studies except for this one recent one by Lamartiniere's group showing that they do exhibit cancer. But every other study done with this has failed to see any kind of low-dose effect with this relatively insensitive model.

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DR. vom SAAL: So just to cover one last set of things I thought you'd be interested in.

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DR. vom SAAL: One of the things that's been seen in a number of studies now is that prenatal exposure to Bisphenol A programs postnatal increase in body weight.

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DR. vom SAAL: A study just came out in Environmental Health Perspectives following up on this, and showing that there's a permanent change in gene activity in the white in the abdominal fat pads of mice, due to developmental exposure to Bisphenol A. And these animals that have this abnormal gene activity, had a three-fold increase in abdominal fat, relative to control animals. So there's really a dramatic impact on fat. And these particular genes control lipid up take into the adipocytes.

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DR. vom SAAL: And the fact that Bisphenol A can alter epigenetic programming was demonstrated by Dolinoy a couple years ago, where they took a mouse with a retrotransposon, a gene spliced into the animal, that if it's demethylated, and therefore active, then this gene causes obesity and a coat color change.

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DR. vom SAAL: What they demonstrated was that Bisphenol A led to a gene where there were no methyl groups available as opposed to the gene being normally silenced by being methylated. So this is a clear example of epigenetic programming and permanent silencing or

activation of genes that totally alter the life history of the animal.

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DR. vom SAAL: Another critical thing is that at very low doses, you can get permanent programming of the liver enzyme activity. And this particular set of oxidation controlling enzymes is of really tremendous interest due to the next finding.

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DR. vom SAAL: If you're aware that the Journal of the American Medical Association published a paper based on the National Health NHANES data set, and found that the same kinds of enzymes were altered as a function of how much Bisphenol A is in the body. And similar to animal data, you see hyperinsulinemia associated with hyperglycemia and insulin resistance.

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DR. vom SAAL: And not surprisingly, the animal -- the humans in this -- you found an association of Bisphenol A with diabetes and heart disease. And the important take-home message from this is anything that adds Bisphenol A to the human body increases risk. Any

increase in Bisphenol A will increase risk of these diseases.

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DR. vom SAAL: So this is my final slide. If you look at the kinds of findings that I just covered in relation to animals, and then you look over on the right side and say here are all these human health trends that are changing over the last 50 years and still changing, and that isn't to say that Bisphenol A is the only cause of them. But the increase in things like uterine fibroids and polycystic ovarian disease and miscarriage and decrease in sperm count and hypospadias increase, these are events that have been increasing since Bisphenol A went in 1970, from 50 million pounds to today, to about eight billion pounds of use in products. And it does suggest that this is a chemical that we need to be concerned about.

I'm happy to answer any questions.

COMMITTEE MEMBER KEEN: Well first, thank you for your presentation. It's, of course, hard to critically evaluate unpublished data and other information that we're seeing for the first time today.

With that aside, you paint what may be a complicated picture for us. Because what you suggest are

maybe a trimodal response effectively to Bisphenol A, where you have very bad effects potentially at parts per trillion. Parts per billion it gets a little bit better. Parts per million maybe it gets worse again.

But to take it at its extreme, if one accepts that as a correct hypothesis, given the NHANES data, there's no such thing as an unexposed BPA, so doing human epidemiology studies becomes actually impossible, because that's kind of the conundrum we have -- at least that I have right now, as I look at the human data. And it says well, there really isn't much of an effect, but if we set the bar that we're seeing, the initial wave of negative effects of PPT, then the natural conclusion, based on the fact that's well over 95 percent of the U.S. population is way, way past that.

So can you help me with this, because I mean I'm winding up with -- you're basically telling me -- I mean, one interpretation of that would be, you can't do a study with humans because there's no such thing as a quote, "a control group non-exposed."

Is that correct?

DR. vom SAAL: You are absolutely correct. And given the animal data -- and again, these cell culture studies indicate that at the cellular level, there's no difference in response to Bisphenol A between rat, mouse,

and human cells. There are some pharmacokinetic differences, but they're not anywhere near great enough to account for the effects that you're seeing down in the part per trillion range.

And given that the CDC is telling us that this is in everybody's bodies, and the Stahlhut data are saying there's constant exposure, and it's not just from food. We really do need to get a handle on where the exposures are coming from. And I think one of the greatest public health achievements was getting lead out of gasoline, because it had such a dramatic effect on blood lead levels, but it didn't completely eliminate them. And there's still concern over residual levels.

I think if we could get Bisphenol A out of some of the worst case products, such as cans where there was a 50 percent drop in exposure in Japan associated with changing the can lining away from Bisphenol A to polyethylene terephthalate. And that's published and there are multiple data sets out on that.

There is an opportunity to have a significant impact. It clearly is not going to totally eliminate it, but anything we do to bring down exposures is obviously beneficial, but we have a terrible problem in terms of epidemiological studies, if everybody is exposed at levels that all of the research from NIH-funded research says is

at a level that can cause adverse effects. You are absolutely correct.

Thank you.

(Thereupon an overhead presentation was Presented as follows.)

DR. WOODRUFF: Good morning. Thank you, Fred for that presentation. And Fred presented a lot of data that has been --

CHAIRPERSON BURK: Would you introduce yourself, please.

DR. WOODRUFF: Oh, I am sorry. My name is Tracey Woodruff. I am an associate professor at the University of California, San Francisco in the Department of Obstetrics, Gynecology and Reproductive Sciences. I'm also the director of the Program on Reproductive Health and the Environment.

And today, I'm going to focus primarily on exposure to BPA, and primarily prenatal exposures to BPA. And while Fred presented a significant number of studies that have been published in the literature, some of them have been published since the NTP report and also since the development of the staff document that you have, I will also be talking a little bit about some of those studies, but also some of the unpublished literature from our own experiments at UCSF.

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DR. WOODRUFF: So as has been pointed out, BPA are -- I'm going to talk a little bit about BPA levels in the U.S. population, though this has been reviewed quite extensively already. I'll talk a little bit more about BPA metabolism, and also BPA metabolism in the context of it being an important determinant of fetal exposures. And then talk a little bit about BPA levels during pregnancy.

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DR. WOODRUFF: As has already been pointed out, there's ubiquitous exposure to BPA in the U.S. population. As data from the CDC NHANES shows, about 93 percent of the U.S. population has measurable levels of BPA in their bodies, as shown from CDC.

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DR. WOODRUFF: And it has also been pointed out that pre-term infants can have significantly higher BPA levels, as from a study that was published by Antonio Calafat in Environmental Health Perspectives.

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DR. WOODRUFF: And as Dr. Vom Saal also pointed

out, while BPA levels can be mitigated by fasting somewhat, we also know from this recent study that was published by Stahlhut in Environmental Health Perspectives, that there are other significant contributors to BPA exposure.

And I think the take-home message from this, as he also pointed out, is that while BPA can be rapidly cleared from an individual dose, upon exposure, that there are so many numerous exposures in the population, that essentially exposure to BPA is chronic.

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DR. WOODRUFF: So what about exposures to the fetus, which is one of the primary considerations in the deliberations today, in terms of looking at developmental effects on BPA?

Some of the important determinants of fetal exposure are whether it can cross the placenta. And animal studies do show that BPA can be transported through the placenta and accumulate in the placenta and in the fetus, such that levels can surpass maternal levels shortly after dosage. And this has been reported on and discussed in the NTP report.

So BPA exposure to the pregnant woman can result in transfer of BPA across the placenta. And then there's

another important factor in the levels that are experienced by the fetus, and that is the ability of the fetus to conjugate or detoxify the BPA. And this has been shown to primarily happen through the UGT pathway, which has also been discussed this morning.

An important feature for fetal exposures is that glucuronidation is anticipated to be substantially reduced in the undeveloped fetal liver because of limited or absent UGT activity.

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DR. WOODRUFF: And just to show a more simplified version of the graphic from this morning, unconjugated BPA, which is considered to be the more biologically active form of BPA, is conjugated through the glucuronyl transferase system into BPA glucuronide in the liver.

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DR. WOODRUFF: So this is some data that we have from a collaborator, Dr. Stephen Strom at the University Pittsburgh, looking at the ratio of fetal to adult levels of the UGT isoforms that are considered to be most -- likely to be most critical in glucuronidation of BPA in the liver: 2B7, 2B17, and possibly 2B15.

2B7 and 2B17 are similar to the isoform that has

been shown to glucuronidate BPA in the fetal rat liver UGT 2B1. And what this slide shows is it's a comparison of the UGT 2B7, 2B1 -- oops that should be 17, and 2B15. Those are mislabeled. The ratio of what the levels in the fetus are -- the fetal liver compared to adult livers. And as you can see from the axis on the Y axis, that the levels in the fetus -- fetal liver are anywhere from one to eight percent of that seen in adults. So the levels of the UGT are significantly lower.

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DR. WOODRUFF: And as shown in a study published by Schoenfelder in 2002 that there is levels of unconjugated BPA that have been measured, both in the mother, but also in the newborn infant, showing that the newborn infant does carry levels of unconjugated BPA in their bodies.

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DR. WOODRUFF: And this is some data from a study that we are doing at UCSF. It's from women who come to one of our clinics at UCSF for pregnancy terminations. And we have collected biological samples, both from maternal serum and from the amniotic fluid. And what this shows is the levels of unconjugated, conjugated and total

BPA measured in the amniotic fluid and in the maternal serum.

Again, I point out the very first part, which shows the unconjugated levels of BPA, which again is expected to be the more biologically active form of BPA. And as you can see, that there are significant levels of unconjugated BPA in the amniotic fluid. And what we have been finding is that it's higher than maternal serum. I would point out this is consistent with what we expect from placental transfer and the lower levels of UGT in the fetal liver.

The amniotic fluid has a contribution both from the fetus itself excreting the BPA, and also possibly from placental transfer. But also importantly the amniotic fluid is a source of exposure to the fetus as the fetus does ingest amniotic fluid during gestation.

So either way, when we find unconjugated BPA in the amniotic fluid, it means that it's a source of exposure to the fetus.

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DR. WOODRUFF: And just to reiterate what Dr. Vom Saal pointed out, is that while most of the studies on BPA are from rodents or mice, that the period of development of mice is somewhat different than the period of

development for humans in terms of the actual timing of birth. So human gestation goes up to about 40 weeks. This is equivalent to both prenatal gestation for the mice and also postnatal growth up to about Day 50. So any experiments done in mice from prenatal or up to postnatal day 50 is equivalent to prenatal experiments in humans.

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DR. WOODRUFF: So just to conclude, BPA is present in almost everyone in the U.S. It can cross the placenta. The fetus has limited capacity to conjugate BPA. And thus, we have to have some concern about fetal exposures to BPA particularly for the unconjugated form.

Thank you.

CHAIRPERSON BURK: Any questions?

COMMITTEE MEMBER KEEN: Yeah. Setting aside the conundrum that may be the PPTs and not to cause a problem, the critical question it seems from your work, since you have almost two-fold differences in unconjugated/conjugated in the amniotic fluid, are you seeing any association with pregnancy complications?

DR. WOODRUFF: Well, the focus of this study, to date, has been to focus on the PBPK, essentially the kinetics of the BPA exposures. We have not -- we are not focusing on particularly on pregnancy complications.

Clearly, that's a very important question, because as you've seen from some of the studies, there has been raised this issue about looking at pregnancy exposures to BPA and what might be some of the relationship with some of the pregnancy outcomes we're interested in, but we haven't gone to that next step yet.

COMMITTEE MEMBER KEEN: Yeah, I mean not to put too fine a point on it, I appreciate where your focus is, but have you or have you not seen an association with complications?

DR. WOODRUFF: We haven't looked at that, so I can't say whether we have or not. I'm sorry. That wasn't clear.

COMMITTEE MEMBER HOBEL: Yeah, very interesting information.

CHAIRPERSON BURK: Speak closer to the mike.

COMMITTEE MEMBER HOBEL: In terms of the pregnancy terminations, you didn't have any gestational age listed?

DR. WOODRUFF: I'm sorry. I forgot to mention that the pregnancy terminations occur between 16 and 24 weeks of gestation.

COMMITTEE MEMBER HOBEL: And did you look at the change over gestational age in terms of the amount of free?

DR. WOODRUFF: We haven't -- that was from nine samples that we have. And we actually have a number of samples that we are currently analyzing right now. So I wouldn't say there's enough data to get a completely clear picture on what might be the gestational changes in BPA in terms of the unconjugated versus the conjugated levels. But clearly, that's a very important question that we're going to be investigating.

COMMITTEE MEMBER HOBEL: Yeah, because with maturation of the fetus and changes in the gestational age, the amount of free should decrease with time.

DR. WOODRUFF: Right. Possibly. I mean, the UGT enzymes that I showed that were also looking at the enzyme levels in the fetus -- fetal liver compared to the adult livers, those were also from a similar gestational age time period. And again, we will also be looking at that as well in terms of both the capacity of the fetal liver to metabolize the enzyme as well as the levels in the fetal liver.

DR. WOODRUFF: Thank you.

CHAIRPERSON BURK: Thank you.

Thank you.

MS. FORSYTH: Thank you. My name is Susan Forsyth. I'm an intern at the NRDC, and a Master's student at UCSF. I have been a nurse for the past 17

years and I am currently a labor and delivery nurse in the East Bay. I am also the mother of a five year old girl, my daughter Anna.

I have looked at some of the science around BPA and I have become very concerned about its toxicity. It appears to be a reproductive and neurologic toxicant. And it is being given by unknown parents in the form of toys, bottles, and food to their children, thinking that they are giving their children a safe object. I know this, because I gave my own child bottles that had BPA in them.

I feel terrible that I exposed my sweet girl to this endocrine disruptor reproductive toxicant and neurologic toxicant. I wish I had known.

Every day at work I see new parents holding their infants for the first time, anxious to do everything they can to keep their babies safe.

Please give them access to this information, so that they are able to do that. Please list BPA. Thank you very much.

CHAIRPERSON BURK: Thank you. So does that conclude all the presentations from your group?

MS. FORSYTH: I believe so.

CHAIRPERSON BURK: Good. Thank you. The next group has asked for 70 minutes. So I think we should probably take our lunch break now. What would be a

reasonable amount of time?

Okay, 1 o'clock.

Carol Monahan-Cummings has something to say.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just a quick reminder to the members of the Committee and others in the audience that the Committee is supposed to deliberate on this in public and together. And so please don't discuss the chemical that's before you today or have side discussions with other individuals.

If you do happen to have a discussion, you'll need to disclose that when you come back.

Thank you.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

DIRECTOR DENTON: It's time to get started. All the panel members are present. And so I'll turn it over to Dr. Burk.

CHAIRPERSON BURK: We will continue with the public comments. And we have next a group of seven individuals speaking as a group. So again, we will follow the same rule of a maximum of ten minutes per person or they can recombine, if they wish, to a total of 70 minutes. We'll use our same timing system.

In this group are Caroline Silveira, the Grocery Manufacturer's Association; Stan Landfair, American Chemical Council; Steven Hentges, American Chemistry Council; Rochelle Tyl, RTI International; Jay Murray, Murray & Associates. Arthur Lawyer, Technology Sciences Group; and William Hoyle, NAMPA.

So again, whoever goes first, please introduce yourself, because people are listening out there.

Speak into the microphone.

MS. SILVEIRA: Thank you. My name is Caroline Silveira. I represent the Grocery Manufacturers Association. GMA represents the world's leading food, beverage and consumer product companies. GMA promotes sound public policy, champions initiatives that increase productivity in growth, and helps to protect the safety

and security of the food supply through scientific excellence.

I'm here on behalf of GMA to emphasize the importance of BPA to the food industry and consumers in California. I'm not here to talk about the science about which you will subsequently hear from other experts.

I am asking this committee to please get it right on the science, applying the weight of evidence approach, because this substance is that important in the safety and quality of our food supply.

BPA allows for the production of safe, technologically effective, and commercially acceptable packaging that is essential for food safety and quality. Current exposure levels of BPA are safe for consumers and the environment as demonstrated not only by repeated testing and review by qualified experts, but also by the history of over 60 years of commercial canned food safety.

I would like to bring to the DARTIC's attention BPA's critical function in protecting the integrity of certain metal-packaging components. While OEHHA's May 2009 report mentioned that BPA is a component in epoxy resins that coat metal products, including food cans, it does not convey the importance of BPA's role.

The DARTIC should be aware that canned coatings are necessary to protect public health. Without them,

interactions between the metal and the canned contents over time leads to corrosion and contamination of the food by dissolved metals and to formation of container defects that allow entry into the product of micro-organisms that causes spoilage and illness.

The use of protective can linings slows down the rate of these interactions so much that modern canned foods, even high acid foods like fruits and vegetables, can be counted on to retain their nutrition, quality, and consumer acceptability for years under a wide range of environmental and handling conditions.

Acidic foods in thermal processing present particular challenges. Although all major coating and can manufacturers are working continually to research and development new coating chemistries for commercial food applications. Epoxy coatings, containing BPA, still have unparalleled performance across a wide range of critical parameters, including toughness, adhesion, formability, and resistance under high-temperature processing conditions.

Because metal packaging enables a significantly longer shelf-life than other kinds of packaging, canned goods are the mainstay for providing nutritious, economical food around the world, and for special programs, for example, USDA's Women, Infants and Children,

otherwise known as WIC, assistance program food pantries, disaster relief, special military rations, et cetera.

Again, epoxy coatings have been used safely to protect the world's food supply for over 60 years. Listing of BPA is unwarranted, would mislead and unnecessarily alarm California citizens and would compromise the availability of safe, affordable, and nutritious foods.

Thank you.

MR. LANDFAIR: Thank you. My name is Stanley Landfair. I'm with the law firm a McKenna, Long & Aldridge. Could we have our first slide, please?

(Thereupon an overhead presentation was Presented as follows.)

(Thereupon the phone rang.)

MR. LANDFAIR: Take that for me, would you?

(Laughter.)

MR. LANDFAIR: There's a story that Ronald Reagan did that when he was President and he was speaking before a trade association. And he deliberately had someone call when he was at the lectern. And when someone came with the phone, he said, "You tell them I'm busy. I'm speaking to some very important people."

(Laughter.)

MR. LANDFAIR: Thank you for having this meeting.

Thank you for the opportunity to speak before you. And thank you in advance. Thank you. I trust you've had the opportunity to read our comments, which we acknowledge were very, very extensive. The extensiveness of our comments reflects the extensiveness of the data and the seriousness of this issue before you.

We want you to know, if you don't, that we asked for this meeting to be held in this format. We thought it was important to the public that we hold a meeting where we could devote exclusive attention to this chemical, because we cannot deny that there is controversy about it, and that there is a great deal of data.

May I have the next slide, please.

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MR. LANDFAIR: Do I do this?

And now I think the hard work is about to start. You have heard a very good, what I'll call, a catalogue of potential effects from the published data, from the OEHHA staff. We think it's comprehensive. And you have also heard a very comprehensive or very sincere, I think, statement from some people who very desperately would like to see this chemical listed under Proposition 65.

But we are going to try to be focused. And what we're going to ask you to do, at the end of the day, is to review the data and to --

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MR. LANDFAIR: -- apply the Proposition 65 standards for listing.

Without doubting anyone's sincerity, the conclusion of the presentation we heard before lunch was that all of the data suggests that BPA is chemical with which we need to be concerned.

And with all respect, that's not the standard and that's not what we're here for. We need to examine all of these data. We need to do it in a systematic way to make a regulatory decision.

So in our presentation, as we have in our comments, we have tried to present for you a paradigm, a way to sort through all of this data and come to a rational conclusion that squares with the regulatory criteria.

So let me introduce our speakers in that regard and see how they fit into this plan. Our first speaker is Dr. Steven Hentges. Steve works with the American Chemistry Council. And he's from the east coast, but we'll forgive him for that, because he got his Ph.D from Stanford. So he's come to speak to us on that.

He's spent ten years studying the physiological and toxicological effects of BPA. He knows the database. He's going to focus his remarks on the metabolism and the

pharmacokinetic data. Because in our view, it's absolutely crucial that we understand the pharmacokinetics, if we are to sort out which data actually can support a regulatory conclusion either way.

Our next speaker will be Dr. Rochelle Tyl. You've heard Dr. Tyl's name mentioned. And if you've reviewed the materials, then you certainly know who she is. She is the principal investigator and the principal author of the studies of one generation, two generation, and three generation studies. She is not here as an advocate. She is here to talk to you about her data and to be available to you to answer questions about her studies.

These are the foundational studies. We refer to them in our comments as the conventional data. They are the basis for every NOAEL for this chemical that has been set by any regulatory agency that has set one. And as one agency referred to her two generation mouse study, it represents the gold standard. We're going to ask you to pay close attention to the conventional studies.

And then, as you go back to the catalogue of potential effects, see which data actually can support a regulatory conclusion that BPA actually causes any one of those effects.

In that regard, we'll introduce our third

speaker. I don't think you need any introduction to Jay Murray. But for the audience, Jay was many years ago a member of this scientific advisory panel. He's an authority in this field. And he will speak to you about, what we call, the non-conventional studies, why they shouldn't be relied upon to support a regulatory conclusion. Just for the same reasons, for the most part, that no other regulatory agency in the world has relied on these data thus far.

And in conclusion, Jay will attempt to make the comparison for you to apply these data against the regulatory standards that apply here.

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MR. LANDFAIR: Now, if I may. This is the one contribution I will make to this presentation. And, you know, it's almost obligatory in these proceedings that a lawyer remind us of what the standard is, but it's necessary that we all stay on the same page and keep the target in mind.

So if you will oblige me, I need to remind us all what the statute says, in that it's "A chemical is known to cause reproductive toxicity only if it has been clearly shown..." -- this is what we all the clearly shown standard -- "...through scientifically valid testing. Testing that's been conducted according to generally

accepted principles." All three of these concepts are very critical in your examination of BPA.

And if there's any doubt about it or about the standard that we are obliged to follow here, this is the charge from the regulations to the Committee, which recites its obligations.

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MR. LANDFAIR: We've looked further to the Committee's guidance criteria. These are your criteria. We don't need to tell you what they are, but we do want to highlight some of the criteria that we think are important in this decision today. The first of which is that we need to apply a weight-of-the-evidence approach.

You are much better than I to know what the weight-of-evidence approach is. But there are some things the weight-of-evidence approach is not, that are reflected in the comments. We're not simply to count up the studies 170 here, six over here. Therefore, you know, an accountant could do that. But a toxicologist or a scientific advisory panel is what we need here to make the weight-of-evidence calculation.

Biological plausibility is important. We'll ask you to look at the pharmacokinetic properties of this chemical as demonstrated in the various studies, and see if the effects that have been attributed to rats, under

some of these studies, are biologically plausible in humans, given the exposure patterns that occur.

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MR. LANDFAIR: In examining the human data, which may be a moot point here, I think everyone acknowledges that the database for human studies is small, and that the consensus appears to be that there are no findings from the human data that would support a finding of reproductive toxicity under Proposition 65.

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MR. LANDFAIR: But there is one aspect of your criteria, which is very important, which we're going to urge you to apply in parsing all of the data. Now, with respect to the conventional studies, which we think are the more powerful studies that really form the basis of a regulatory conclusion, it has been candented that some of these studies demonstrate reproductively toxic effects.

However, we're going to ask you to keep in mind that never have these effects been observed in the absence of maternal and systemic toxicity.

And when you look at the non-conventional studies, we want to ask you to ask questions concerning the experimental design of these studies, such things as the route of administration, dose response relationships, and see whether these studies, no matter how earnest they

were conducted and how much their principals believe in these studies, whether they really form the basis of a sound regulatory conclusion.

Obviously, we believe they do not.

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MR. LANDFAIR: Finally, just as a reminder, and this did come up in one of the presentations, we had many reference to effects from postnatal exposure. That's not a consideration under the terms of Proposition 65.

Now, if I may introduce our next speaker, Dr. Hentges.

CHAIRPERSON BURK: Before you start, could we just hold for one second for technical issues.

MR. LANDFAIR: Yes.

CHAIRPERSON BURK: But in the meantime, are there any questions?

All right, we'll just wait till they give us the all-clear here.

MR. LANDFAIR: Perhaps, I could take advantage of that lapse of time. I neglected to provide you some of the credentials from Shelly Tyl. And I know that many on the panel know who she is. But I think it will be useful for the record to note that Dr. Tyl is the past president of the Teratology Society. She's also past president of the Reproductive and Developmental Toxicology Specialty

Section at the Society of Toxicology, and she also is an invited member of the United States EPA Endocrine Disruptors Screening and Testing Advisory Committee.

Again, we brought her here as an authority on the data. And we hope that her discussion of those studies will be informative to you and we truly invite you to ask all the questions of her. She's yours.

Thank you.

DR. HENTGES: Is it ready?

Okay. Dr. Burk, members of the Committee, thank you for your time today.

As Stan mentioned, I'll be speaking -- I'm Dr. Steve Hentges at the American Chemistry Council. And as Stan mentioned I'll be speaking to the metabolism and pharmacokinetics of Bisphenol A.

(Thereupon the phone rang.)

DR. HENTGES: I'm not taking calls either.

(Laughter.)

DR. HENTGES: I assume we still have a problem?

I can go? Okay.

You heard a brief introduction to metabolism and pharmacokinetics at the beginning of your day. And you've heard little bits and pieces of it throughout various other presentations. And I'm going to come back and go into a little bit more detail on pharmacokinetics and

metabolism.

And the reason is this, although there are not very many human studies on Bisphenol A. As you've seen and read by now, there's a huge volume of animal studies. They are very diverse. You've probably noticed that already. And in order for you to efficiently sort through these studies and get to the ones that are most relevant for the decision that is in front of you today, I think it's very important to have a good understanding of the basic parameters of Bisphenol A pharmacokinetics and metabolism. And that's what I'm going to try to get to.

There are quite a few studies that examine pharmacokinetics and metabolism. I'm not going to try to go through any of them in detail. There's not time for that. But what I will to do is distill out from those studies a few key points and highlight the implications of why those key points are important for what you're here to do today.

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DR. HENTGES: So let's take an overview of the subject matter. Again, this has been summarized in much more detail in the HID and also in even more detail in the NTP and European Union documents, all three of which hit your mail box with a very heavy thud about a month ago.

The metabolism and pharmacokinetics of BPA are

fairly well studied. We have quite a few studies in rodents, in particular, but we also have some studies in non-human primates. And perhaps most importantly, we have at least four human volunteer studies, as well as other observational studies on humans. Those studies are the ones that tell us directly about how BPA is processed in the human body.

From the human studies, we know that BPA is efficiently converted to non-estrogenic metabolites and rapidly excreted after oral exposure. From the human and animal studies combined, we can see very significant interspecies differences, in particular differences between rodents and humans. And that's very important, because most of the animal studies on Bisphenol A are studies on rodents.

And then finally from the animal studies, we can see very significant route dependent differences, differences between oral versus non-oral routes of exposure.

So taking all of this data together that indicates that metabolism and pharmacokinetic data are crucial for BPA hazard assessment as a way to sort through this very large volume of studies, the very large volume of data and extract out the studies and data that are most relevant for what you're here to do today. And indeed, if

you look in detail at the NTP or the EU reports, that's exactly what they did. They applied this pharmacokinetic data to the large volume of data, in order to sort through it and get to the decisions that they had to make.

And although, I won't pretend to know anything near as much about Proposition 65 as you all do, I wonder if there has been any other chemical or pharmacokinetics that's been as important as in this case.

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DR. HENTGES: Let's turn first to the interspecies pharmacokinetic differences. In humans, and this is coming from human volunteer studies, we know that Bisphenol A undergoes very extensive first-pass metabolism after oral exposure. And that first-pass metabolism dramatically limits the systemic BPA dose. Where that data comes from is again there's been at least four human volunteer studies, the one that is perhaps the most relevant or the most important here is the first one that was published back in 2002. It's Volkow et al., 2002.

And in that study the human volunteers were dosed with a single dose of five milligrams of Bisphenol A. And just for reference for those that adults that works out to about 60 to 80 micrograms per kilogram. And then to put that into perspective, according to CDC's NHANES biomonitoring data, median human exposure to BPA is about

50 nanograms per kilogram per day. So on a relative scale this is a very big dose for people.

And what they found in the study is that even at the T-max, when the maximum amount of BPA metabolites were found in blood, no apparent BPA was found in blood. No free BPA was found, even at the T-max.

From other studies, not this one in particular, but from quite a few other studies, the metabolites that are formed are primarily BPA glucuronide, some BPA sulfate is also formed. And both of those have been tested and determined to be non-estrogenic. And that's a very important point, since as you have seen estrogenicity is suggested as one possible mode of action for Bisphenol A.

The half-life of those metabolites in humans is about four to six hours. They are entirely excreted into urine, and that's also a very important point. And the pharmacokinetic data indicate that there is no potential for bioaccumulation.

Another very important point is that in a very recent study, extensive metabolism has also been confirmed in premature infants. This is a study that was mentioned briefly two or three times, but only very briefly in passing. Probably the most important piece of information that came out of that study, is that that study unambiguously shows that even premature infants have

extensive capacity and capability to metabolize BPA into conjugated metabolites and then excrete those into urine.

It's not a complete pharmacokinetic study. This is more of an observational study. But it did show that the form of BPA that is excreted is predominantly the conjugated metabolites.

In contrast in rodents, biliary excretion is the primary route of exposure -- route of elimination. And what happens then is that the BPA -- conjugated BPA metabolites, once they get back into in the intestine carried there by bile, they are hydrolyzed back to free BPA, where they can be reabsorbed and recycled via enterohepatic circulation. And the result of that is a significantly longer half-life for BPA in rodents and significantly greater systemic bioavailability.

Because of these key differences, extrapolation of any effects in rodent studies to humans would be tenuous. And in particular, effects that are observed in rodent studies are likely to over predict what could happen in humans.

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DR. HENTGES: Turning next to route dependency. Again, as you know there are a very large number of toxicity studies on Bisphenol A. They're very diverse. And one aspect of that diversity is that quite a few

different routes of exposure are used in these studies.

Of course, many of them do use the oral route of exposure, but you'll also find studies with subcutaneous exposure, implanted mini pumps and some studies with I.P. exposure, I.P. injections.

Of these many studies, the ones that use oral exposures or the oral route of exposure are most relevant for hazard assessment. And that's based on a couple of primary points. One is that human exposure to BPA is oral. It comes through dietary sources. For example, migration of BPA from food packaging. And, of course, as we've mentioned, extensive first-pass conversion of BPA to non-estrogenic metabolites occurs quite efficiently after oral exposure.

In contrast, though non-oral routes of exposure exaggerate bioavailability quite a bit. And the reason is primarily because their is no first-pass metabolism. BPA is injected by the non-oral routes. It gets into systemic circulation directly. It bypasses the first-pass metabolic route completely.

And as a result, parent BPA, which is the biologically active form of BPA gets into circulation directly. And the conjugated metabolites are not formed, at least not quickly, and those, of course, are not estrogenic, not biologically active, as far as we know.

In addition, some data shows that additional metabolites can be formed with non-oral routes of exposure. This has been shown in mice in particular. The toxicity profile of those metabolites is unknown, but it appears that oxidized metabolites can be formed with non-oral routes of exposure.

So due to the significant differences between routes -- studies with non-oral routes of exposure are of limited utility and relevance for humans.

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DR. HENTGES: The HID also discussed at length estrogenicity of BPA and that was summarized earlier in the day. Pharmacokinetic data are also relevant here to assess the relevance and importance of estrogenicity. It's well known. As you've heard, that Bisphenol A is weakly estrogenic. That's been demonstrated in quite a few in vitro studies. And estrogenic potency is generally about four to five orders of magnitude below that of estradiol.

It's also notable, just for some context, that Bisphenol A also has lower estrogenic potency than phytoestrogens that are very common in the diet. For example, things like genistein, and other similar components are extensively present in soy.

And if any of you had a glass of red wine with

your dinner last night, you would have ingested resveratrol, which is another estrogenic phytoestrogen which is present in red wine.

However, because Bisphenol A is quickly converted to non-estrogenic metabolites after oral exposure, which of course is the most relevant route for humans, biological plausibility of reproductive or developmental effects in humans through an estrogenic mechanism is limited, and that is because with the oral route of exposure, conjugated metabolites are what go into circulation, not parent BPA.

So weak estrogenic -- estrogenicity of BPA is not really relevant for humans.

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DR. HENTGES: And then finally, I want to touch on one last thing. I'm not going to spend much time on epidemiology studies, but I want to touch on one aspect of pharmacokinetics that is relevant -- as certain most of the Epi studies that exist for BPA.

So as you've heard, most of the epi studies that are available now are cross-sectional in design. And what that means is that the biological samples that were collected for BPA measurement were collected at the same time as the health information.

A serious limitation of these studies is that because humans rapidly eliminate BPA after oral exposure, measurement of BPA in a spot urine or a spot blood sample measures exposure of BPA today basically, but it doesn't really tell of much of anything about exposure far in the past or into the future.

And the result then is that cross-sectional studies cannot determine exposure during the etiologically relevant periods of time, when during the onset and development of disease.

So the cross-sectional studies are really quite limited, just due to that basic study design issue. There was one study that was, again, I think briefly mentioned, which was described as a case control study, but it has the same problem, because the biological samples were collected at a time period which was quite different when, I think it had to do with serial miscarriage, but the biological samples, the blood samples were collected at a time point quite different from when the miscarriages were occurring. So it was very difficult to make any connection between BPA exposure and the health events.

So that's all I had. I just wanted to give you a brief summary of some key points on a pharmacokinetics and metabolism.

Hopefully, those will help you sort through the

many studies on Bisphenol A.

CHAIRPERSON BURK: Thank you. Are there any questions?

Linda Roberts.

COMMITTEE MEMBER ROBERTS: Thank you. A couple of questions. There was some data suggested that after fasting, the level of Bisphenol A didn't drop that far. And I've also seen in our packet of paper that dermal absorption is considered fairly low. Do you have any dermal absorption information?

DR. HENTGES: There's a couple pieces of data. It's not something I'm real familiar with, but my recollection is that dermal absorption has been observed to occur to only about 10 or 20 percent, something in that range, so relatively low. Dermal route of exposure, other than possibly for occupational exposure, and even there, I'm not sure there would be much. It's not likely to be significant for humans, because where we contact BPA is really through our diet.

COMMITTEE MEMBER ROBERTS: There was also on one of the slides this morning an indication that premature infants had a much higher level of Bisphenol A, I believe. And you mentioned that you had some information about premature infants and their metabolism. I was wondering, could you elaborate on that a little bit.

DR. HENTGES: I will. I realize I didn't answer your other question. I answered one of the two that -- the first two, about the longer health half life in humans. That's a statistical analysis coming out of the CDC NHANES data. One limitation of that kind of analysis is that for those participants, those are not controlled dosing. They're not controlled human volunteer studies. So nobody knows for all of those participants what level they were exposed to, what time they were exposed. So it's a little bit difficult to really draw a firm conclusion from it, beyond developing a hypothesis that could be tested in a more appropriately designed study.

On the other hand, we do have human volunteer studies where -- and again, there are at least four of them that I know about where humans are dosed with a specific dose of BPA. It's followed through the body where it goes, what form it's in, when it comes out. So from those, we can get pharmacokinetic parameters. You can't really get them quite the same way from the other study, which is really a statistical analysis.

It's an interesting hypothesis, but it's going to take some other kind of research to really look into that.

And now I've forgotten the other questions you've asked.

COMMITTEE MEMBER ROBERTS: About metabolism by

premature infants.

DR. HENTGES: Right. There's several pieces of data that are relevant there. The one that I think getting right to human infants that's probably most relevant, is a study that was published by researchers from Harvard. I think there was another university. And then also with CDC researchers. And what they did -- what they were trying to do really is just measure or look for exposure of premature infants in neonatal intensive care units. Look at exposure of those infants to BPA.

But what they found along the way, they collected urine samples, which probably can't be real easy to do with a premature infant, they collected urine samples and analyzed the urine for BPA. And they did very careful analysis looking for both free BPA, but also conjugated BPA. And what they found is that in this analysis, more than 90 percent of the BPA was in the form of conjugates.

So what that really says, and again that shows unambiguously, that even premature infants have substantial capability and capacity to metabolize BPA. And the part of that study that I think you did see very quickly. It flashed by at one point, is that the concentration of BPA found in the urine of the premature infants was significantly higher than levels that would be found in the normal population.

So that's not exactly exposure, but it indicates that exposure of these infants was higher than even for a typical adult exposure. So putting that together, even at a relatively high exposure for those infants, they still had ample capacity to metabolize BPA.

Now, that would be consistent with one laboratory Animal study on rats, inconsistent with one on mice. So there's mixed data at the laboratory animal level that I think the human data is what you really want to get to.

COMMITTEE MEMBER ROBERTS: Thank you.

DR. HENTGES: I thought you had another one. Did I get them all?

COMMITTEE MEMBER ROBERTS: No, it was just the two.

CHAIRPERSON BURK: Thank you.

DR. HENTGES: The next speaker will be Dr. Shelly Tyl.

DR. TYL: With a small pause while they make telephone calls.

Good afternoon, thank you for allowing us to talk to you today. You have a very difficult job in front of you.

CHAIRPERSON BURK: Why don't you just wait a second. I won't take it off your time. I just want to make sure that this is working properly for the people

that are listening.

Is it okay?

Thank you.

DR. TYL: Because my name has been invoked a number of times this morning, and it a lot of publications recently, what I wanted to do is come, not as an advocate, but just simply to present the data.

Can I have the slide. Are you guys running it or am I running it?

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DR. TYL: Thank you.

What I thought I would do is go over the five studies that my staff and I have done at RTI with Bisphenol A. I'd like to just indicate that RTI is a nonprofit contract research organization. We celebrated our 50th anniversary in 1958. We're about 80 percent funded federally and about 20 percent funded commercially.

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DR. TYL: We did a one generation -- a somewhat a abbreviated one generation study in mice, because we had done a reproductive assessment by continuous breeding protocol awhile back, when we had that contract. We've got it again, but anyway.

And based on the way the protocol is written, you don't look at the initial parental -- F0 parental animals.

You look at the offspring adults, but you don't look at the parental animals. So they found significant developmental toxicity, that is reduction in litter size of the newborns, but there was no context. That is what was the context in terms of the maternal toxicity. So what we did was we ran a very abbreviated study. It's not designed for short people.

So we ran a very abbreviated RACB study, where we looked at very high doses, because the RACB study ran at high doses and we looked at 5,000 and 10,000 parts per, million about 860 milligrams per kilogram per day. And we went through the same procedure that is pre-breed mating gestation. And at delivery, we looked at the moms, we looked at the dads and we looked at the offspring.

And what we found was, in fact, that there was significant maternal toxicity at both of those doses. This was expressed as reduced body weights, and feed consumption, increased liver and kidney weights and altered histopathology of the liver, hepatocyte hypertrophy of the kidneys, renal tubule epithelial degeneration.

Next.

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DR. TYL: No you skipped one. That's okay.

Thank you.

I can do this.

Okay. The offspring data indicated that only in 10,000 parts per million, there was reduced litter sizes, slightly reduced total live pups per litter. That's exactly what the RACB original study did, but we could put it in the context of maternal toxicity or at least possible.

No other significant effects on reproductive or developmental parameters. The point about maternal toxicity, it's really not that simple. And that is, if it's occurs in the presence of maternal toxicity there is a possibility that, in fact, the maternal toxicity is primary and the offspring toxicity is secondary, but there's really no current way to show it.

So what you have to do is err on the side of caution. In fact, I'm on the a working group, where we're doing seminars across the country at various meetings talking about maternal toxicity versus reproductive or developmental toxicity. The interesting thing is that we only saw these effects at the top dose, the 10,000 parts per million, which there was more profound, if you will, maternal tox. We saw maternal tox at 5,000, but we didn't see any embryo fetal tox.

So the assumption was in lieu of any additional information, it is possible or even likely that the

developmental tox came from the maternal tox. If you impair her liver, if you impair her kidneys, then she's not going to be able to digest the food. She's not going to be able to excrete waste. She will certainly have a -- probably in terms of in utero nourishment of the babies and postnatal nourishment.

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DR. TYL: But the studies that we did start to finish, started with a three-generation study with Bisphenol A. Its dietary study was done in rats. And we ran six dose groups. We ran 30 per sex per dose group per generation over three generations through the adult F3 offspring. And let's examine, this was a guideline study. We did it under the U.S. EPA OPPTS testing guidelines, Office of Prevention -- OPP, Pesticides and Toxic Substances. They had put the draft protocol out in '96. They finalized the guideline in '98. We ran this in '99.

So that we looked at things like, obviously body weights, feed consumption, body weight gains obviously, mortality, clinical signs. We looked at all of the mating parameters, pre-coital, interval, gestational length, number of total pups, number of live pups, sex ratio, body weight gain over time, testis descent as an early marker of adequate androgenicity, acquisition of puberty, which is vaginal patency in the girls, preputial separation in

the boys. We looked at estrous cyclicity by looking at a three-week sequence of daily vaginal smears.

At termination, we looked at andrology, which would be the coital epididymal sperm number concentration motility and morphology. We also looked at the testicular spermatid head count, so we could look at daily sperm production and efficiency of daily sperm production. And we did histopathology and absolutely everything that wasn't nailed down.

And we did this in both sexes. And we did these in the F0 parents, the F1 parents, F2 parents, and the F3 adults that we didn't breed.

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DR. TYL: Okay. And if you're not unconscious by now, I can list all six of the dietary concentrations. But they went basically from .001 to 50 milligrams per kilogram per day. In the diet, all of the diets were analyzed, so we could do dose response curves and we could document in fact that we gave them what we thought we were giving them.

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DR. TYL: Okay. What did we find?

Well, we found adult systemic toxicity at 50 and 500 milligrams per kilogram per day, the top two doses. We saw reduced body weights. We saw reduced body weight

gains. We saw reduced absolute and increased relative weanling and adult organ weights. That meant that the absolute organs were smaller, but the pups were smaller. So when you did a relative organ, the organ weight divided by the body weight, in fact, that value was higher.

So the body weights were, in fact, driving the reduced body weights -- the reduced organ weights at those doses. So what you're really looking at is systemic toxicity.

Okay. God, I can't even read the slides. It's rough when get old.

Female renal and hepatic toxicity at 500. So we're looking at effects at 500 and at 50. Reproductive developmental toxicity only occurred at 500 milligrams per kilogram per day, which exceeded the maximum tolerated dose. These animals could not maintain their body weights. Their feed consumption was bad. Their organ weights were bad. We saw clinical signs. We saw a whole series of things.

We didn't lose anybody. Nobody died, but there was clearly profound toxicity.

What did we see? We saw decreased ovarian weights and total and live pups per litter. Delays in acquisition of F1 male and female puberty.

If it were an estrogenic thing, you would see

acceleration in vaginal patency, the age of vaginal patency and a delay in preputial separation. That is, you would accelerate those female endpoints and you would delay those male endpoints. We saw delays in both. That says that it's not an estrogenic mechanism. It's a tox mechanism. It's secondary to the systemic tox in the offspring.

We saw no adults on -- no effects on the adult reproductive structures or functions in either the parental F0, F1, F2 or F3 animals.

We saw no BPA effects at low doses from .001 to 5 milligrams per kilogram per day. We saw no non-monotonic dose response curves for any parameter at any dose in any generation.

Since we only saw effects of the -- reproductive and developmental effects of BPA at a dose that was clearly systemically toxic and at a dose that was lower than that and still toxic, we didn't see anything.

We concluded that BPA was not considered a selective reproductive or developmental toxicant in rats. Okay, because you didn't see the reproductive or developmental effects, unless you also saw maternal toxicity. And even at lower maternal toxicity, you didn't see the effects. We reported this to everybody and their half brother, including my mother at their request. Our

results were confirmed at the NTP endocrine disruptors low-dose peer review workshop in 2001 and we published the stuff in Tox Sci in 2002.

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DR. TYL: Okay, but there was some criticism as to the use of the CD Sprague-Dawley rat, because it has been viewed as either insensitive or less sensitive than mouse or other rat strain. And although -- oh, I just did it.

So the one point I want to make is that the -- if you look at Bob Chapin's paper on the RACB studies, there's really no such thing as an insensitive animal. There are certain endpoints and certain organs that may be more sensitive in the Fischer than in the Sprague-Dawley or more sensitive in the Sprague-Dawley than in the Wistar, but there's really no way to define a strain as insensitive. It's not insensitive, okay.

But anyway, since the criticism was that the rat was probably less sensitive than the mouse, we switched -- we were requested to switch over and run a mouse study.

The mouse is not your typical animal model for multi-gen. And we had never run an estrogenic compound in a multi-gen in mice. So what we did was -- and I say we, I really mean that. I have a superb staff, and I could

not do it all myself.

We're running tremendous numbers of animals. So we ran a one-generation dietary E2 study in CD-1 mice, with a range of doses so that we could look at -- because there really was no data on what doses did you have normal mating, pregnancy, parturition, lactation and what doses didn't you.

So we ran 1, .001, .005, .05 -- no, I'm reading you the wrong one. Sorry, that was the second one.

The first one was .005, .05, .5, 2.5, 5, 10 and 15 milligrams per kill -- parts per million, which went from one microgram per kilogram per day to ten milligrams per kilogram per day. This is 17 beta-estradiol a potent endogenous estrogen.

So we ran this range of concentrations and we went to look at the appropriate and sensitive endpoints to a potent endogenous estrogen. So we were getting multi-generation data on the mouse control and treated with an estrogen. Okay, and what we found was that at .5 parts per million, which was about 80 to 90 micrograms per kilogram per day. Now, remember this is in the diet, so they're nibbling their way through the day. They're metabolizing it as they're eating it. Everything from that point down lower doses was fine. That is the animals bred. They got pregnant. They had babies. They

developed the babies. They went through puberty. They grew up. They had babies. Anything above that, the animals mated but there were no pregnancies.

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DR. TYL: So the second study then was, okay, since we know that, let's take a look at the range from .5 down parts per million to see what is the best dose -- the concentration and dose to run as a positive control, because that's what I wanted to do. Once I had defined the parameters of what an estrogen should do, I wanted to run that against BPA. I also wanted to collect enough positive and negative data, so we'd be very comfortable running the mouse study.

So we ran .005, .05, .5 -- no now I'm reading you the wrong one again, sorry.

.001, .005, .05, .15, and .5.

Okay, which is a about .2 to about 80 to 90 micrograms per kilogram per day.

And what did we find?

Well, we wanted to identify the appropriate dietary concentration in which we saw the full spectrum of we what we considered to be hallmark estrogenic endpoints. That was at .5, which is about 80 to 90 micrograms per kilogram per day to be used as a positive control. We also wanted to confirm the kinds of data we would generate

for the mouse in control situations and in the estrogenic environment. These are the hallmark findings of an estrogenic compound: Prolonged gestational length, decreased litter size, total and live pups. We saw those at the top dose.

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DR. TYL: Reduced numbers of litters, top dose; increased incidence of undescended testes, okay. It was a delay. They ultimately did descend. They simply descended slightly longer. We saw those at the high dose and the next to high dose.

Accelerated acquisition of puberty in the girls and delayed acquisition of puberty in the boys. It's classic estrogenic.

We saw the acceleration at the high and next to high. We saw the delayed puberty in males at the top 3 doses. Increased female reproductive organ weights and swollen vaginal area. We saw that in the top four doses. So the NOEL is one microgram per kilogram per day.

And we saw decreased weight of testes and epididymides even in the weanlings.

As I said, this is really the hallmark of an estrogen.

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DR. TYL: Okay, so we felt comfortable then in

going to the multi-gen. Okay, oral diet, number of dose levels, we ran six. We ran 28 per sex, per dose, per generation. We looked at the same endpoints that I went through with you for the rat. We looked at both males and females for all of those systemic reproductive and developmental endpoints. We ran the positive control.

And because again there's not much data out there, we ran two negative controls. Again, each of them with 28 per sex, per group, per generation.

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DR. TYL: This study exceeded the OECD regulatory guidelines. By this time OECD had come out with their 416, which is the two-generation study, which was finalized in 2001, very similar to the OPPTS, but we ran the OECD one. We used a sensitive strain of mice exposed to dietary BPA over two parental and two offspring generations. We ran a tremendous range of doses. We ran .018, .18, 1.8, 30, 335 parts per million, which is .003 to 600 milligram per kilogram per day, plus we went the positive control.

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DR. TYL: So we did a wide range of doses, so that we could look at the high dose to the low dose. That's why I hate it when people call these high-dose studies. We expose it through the diet. It was a very

large study. We ran the appropriate statistical tests, and we had a lot of power. We had a lot of animals per group. We had a lot of groups. We had a lot of generations.

Okay, and because the concern was those F1 animals, animals that have been exposed womb to tomb, if you will, we only keep one per sex, per litter, because that's what the guidelines call for. We added an additional male from every litter, which gave us at least 25 males per group, because they were very productive.

And so nine groups and multiple reproductive and developmental endpoints, as well as a complete histopathologic evaluation, not only of the adults, but also of the weanlings, which nobody else had done.

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DR. TYL: We got adult systemic toxicity at the top two doses, sound vaguely familiar. Hepatic histopathology at 50. And at 600 milligrams per kilogram per day, we got reduced body weights. We got increased liver and kidney weights. And we saw the same kind of histopathological problems in the liver and the kidneys.

The developmental effects at 600 milligrams per kilogram per day, included delayed testis descent, which you normally see in the last week of lactation. It ultimately happened, but it happened slightly later.

Transient hypoplastic testes, because we looked at weanling animals histopathologically, and slightly delayed acquisition of puberty in offspring males okay, considered not driven by estrogenic activity, but likely secondary to systemic tox.

We saw no effects on adult reproductive functions, including andrology or structures, included testes, epididymides, prostate, ovaries, mammary glands, uterus/cervix. And we looked at those in the weanlings and the adults for the F0 adults, the F1 weanlings, the F1 adults and then the F2 weanlings. There were no low dose effects again at .5 to .003 milligrams per kilogram per day. No evidence for non-monotonic dose response curves for any perimeter at any dose in any generation. Responses to the E2 positive control, confirmed the sensitivity of the CD-1 mouse to estrogens and confirmed the findings that we had presented for the one-gen and the two-generation study, because we only saw effects in the presence of systemic tox, and only at the highest dose. And the second to highest dose also has systemic tox and no reproductive or developmental effects. We considered BPA was not a selective reproductive or developmental toxicant in mice either.

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DR. TYL: So in conclusion based on our study

guidelines -- and our studies are guideline studies under good laboratory practices. So we're looking at endpoints that indicate adverse outcome, okay. We're not looking at the early molecular biochemical kinds of markers. Not that they're not interesting and fascinating and not that they shouldn't be pursued, but we're looking at endpoints. What is the -- is there an adverse consequence to these early changes?

We didn't look at the early changes. That's not part of the guidelines, but we did look at those endpoints that you would expect to be affected if those early changes had adverse consequences. We didn't see them.

Okay, so BPA is not a selective developmental reproductive toxicant in rats or mice. The reproductive and developmental effects seen at high BPA-dietary doses are only observed in the presence of systemic tox. So they are considered secondary to the systemic toxicity observed.

Okay, there was no evidence of effects at low BPA doses and no non-monotonic dose response curves in any parameter in either species in rats or in mice at any dose level.

Okay, the interesting thing is the insensitive rat and the sensitive mouse have exactly the same systemic and reproductive NOELs, which I think is fascinating.

Okay, the final comment is that BPA reproductive and developmental effects observed at these high doses are not consistent with estrogenic activity. We know what the normal estrogenic activity should be, because we did the one- and two-generation E2 studies to make sure we could document those. And the effects we saw at high doses are not those associated with an estrogen.

Anyway, thank you very much.

Any questions?

CHAIRPERSON BURK: Linda Roberts.

COMMITTEE MEMBER ROBERTS: Okay. The first questions, Dr. Tyl, are on the two-gen mouse.

You did the E2 as a positive control concurrently. You mentioned that it had the typical findings. Did it also delay vaginal opening -- I mean, excuse me, accelerate vaginal opening?

DR. TYL: Yes, it did and it delayed preputial separation.

COMMITTEE MEMBER ROBERTS: And Bisphenol A. None of the exposure levels had any effect upon vaginal opening?

DR. TYL: No, but we did see delay in preputial separation at the high dose.

COMMITTEE MEMBER ROBERTS: Okay. In the rat, how severe was the maternal toxicity?

DR. TYL: The rat was more severe than in the mouse, but we saw reduced body weight, reduce feed consumption, reduced body weight gain. We saw clinical signs of toxicity. And we also saw those -- the changes in a number of organs at necropsy and the histopathology in the kidneys and the liver. The kidneys and liver are typically the endpoints of BPA toxicity at high doses.

COMMITTEE MEMBER ROBERTS: And the last question is not specific to the study, but because you run a lot of studies. There was a statement earlier and also in our binders that when the rat has vaginal opening, that that's when estrous occurs. Is that your experience also?

DR. TYL: Yes, but not in the mouse. I mean, Dr. Vom Saal is absolutely right, that is it's three stages in the mouse. One is the vaginal patency, then there's age at first estrous and then there's age at first full estrous cycle.

COMMITTEE MEMBER ROBERTS: All right. And I guess the last thing I would do is just make a statement that typically guideline studies have three exposure levels, maybe sometimes four. Six is almost --

DR. TYL: Nuts.

(Laughter.)

COMMITTEE MEMBER ROBERTS: -- non-existent.

DR. TYL: Well, we wanted to make sure we covered

the high doses and We also covered the low doses. So I was very fortunate to be part of that program.

Thank you.

CHAIRPERSON BURK: Thank you.

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CHAIRPERSON BURK: How much time is left for this group?

It looks like you have about ten minutes left.

We'll give you a little more total, because we shouldn't count off for us asking questions.

DR. MURRAY: Dr. Jay Murray. And also on the timing, there were a lot of questions asked of our speakers. Does that get subtracted or how does that work?

CHAIRPERSON BURK: Yes, that won't count against you. So add in -- I don't know how many more minutes do you think we asked questions?

DR. MURRAY: I think it will take me about 15 minutes. And the last speaker, I think was five to ten minutes.

CHAIRPERSON BURK: Okay, well that's way over what -- I would say you have 15 minutes total. So do your best, please. We're trying to keep it fair.

MR. LANDFAIR: We didn't start till way past 1

DR. MURRAY: I thought we had started at seven after 1:00 and we had 70 minutes. Did I miss something?

CHAIRPERSON BURK: Okay, that is correct. So if you had 70 minutes -- all right, so what's the end time that you had. 2:15 would be 70 minutes -- it would be 2:20 and we will give you another five minutes.

DR. MURRAY: That should be fine.

CHAIRPERSON BURK: So 2:25 should be fine.

DR. MURRAY: Much appreciated. And I'll go as fast as I can to reduce that.

I am Dr. Jay Murray. Thank you for the opportunity to be here and thank you for reading all the materials that were provided to you by OEHHA and by everyone from the public.

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DR. MURRAY: This slide -- I'm going to focus on this slide. And this slide has the topics I'm going to cover. I'm going to do this very quickly. I don't think I have more than two slides on any one of these topics.

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DR. MURRAY: These are the agencies -- a partial list of the agencies that have reviewed BPA. In the time that I do have, there's no way I could go through, you know, 200 studies and summarize them. So fortunately we have six well-respected agencies that have independently and exhaustively reviewed the literature on developmental and reproductive toxicology. And they've all done it

recently. I think most of these were published in 2008. So it's current. It's relevant.

The written submission that we made, I think the first eight pages were a summary of what these organizations said with a number of quotes. I'm not going to go through all those.

None of those agencies reached a conclusion that would support listing BPA. And earlier this morning it was pointed out to you that the one that came the closest was probably CERHR, when they said that there was clear evidence of adverse effects for high dose developmental toxicity in animals.

And they also said limited evidence for low-dose developmental toxicity. But this doesn't mean that BPA meets the Prop 65 listing standards. It was suggested that your standards are about the same as CERHR's, and they're not.

First, the effects were seen only at high doses associated with systemic toxicity. It was suggested that CERHR looked at this issue and somehow concluded that the maternal toxicity was not explaining the developmental toxicity. That's not my understanding. I've read through that report cover to cover. I've attended a number of CERHR meetings. And, you know, when they make a determination of clear evidence, they are not factoring in

systemic or maternal toxicity. And if you read the CERHR report, they summarize the maternal and systemic toxicity for each of those studies.

The second point I want to make is that CERHR has a different definition of developmental toxicity. They include prenatal and postnatal exposure. And as you well know, Prop 65 is different.

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DR. MURRAY: Epidemiology. This one I can go through very quickly. Others have done a fine job of summarizing the epidemiology. And unless I've completely missed the boat, I don't think the epidemiology is likely where the action is.

And if I'm wrong and you want to hear more about that, I'll come back and talk about it more. But in the interests of time, I'll move forward.

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DR. MURRAY: Conventional animal studies. And I've used the term "conventional" as a shorthand here in describing some of these studies. What I'm talking about as the conventional studies are the three developmental tox studies, the two by Morrisey at NTP and the third one by Kim. And the five reproductive toxicity studies, the three by Dr. Tyl, which she's already described to you. There's one by the Japanese government, Ema et al., and

also the NTP Continuous Breeding Study.

Those studies show, first, that BPA is not a selective developmental or reproductive toxicant. If you look at the degree of maternal toxicity that was seen in those studies, it's not surprising that they saw some evidence of developmental toxicity at those high doses.

What those studies also show, you know, some of Dr. Tyl's study, because of the wide range of doses, also the Ema study, which focused on low doses, is that low doses don't have an effect on these developmental or reproductive parameters.

And finally, the studies showed that BPA does not produce the same reproductive effects that you see with estradiol and that was already covered very nicely by Dr. Tyl.

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DR. MURRAY: Then we have a lot more studies, which I've described in this slide as unconventional low-dose animal studies. And many of these studies were described by CERHR as either inadequate or of limited utility for a variety of reasons. And some of those examples I have in this slide.

A lot of them are small screening studies, subcutaneous or I.P. dose routes, unvalidated methods, insufficient replication. A lot of them are one-dose

studies. One of you had a question this morning about trimodal dose response. Well, a little tough to study trimodal dose response when you only have one dose.

Statistical issues. A number of the studies used the fetus rather than the litter as a statistical unit.

So I can't go through all of these studies. You saw summaries of some of the studies this morning. And it's very difficult to look at the results of a study based on a single slide with results without really knowing the details.

And what I'm going to do is I'm going to illustrate this point with one example, and that's the most recent study you received, the Nakagami study. This was the monkey study showing behavioral effects in male offspring.

And to me it's a classic example of what's wrong with relying on the low-dose studies. You've got to know the details behind these things.

One dose, small group size, four male offspring, six female offspring in the BPA groups. So very small N. You know that it was subcutaneous pump, but it was actually five surgeries to implant five subcutaneous pumps, because the pump only lasts for 28 days. So they had to do it five different times.

Author is unable to detect BPA in blood,

behavioral study, monkeys observed infrequently by the author's own description, ten minutes, two times a week.

The most prominent effect that they saw was an increase in outward looking, which was described to you this morning. And the authors theorized that BPA might be affecting sexual differentiation because of this. The authors also had a possible alternative explanation. And I call the hypothesis Simply Monkey See Monkey Do.

And what it is, as it was pointed out to you, the mothers had exactly the same effect. Well, the mothers and their offspring were pairs that were separated. They weren't allowed to see any other monkeys. So another possibility is that the offspring merely copied the behavior of the mothers, so that it was not really a BPA effect at all. Monkey See Monkey Do.

I want to come back to this slide. On the second bullet, no regulatory agency has relied on any of these studies for risk assessment purposes. There have been a lot of risk assessments established. And everyone that I'm aware of uses the NOEL from Dr. Tyl's studies. So these studies don't show that BPA is clearly shown to cause developmental or reproductive toxicity.

Another point I want to make is most of these studies do not take it out to a reproductive endpoint. A lot of them focus on unique endpoints. Some of them look

at molecular approaches and there's nothing wrong with that, but they're not tied to an adverse effect. And in order to improve credibility, those studies have to tie some of these molecular changes to an adverse outcome. And if I had time, I would say more about that.

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DR. MURRAY: This is a quote from CERHR describing, what I call, the unconventional low-dose studies. It's not just CERHR. FDA has said similar things. The Harvard School of Public Health did a review, said the same thing. Goodman updated it. Goodman et al., you probably saw that paper. Dr. Calvin Willhite also did a review on this, and drew similar conclusions about these studies.

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DR. MURRAY: Biological plausibility. Developmental and reproductive effects from BPA are not biologically plausible in humans for the pharmacokinetic reasons that you heard from Dr. Hentges. First-pass effect from oral exposure converts it to non-estrogenic metabolites. It's rapidly and completely excreted from the body. So there is really limited opportunity for BPA to hit target organs where you would cause these effects in humans exposed orally.

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DR. MURRAY: Species difference. Enterohepatic recirculation of BPA is significant in rodents, not in humans. And as a result, effects in rodents would tend to over-predict potential responses in humans. The animal studies using parental routes are not relevant to human hazard identification. Thus, extrapolation of the effects of BPA from the rodent studies to humans is tenuous at best. It certainly has to be done carefully.

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DR. MURRAY: Estrogenic activity. You've heard a lot about estrogenic activity. We all know BPA binds weakly to the estrogen receptor, but there is no opportunity for estrogenic activity in humans, since BPA is rapidly converted to non-estrogenic metabolites and rapidly excreted.

And the other thing is BPA has to compete with estrogenic substances, both endogenous and dietary, that have a greater affinity to bind the estrogen receptor. And you've heard about some of those things already, phytoestrogens, lignans, genistein in soy products. If all it took was estrogenic activity to land on the Prop 65 list, then genistein in soy would be on the Prop 65 list certainly.

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DR. MURRAY: So estrogenic activity is not a

basis to list. It's not a reproductive effect per se. It is a potential mechanism that might induce effects under certain circumstances, which are not present with BPA.

And if you go back and look at your guidance criteria, you'll see there's a long list of reproductive endpoints, and estrogenic activity is not there.

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DR. MURRAY: So the last two slides. Overall evaluation. The human data do not support listing. The most reliable animal studies show BPA is not a selective developmental or reproductive toxicant. And the unconventional -- what I call the unconventional low-dose studies are certainly thought-provoking. They raise a lot of questions. They're suggestive. You know, they certainly call for studies that more clearly define some of these things.

But they're of low utility and insufficient to list. One of the problems is you've got a lot of inconsistent results and the evidence is just not very compelling in those.

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DR. MURRAY: Last slide, conclusion. Neither human nor animal studies demonstrate that BPA has clearly shown to cause developmental or reproductive toxicity. And even if they animal studies were, which they're not,

the pharmacokinetic data showed that a human hazard of developmental and reproductive toxicity is not biologically plausible.

Thank you.

I'd be happy to answer any questions if it doesn't eat into my clock here.

CHAIRPERSON BURK: No, it won't eat into your clock.

Are there any questions for Dr. Murray?

Okay, maybe later.

DR. MURRAY: Thank you. The last speaker is Dr. William Hoyle, who is going to take you back to food and food packaging and the importance of your overall decision.

Thank you.

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DR. HOYLE: Good afternoon. My name is Dr. William Hoyle. I'm here on behalf of NAMPA, the North American Metal Packaging Alliance, which is a nonprofit corporation, committed to the safety of metal packaging and metal packaged products. And I'm here to urge the Committee to consider all the relevant hazard information in developing their listing recommendation for BPA.

But part of that too is I also would ask the Committee to be aware of the potential health hazards that

might arise, as what I'll refer to, as unintended consequences of listing BPA as a Prop 65 reproductive toxicant.

If BPA, and therefore epoxies, are no longer available for certain applications, this would have a high potential for unintended consequences. The use of BPA, what I want to try and do is explained how it's used in can coatings. We've heard from Dr. Vom Saal and he talked about that and its use in Japan and other places.

The use of BPA in epoxy coatings provides real, important, and measurable health benefits. So in reality, instead of reducing the potential for serious and deadly effects, if you ban epoxies, you're actually adversely affecting the health of the citizens of this State.

By reducing these potential, essentially what we've done with metal coated cans is protect human health. And NAMPA represents the industries that are responsible for providing this packaging that ensures safe and nutritious food throughout our system. And we are seriously concerned about the impact that would arise if we had -- warning labels were required to put on food products.

BPA and epoxies are a critical component in the manufacture of our epoxy coatings that are used to line metal food packagings and closures for glass packaging.

Epoxy coating enable -- I really refer to it as an enabling technology. It's actually what's enabled the can to go lighter, faster. And that light-weight and the combination of the chemical resistance of epoxy coatings has enabled us to heat the cans faster when they're filled, so the food is more nutritious and also that epoxy coating is more flexible, so it resists denting and cracking and other things that happen as it goes through the transportation system.

So because the epoxies are also resistant to a wide range of, what I'll call, chemistries found in the food and beverages which are put into these metal packages, this chemical resistance and other attributes of the epoxies virtually eliminate any interactions between that coating and the food and the metal that it separates.

And this chemical resistance is critical for maintaining the sterility of the food. Because through the transportation if it's dented and things like that, what would happen in the past, if you go back 30 years, you would see that dent would -- the food would seep through it and cause micro-perforations and then you'd result in a swelled can.

If you look in the market today, you don't see those swelled cans. They just -- you may see some dented cans, but they're not swelled. They're no longer out

there. And if you look at the data, FDA's data shows that for the past 30 years, there's not been a single recall of a -- in a metal food package can for a health borne -- food borne illness reasons.

So it's this coating and the food product by preventing that, it allows us to do it. The public health consequences of deselecting epoxies are indeed real. The use of epoxy coatings is the most effective way to protect the food product.

The initial high temperature sterilization coupled with the continuous product protection enabled by the epoxy coatings eliminates these dangers. You don't hear about botulism in food for the last 30 years. And it's this enabling technology of epoxies that has allowed this to occur.

The other part is, is that de-selection of epoxy coatings will also affect the most needy in our society. California citizens, and I'll be specific to the numbers here, that receive assistance from food pantries, as well as the WIC Program rely significantly on metal packaged products.

In 2008, the total births in California were approximately 550,000. Of that, 325,000 of those births, those infants, rely on the WIC Program. The WIC Program solely uses either glass or metal packaging. The glass

packaging having a closure, which cannot be substituted. There is no known substitute for the epoxy that's in there. As a matter of fact, the very first meal that most infants get, comes in a small little container that you take the top off and you put a nipple on it and feed it to them. That sterility is maintained, believe it or not, because of the nutritions and things that are in those, the supplements that are in that feeding, it requires actually a stainless steel closure, a stainless steel closure, because the food is so aggressive towards the metal to keep it separated.

And I used to work at the company that made that. That is the most single expensive product that we make. We've been trying to replace that for 15 years. It's just not -- we've not found anything that will work.

And so we continue to supply that into the hospital, so that the -- you know, that the very first foods that they get are indeed sterile and safe and nutritious, because that prevents the nutrition of the foods from being reduced by the interaction, if it was able to contact the metal. And it's an epoxy coating that keeps that separation.

So with that, you know, if epoxies are banned, those products will go away. If they are required to be labeled, those -- I've been told by the companies that

produce them that the liability would be such that those products will go away period.

There is also other food assistance programs. If you look at the paper that was published here in California in 2009 by the California Association of Food Banks. And essentially the working parents and senior citizens of this State, among others, have found that the need for food banks and assistance is increasing. As a matter of fact, there was -- in June of this year, the Los Angeles Regional Food Bank policy brief indicated that the distribution rate for food banks in that area increased 31 percent in the past year, and 24 percent just over the last six months.

So with that, also I think it's important to know that even though those that may not typically use food assistance could find themselves in relying on metal packaged products in situations such as power outages, earthquakes, and other natural disasters, hurricanes, et cetera. And even in the military relies on metal packaged food. Those foods are, for the most part, predominantly rely on epoxy coatings, because they are the most technologically advanced.

They're also unintended --

MR. LANDFAIR: I think we've exceeded our time.

CHAIRPERSON BURK: You're on orange. You still

have a couple more minutes.

DR. HOYLE: I wasn't looking sorry.

Well, if you would, I'd like to say one last thing.

CHAIRPERSON BURK: Are you the last speaker in the group?

DR. HOYLE: Yes.

CHAIRPERSON BURK: Okay. Why don't you two more minutes.

DR. HOYLE: Okay. Thank you. I do appreciate that, because I do think this is something that most people, you know, they don't hear about this side of what I'll call the unintended consequences. And I think there's also a series of unintended risks associated with moving to, what I'll refer to as, untested alternatives. You'll hear that quite frequently that there are alternatives available. They're readily available.

You heard this morning that Japan moved away from epoxies. Well, considering in my dealings with Japan, which -- and I was responsible for some of the R&D that went over there, 70 percent of the coatings that are used today in Japan are epoxy based period.

The PET that you hear about -- and I'll say it maybe a different way. They depend, there's at least one or more components in those packages that rely on epoxies.

You hear about the PET-lined cans. The PET is great. Two things, it will not adhere to the metal can without an epoxy base coat. So you put the metal, you put an epoxy coat, then you cover with a PET. If it wasn't for the epoxy, you wouldn't be able to adhere it.

The other part is, is that the epoxy -- the PET is not a barrier to the epoxy migrating, so you see the same amount of BPA go through whether the PET is there or not.

So with that, despite, what I'll call reports to the contrary, the simple fact is there is no readily available, suitable, fully tested material that you can drop in as an alternative.

With that, I think finally, what I'd like to remind the Committee that the chemical migration into food products will occur in any food container, whether it's an alternative for an epoxy can, whether it's a plastic, a paper package, or a glass. All of those rely on not -- I should say with the exception of the plastic, rely on epoxies.

The epoxy -- we also believe -- well, I'll stop there

(Laughter.)

DR. HOYLE: If there's any questions, I'll be happy to try and answer them.

CHAIRPERSON BURK: Are there any questions?

Thank you.

MR. LANDFAIR: I want to thank the panel on behalf of our speakers.

Thank you.

CHAIRPERSON BURK: Thank you.

All right. I think for the sake of the court reporter, we'll take ten minutes max and then we have another group of speakers, quite a few actually and we'll continue.

Ten minutes.

(Thereupon a recess was taken.)

CHAIRPERSON BURK: All right. If we could get started again, please. We have a number of additional cards for people that wish to speak, all as individuals. In concern for our time, we want to be sure that there's enough time left for the Committee to adequately deliberate on this matter. I would like to ask that these folks be as brief as possible and that if you have new information to offer to us, we would like to hear it. If it's just reiterating something, then I think it would be perfectly fine if you say, I agree with so in so, and that would move things along.

Again, we want to be fair about this, but please try to be brief, so we'll have time left for our

discussion.

And what I'll do is I'll call like the first ten names, so that you're ready to go and perhaps we can move it along.

So there's 17 altogether. So we have Julie Silas, Healthy Building Network. Bill Allayaud, I guess, Environmental Working Group. Luis Cabrales, maybe, Coalition for Clean Air. Caroline Cox, Center for Environmental Health.

You can start coming down.

Pamela Palitz, Environment California. Janet Nudelman, Breast Cancer Fund. Why don't we start with those folks. And first up will be Julie Silas, Healthy Building Network.

MS. SILAS: Thank you. My name is Julie Silas and I'm the Director of Healthcare Projects for the Healthy Building Network, or HBN.

HBN is the leading national nonprofit organization advocating for health-based green building standards. Launched in 2000, the mission of HBN is to transform the market for building materials in order to advance the best environmental health and social practices. By doing this, we believe we can decrease the toxic chemicals that are used in buildings and even reverse the profound negative impacts of the contemporary

building industry on the environment, human health, and society

Today, I'm here to urge this committee to list BPA as a developmental and reproductive toxicant. While many are aware of the existence of BPA in baby bottles and food can liners, few are aware that BPA is a chemical component of epoxy resins used in building materials. Most notably, BPA-based epoxy resins are used in high performance paints and coatings, as well as in adhesives to hold down floors, carpets and wall covering.

Emerging science regarding occupational exposure to epoxy resins made from Bisphenol A raises reproductive health concerns and makes clear that Prop 65 labeling is warranted to inform users of potential developmental and reproductive hazards associated with BPA.

Epoxy resins are used in building materials often listed on the Material Safety Data Sheet as a proprietary mixture, without disclosure that the resin actually contains Bisphenol A.

While manufactures claim that the Bisphenol A in epoxy resins is consumed entirely in the production process, and does not show up in the final products, scientists investigating the metabolic breakdown of epoxy resins during the occupational exposure have found that the resin products can be metabolized in the human body

back into BPA and may impact the reproductive system of those exposed.

In both epidemiological studies referenced earlier, looking at occupational exposure, those workers exposed to BPA had greater reproductive effects than those not exposed to the BPA-containing products. Thus, the answer to the question posed earlier in the morning about ubiquitous exposure in humans, is that those directly working with products containing BPA are showing greater effects than the control groups.

A Japanese study of workers spraying epoxy resin coatings in a factory at least three hours per day found that the epoxy resin metabolized to BPA in the human body, and they found disruption in the secretion of gonadotrophic hormones in the workers exposed.

A similar study of workers applying paint consisting of 10 to 30 percent epoxy resins reported significantly higher urinary levels of total BPA and alterations in reproductive hormones in the exposed population.

The authors of this occupational study reached a conclusion different than the OEHHA staff reported earlier this morning. And I'm going to quote those peer reviewed -- that peer-reviewed journal. The authors concluded that quote, "The painter had follicle

stimulating hormone levels of 7.68 international units, which was significantly higher than the non-painter mean of 5.33 international units."

"Further...," and this is another quote, "...painters had a testosterone level of 3.5 nanograms per milliliter, which was quote 'significantly lower' than the non-painter level of 5.818 nanograms per milliliter."

They also stated that quote, "As the Bisphenol A exposure level increases, testosterone level decrease."

A significant drop in testosterone levels is an early effect that should be considered adverse, since changes in testosterone production have consequences for the functioning of the reproductive system.

The BPA expert panel from the Center for Evaluation of Human Risks to Reproduction reviewing these same occupational studies reported to the National Toxicology Program, and I quote, "Several studies collectively suggest hormonal effects of Bisphenol A exposure, including one in occupationally-exposed male workers likely exposed through multiple routes, including inhalation."

The NTP's final monograph states, again a quote, "A number of studies, when considered together, suggest a possible effect on reproductive hormones, especially in men exposed to higher levels of Bisphenol A in the

workplace."

The scientific evidence linking occupational exposure to Bisphenol A-based epoxy resin and effects on reproductive hormones suggests other signs showing BPA effects on male reproduction.

Given the ubiquitous use of epoxy resins in building material, adhesives and coatings, and the lack of disclosure that BPA is even in the product, those of us who work to make safe and healthy buildings deserve to be informed that the products may contain BPA.

Scientific research has only recently begun to address potential exposures to BPA from building materials. Recent NHANES research suggests, as you heard this morning, that substantial non-food exposure to BPA, and -- that there is substantial non-food exposure to BPA and there are likely to be a wide range of exposure pathways including building materials, as sources of those exposures.

In summation, compounding evidence about BPA and its associated effects on the endocrine and reproductive systems, and emerging science that building products made from BPA-based epoxy resins are metabolizing into BPA in the body and may result in changes to the reproductive system, indicate that use of BPA in products exposes users to unnecessary harm.

You have an authoritative body in the NTP to rely on listing for Bisphenol A. This body has relied on the NTP CERHR in the past when listing Proposition 65 chemicals and should do so again today.

The Healthy Building Network urges the DART IC to list BPA as a developmental and reproductive toxicant under Prop 65, so that consumers and those working with BPA-containing products can make informed choices about the chemicals they are exposed to.

Thank you.

CHAIRPERSON BURK: Thank you.

Go right ahead, please. Introduce yourself, because I'm not sure I said this --

MR. ALLAYAUD: Hi. My name is Bill Allayaud. I am director of governmental affairs for the Environmental Working Group. And I'm also giving these remarks on behalf of Renée Sharp, our California Director who's unable to attend today.

Environmental Working Group, or EWG, strongly urges the Committee to list BPA as a reproductive and developmental toxicant. We believe that the draft report prepared by OEHHA and the overall weight of evidence from laboratory studies clearly supports this listing. OEHHA's draft summary of the evidence details dozens of studies showing permanent effects in the male reproductive system,

impacts to brain and behavior, and a variety of other low-dose effects, including early puberty, female reproductive development -- problems in female reproductive development, including fertility.

I'd like to make three main points to support the case for a listing of BPA. One is that industry is misrepresenting the findings of the NTP and the FDA. Industries that produce or use BPA regularly misrepresent the state of the scientific evidence and regulatory decisions. In particular, the American Chemistry Council and the Grocery Manufacturers Association, or ACC and GMA, in the written comments to the Committee -- and our comments are based on reviewing the written comments to the Committee -- mischaracterize the findings on BPA toxicity of both the NTP and the FDA.

In September 2008, the NTP published its final monograph on BPA, finding quote "clear evidence of adverse effects" unquote, for developmental toxicity at high doses. This alone would be a sufficient basis for adding BPA to the reproductive and developmental toxicants list. The NTP went on to assess the possible effects of current exposures to BPA on human development and reproduction, framing its conclusions in terms of a five-level scale, negligible concern, minimal concern, some concern, concern, and serious concern.

The NTP expressed quote "some concern for the effects of BPA on brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA." unquote. The NTP explains on its website that the term of art "some concern" is the mid-point on its five-level scale. It assigns the "some concern" ranking a deep yellow color, lighter than the alarm red of serious concern, but a sharp contrast to the green color of negligible concern.

NTP did assume minimal or negligible concern for some endpoints. But when the Grocery Manufacturers asserts the NTP quote, "expressed on the minimal or negligible concern regarding most alleged health effects," unquote, it selectively ignores the gravest NTP findings about BPA's possible effects on the developing fetus and young child.

This blatant attempt to mislead the panel and the public should not be allowed to stand. Nor should the panel accept the claim by the GMA and the ACC that the NTP did not formally or definitively identify BPA as causing developmental or reproductive toxicity. These verbal sleight of hands ignore the seriousness of the NTP's conclusion about BPA's effect on the developing fetus and child.

The NTP did not, as the ACC and GMA implied, give

BPA a green light, a green ranking. Instead its monograph asserted that there was, "more critical data needs for assessing the dangers of BPA at current human exposures." And it detailed nine types of research that should be pursued to fill crucial data gaps.

We would like to note that it is relatively unusual for the NTP to express such concerns about contaminant exposures for the general population, in this case, all American pregnancies, infants, and children. Previously, few chemical exposures have achieved the designation of "some concern".

It is generally applied to very specific subpopulations. For example, some concern describes the NTP's assessment of the risks of fetal amphetamine exposure.

Given that BPA exposure in early life is unnecessary and largely avoidable, the designation of "some concern" for the fetus, infant, and young child is clearly a matter that should be seriously considered by regulatory bodies, despite industry's assurances to the contrary.

The ACC also misrepresents the status of the federal FDA's safety review for BPA in food packaging. When the ACC claims that the FDA has found quote, "an adequate margin of safety exists for BPA at current levels

of exposure from food contact use," end quote, it neglects to mention that last November, the agency's science board firmly rejected the agency's conclusion that present day BPA exposures are safe, and found that the weight of evidence pointed to toxic levels at less than one order of magnitude lower than those considered by the FDA.

In fact, FDA's draft assessment actually led the science board to conclude that present day exposures are unsafe. Science board reviewers observed that the FDA's assessment quote, "provides sufficient scientific basis to conclude that margins of safety, defined by FDA as adequate are, in fact, inadequate."

Our second point is that scientific reviews by OEHHA, NTP and FDA advisors support listing BPA. Thorough reviews by your staff, the NTP and the concerns raised by the FDA's science board point to a consistent and credible association between low-dose exposure to BPA during pregnancy and effects to the brain and reproductive system.

The NTP monograph finds compelling evidence of low-dose toxicity, specifically citing 12 high quality studies showing reproductive and developmental effects. Notably 8 of the 12 studies using oral dosing directly relevant to a pregnant woman or newborn and several employ concentrations as low as ten micrograms per kilogram body

weight.

There is ample evidence of BPA's toxicity in the male reproductive system, particularly the prostate. Many studies have found that developmental exposure to BPA causes a variety of functional changes, including abnormal differentiation of cytokeratin ten cells altered -- and I'll skip some of this for time.

These sensitive indicators of prostate impacts were simply not studied by industry funded guideline studies, which often use more crude measures of toxicity. BPA has also shown to provoke a variety of changes to brain development and behavior.

The Canadian Government used this body of research as the basis for listing BPA as toxic. It took immediate action to reduce infant exposures last year in the United States both OEHHA and the NTP highlight studies showing loss of sexual dimorphic behavior as the strongest and most consistent findings of developmental toxicity. NTP highlights seven high-quality oral studies showing these effects consistent with known impacts of estrogenic chemicals and currently focused on gestational exposures.

We concur with OEHHA's assessment and would like to call the Committee's attention to two recently published studies confirming similar effects in non-human primates. These studies, which Dr. Sarah Janssen is going

to testify from NRDC, described in written comments to OEHHA, extend the findings of loss of sexually dimorphic behavior in rodents to more closely related species.

The third and last point. Human exposure to BPA is wide spread and its exposures are perilously close to toxic levels in low-dose studies.

BPA is widely detected in Americans in more than 92 percent of urine samples -- and I'll skip some of this. You've heard a lot of this today.

Most worrisome is the detection of free BPA in maternal serum, ovarian follicular fluid, umbilical cord blood, and amniotic fluid, premature infant's urine and the placenta. The widespread detection of the chemical with a rapid half-life suggest Americans have daily contact with BPA from common sources. Food and food packaging are thought to predominate.

The EWG, our organization, tested 97 canned foods and formula samples for BPA. We found detectable residues in more than half of the samples. Concentrations ranged from one to 385 parts per billion, with the highest concentrations noted in canned pastas, soup, tuna, and vegetables.

We calculate that pregnant women of average weight could consume from .5 to 1 micrograms BPA per kilogram of body weight by ingesting a single serving of a

highly contaminated food. Because formula can make up a hundred percent of their daily diet, infant-fed formulas with metal cans -- from metal cans had even higher daily exposure values.

It is important to note that these intense exposures from bottle-fed infants likely persist over the duration of formula feeding.

In 2008, the Canadian government confirmed EWG's finding with tests of 56 liquid samples, many of which were produced in the United States.

A recent Harvard study -- I don't think it's been mentioned today, it came out in May -- found that polycarbonate drink bottles are another significant source of BPA for adults. The bottom line is they found that just drinking cold beverages, not the typically hot or acidic things in a normal polycarbonate bottle leached, urine levels spiked. When they went off it, they went down.

This research suggests that high-end adult exposures can routinely exceed one microgram per kilogram of body weight and infant exposures can be even higher.

Skipping ahead here a little. The lowest dose studies shown to affect brain and behavior in male reproductive development employ doses of just ten micrograms BPA per kilogram of body weight, which is by

any measure an unacceptably low margin of safety for effects as serious and permanent as those caused by BPA.

Before my closing paragraph, I want to mention one thing about the WIC, Women, Infants, and Children Program. The previous speaker from the industry said that, you know, there's three hundred and something thousand babies relying on this, so WIC is really concerned about this.

WIC supports a ban on BPA in infant formula in the State of California. They're on record with that in the California legislature. The reason is, they said almost all their babies are fed with powdered formula. They're confident they can get BPA-free powdered formula. Therefore, they support a ban on BPA in these baby products. And that's not what you're being asked today is to place a ban on anything. But I just wanted to clarify WIC's position here and not let it get misconstrued.

In closing, we urge the Committee to consider carefully today's decision. BPA clearly meets the Committee's 1993 criteria for listing as a reproductive and developmental toxicant on the basis of sufficient evidence in experimental animals, such that extrapolation to humans is appropriate.

This includes careful experimental design, relevant routes of exposure, and dosing levels well below

those that result in maternal or systemic toxicity. As the NTP and FDA science board have determined, the weight of evidence supports concern for present day BPA exposures. EWG urges the Committee to join these authoritative bodies and list BPA accordingly pursuant to Prop 65.

Thank you very much.

CHAIRPERSON BURK: Thank you.

Next.

MR. CABRALES: Good afternoon, Committee members. If any of you cannot see me, I'll raise my hands.

(Laughter.).

MR. CABRALES: Thank you very much for the opportunity to address you today and also for the patience you've had so far with all of us.

My name is Luis Cabrales. I am senior campaign and outreach associate at Coalition for Clean Air a statewide organization working to clean the air and protect public health from toxic chemicals.

Now, today and prior to today, you have heard and read everything there is to know about BPA. That is why I'm not hear to tell you more about BPA. In fact, I will neglect to tell you my background. Instead, I want to focus on the fact that I am -- besides a health advocate, I am a father, and I am a consumer like everybody here.

And because of my lack of expertise and my humble background, I want to trust you today with the decision that you are going to make, because it is you, as an entity, the ones whose technical background we are relying today. And it is up to you to make a very important decision. It's not an easy decision, but it's a very important decision, and that is why I think we have heard from representatives of some of the most powerful companies telling you that the decision today is not the right decision. And, in fact, if you chose to list BPA on Prop 65 will be the end of food as we know it.

(Laughter.)

MR. CABRALES: Now, to do so, they're asking you to ignore the facts. They're asking you to ignore your common sense, and they're pointing towards flawed and biased data or studies that they may have sponsored. But I want to remind you and I want to remind everyone in this audience that that is the MO of industries that see their interests in danger when an action -- a regulatory action is going to be taken.

Not too long ago, we saw the expense that some industries took to influence and prevent scientists from President Bush's EPA from actually making decisions based on their expertises.

And so -- but fortunately for me, as a father, as

a consumer, and as an environmental health advocate, this is not Bush's EPA. But your decision though will go beyond California. It will definitely have an impact nationwide. Maybe beyond the U.S. And so that's why this decision is so important to us. And that's why I want to rely on your expertise and your common sense to separate the good science from the biased flawed science.

I want you to remember that we are not asking you to ban BPA as we were told earlier. That's not what we are asking. We are asking you to use your expertise, your common sense, to look at all the information you received, and to list BPA as a possible developmental and reproductive toxicant. That's all we're asking.

So contrary to what we were told earlier, listing BPA is not going to be the end of food. I mean, we're not going to stop eating, because you're listing BPA in Prop 65.

But as a consumer, as a father, and as a advocate, it will give me the opportunity to make educated decisions about the foods I want to purchase and the foods I want to feed my child. And I'm sure everybody in this room would like to have that opportunity.

So common sense tells me there's enough evidence to make a decision. And that's why I'm humbly asking you to look at all this information and based on your

expertise, you make that decision today.

Thank you very much.

CHAIRPERSON BURK: Thank you.

Caroline Cox.

MS. COX: My name is Caroline Cox. I'm from the Center for Environmental Health. And I know it's been a really long day, so I'm going to try to be really brief. I'm here to speak in support of listing BPA. And I wanted to address just one of the issues that's come up earlier today.

We started off the morning with a presentation from the OEHHA staff that, I think, did a really good job of summarizing the enormous amount of research that's been done on this chemical. And then more recently we had a presentation that asked us to basically just focus on a few of the studies that have been done, because they're the studies that were designed to be used for regulatory purposes.

And I have the privilege of serving on an advisory group to U.S. EPA. It's called 21st Century Toxicology Testing. And it's under the auspices of the Office of Pesticide Programs. So it actually doesn't specifically address BPA, but it's looking at the general issue of how toxicology testing should change in the 21st century.

And this process started actually in Europe when they started looking at a switch to non-animal toxicology testing methods. And many of them are the molecular and cellular kinds of tests that we've been talking about with BPA today. So what the U.S. EPA did was ask the National Academy of Sciences to sort of evaluate this 21st century toxicology and give the agency some advice about how they should proceed. And what the National Academy of Sciences said is that EPA should be moving, and relatively quickly, in this direction.

So they convened an advisory group that I'm on, not to decide whether or not this transition was a good idea, but to advise the agency on how to communicate to the public why they were making this change and what the benefits of it are.

So I think that the speakers today who asked you just to look at the quote "conventional" toxicology tests on BPA and not look at, I think what was referred to as, low-dose unconventional methods, are basically asking you to stay back in the 20th century, as far as toxicology testing, and not take advantage of all of the new developments and toxicology testing that are coming about because of current research.

So I'd really encourage you to look at the whole breadth of the research that's been done on BPA, and not

confine yourself to studies that may very quickly be shown to be -- have been done with the protocol that's not really up to current standards.

Thank you.

CHAIRPERSON BURK: Thank you.

Janet.

MS. PALITZ: Good afternoon. I'm Pamela King Palitz. And I'm the Environmental Health Advocate and staff attorney for Environment California. We are a statewide grassroots advocacy group.

And we've been educating Californians about the links between exposure to toxic chemicals and increases in developmental diseases since our 2004 report, Growing Up Toxic.

But today I'm actually speaking more as an attorney than as an environmental health advocate. I have reviewed carefully the criteria you follow in recommending chemicals for listing and I'd like to briefly outline why BPA meets those criteria.

As you heard from Mr. Landfair, the criteria state that in evaluating the sufficiency data, you should use the weight-of-evidence approach. This approach involves the integration of all the available data to arrive at an answer. That's kind of what Caroline was just saying.

It's no secret that our knowledge about mechanisms of toxicity is still developing and that good epidemiological evidence is seldom available, and the animal studies are not always conclusive.

And perhaps you believe that the information available at a given time provides only persuasive rather than hard evidence. Well, what I would say to you is that persuasive is sufficient based on the clearly shown burden of proof. In a few minutes you'll hear from Dr. Joe Guth more on this subject.

But in addition to the clearly shown burden is also the weight-of-evidence approach. And weight of evidence is a concept in law as well as in scientific and policy making literature. And it's simple, it's the measure of credible proof on one side of a dispute as compared to the credible proof on the other. And it's particularly the probative facts, the important facts that really prove something.

Probative facts make the existence of something more probable, or even more important, less probable than it would be without them. So the guidance criteria tell you something very important about this approach that data on more than one species or for more than one study increase confidence. In other words, they tip the scale in the weight-of-evidence approach.

So let me give you a couple of examples. For female reproductive toxicity, there's a lot of laboratory rodent data that Dr. Wu reviewed this morning. And many of those reports report the exposure of female lab rodents to BPA during gestation, lactation, adolescence and adult reproductive age, and the effects that they have on the reproductive system. The onset of puberty, the length of menstrual cycle, mammary gland develop all appear to be most profoundly affected. This data is applicable to humans. And girls exhibiting early onset puberty may be more at risk for the development of reproductive tract cancers later in life. And early onset of puberty is risk factor in breast cancer.

As for developmental toxicity, the results of the study of sexually differentiated behavior in monkeys, rats, and mice are striking. So this is where we're going to talk about the monkeys that everybody is mentioning.

There's this new study of monkeys by the Japanese that, you know, says that exposure to BPA in the womb makes male monkeys behave more like infant female monkeys. And what's interesting about that is that there's very similar studies that describe the same kind of behavior in mice, and similar studies that describe the same kind of behavior in rats. And so this is what we have, we have three different species, monkeys, rats, and mice, all

exhibiting behavioral changes, all as a result of exposure to BPA in utero.

So let's go back to the criteria that data on more than one species increases confidence. So I ask you to remember the weight-of-evidence approach suggested by the guidance criteria, the number of studies that come to the same conclusions and the different species that respond to BPA in markedly similar ways should increase confidence that this is probative evidence. This is the kind of evidence that makes a fact more credible.

I urge you to decide that BPA is a reproductive toxicant and that Californians are entitled to be warned when they're going to be exposed to it.

Thank you.

CHAIRPERSON BURK: Thank you.

MS. NUDELMAN: Hi. My name is Janet Nudelman. I'm the director of program and policy at the Breast Cancer Fund. We are a San Francisco based national nonprofit organization working to prevent breast cancer by identifying and eliminating the environmental links to the disease.

As you can imagine, our organization is very seriously concerned about the growing body of scientific evidence linking exposure to Bisphenol A to an increased risk of breast cancer.

I, however, am not going to be talking about that issue. My colleague Gretchen Lee will be coming up in just a few minutes to do so.

I am here instead today to speak on behalf of the Dr. Patricia Hunt, who could not be here, but whose remarks were previously submitted to this committee as a part of the formal public comment record.

Dr. Pat Hunt is a Meyer Distinguished Professor at the School of Molecular Biosciences at Washington State University. Her current research focuses on determining the reproductive effects of exposure to chemicals with estrogenic activity, including BPA, during different developmental time points.

And I do have extra copies of Dr. Hunt's remarks if you need them. So just let me know.

"To the members of the DART Committee. I understand that you are considering whether to list Bisphenol A on California's Prop 65 list. I am writing to urge you to take this action. Studies from an increasing number of academic laboratories, including my own, have demonstrated that in rodents very low doses of the hormone-like chemical BPA can exert very powerful effects on the developing fetus and the neonate. These effects alter the reproductive ability of

both males and females, affect the brain and behavior, lead to an increased risk of breast and prostate cancer in the adult animal, and cause metabolic changes that can lead to diseases like diabetes and heart disease.

"My laboratory entered into BPA research in an unexpected way. An accident in our mouse facility led to leaching of the plasticizer BPA from caging material and water bottles causing a sudden change in the data of several ongoing studies. Because the onset of leaching was abrupt - the result of inadvertent damage to caging materials through the use of the wrong detergent - we were quickly able to detect changes in the results of individual experiments to determine the cause.

"Our studies involved analysis of periovulatory eggs and the sudden exposure of our animals to estrogenic chemical BPA, caused a spike in meiotic disturbance in eggs from control females. Indeed, we observed changes in two separate sets of studies, an increase in chromosome alignment defects in cells undergoing the first meiotic division, which normally occurs just prior to ovulation, and an increased level

of chromosomally abnormal eggs in the metaphase II stage, the stage at which an egg is ovulated. The changes in the data sets for both studies suggested that BPA exposure had the potential to disrupt the final stages of egg development.

"Although I believe the evidence for effects of BPA on the final stages of egg development is compelling, these results pale in light of our more recent studies. The earliest stages of egg development take place in the fetal ovary. And studies in humans have demonstrated that events that occur during this period set the stage for errors in the adult ovary that give rise to chromosomally abnormal eggs. We tested the effect of BPA exposure on the fetal stages of egg development by exposing pregnant mothers to low doses of BPA for several days and then analyze the eggs developing -- sorry -- the eggs developing in the ovaries of the female fetuses.

"The results were stunning. BPA caused major disturbances in the fetal ovary, and, if exposed females were allowed to be born and mature, we found that 40 percent of the eggs they ovulated and the embryos they produced were chromosomally abnormal. This is a grand maternal effect. By

exposing mother, we are affecting the likelihood that her grandchildren will be chromosomally abnormal. The fact that a brief exposure during fetal development can dramatically impact the reproductive ability of the female has very serious implications for humans, but importantly it would take us two generations to detect an effect like this in humans.

"Over 200 papers from academic laboratories like mine have reported adverse effects as a result of low dose Bisphenol A exposure. How, if these findings are true, can industry claim that this chemical is perfectly safe.

"In addition to trying to discredit the work of scientists like me, the American Chemistry Council and its chiefs spokesperson, Mr. Hentges, claim that a few studies conducted by industry are more meaningful than all of the studies conducted by academic scientists.

"They make this claim because their studies use a very expensive standard testing protocol that is conducted under federally approved strict quality control guidelines called Good Laboratory Practices. This enables regulators to document the data in a court of law, but it is not an

assurance of the quality of the science. Indeed, this standard study design has serious limitations and is not suitable for studies of chemicals like BPA that have hormone-like action.

"Importantly, the industry studies Mr. Hentges uses in his argument are deeply flawed. And concerns about the use of these studies by regulatory agencies are sufficiently serious that a number of scientists, myself included, felt compelled to write a commentary detailing the flaws and limitations for leading journal in the field, Environmental Health Perspectives."

And I have copies of this commentary as well if you're interested.

"What should you believe? The results of studies conducted by an industry that makes billions of dollars from this chemical or the results of studies conducted by some of the countries best academic scientists using innovative new techniques.

"I don't think you should be forced to choose. I think you should consider the evidence. If you do, you will find that as of August 2008, there were 218 studies of low-dose effects of BPA, 189 reported significant adverse

effects and 29 reported no evidence of adverse effects. Those of us who have been in this field for over a decade don't like those figures and we are very concerned.

"In my opinion, the evidence against this chemical is strong and very damning. Academic scientists don't have the financial backing or the professional spokespeople that the industry has, so our side of the story tends to be underrepresented, which is why a growing number of us have decided that we need to speak out about the flawed science that is being used to argue the safety of this extremely toxic chemical

"If you have further questions, I would be happy to speak with you by phone, by Email or in person.

"Sincerely, Dr. Patricia Hunt, Ph.D., Meyer Distinguished Fellow."

Thank you.

CHAIRPERSON BURK: Thank you.

I am getting nervous, so I please urge you when you come up to -- don't repeat what we've already heard. I know that everyone wants to be heard, but we really need to leave enough time for us to discuss this. And I will start timing you now.

Okay, next we have coming up -- yeah, I think we'll do that because we're never going to get done at this rate.

So the next group will be Anita Sarah Jackson, MomsRising.org. Rivka Gordon, Elisa Batista, Sophie Noero, Andria Ventura. Why don't we go with those people.

Well, you asked for five minutes, so we're going to hold you to five minutes.

MS. JACKSON: That's just fine.

CHAIRPERSON BURK: Okay.

MS. JACKSON: Good afternoon. Thank you so much. It's an honor to be able to make public comment before this Board.

My name is Anita Sarah Jackson, and I'm a member of MomsRising.org, which has over 40,000 members in California and over a million members nationwide. I'm a lawyer and I'm married to a physicist, which is just to say that there's a natural desire to dig up facts in our family and to consider the source of those facts. I'm a lay person when it comes to BPA. I'm a mom and the primary consumer for our household.

I'd like to make three simple points.

Point one, as a mom and the primary household consumer, I want to know what it is exactly in the products I buy for my family.

Point two, this science is clear, not just to me as a lay person, but among scientists and peer-reviewed studies. It's not about our feelings or my earnestness. It is about the facts brought to light by scientists with no ties to industry, who are based at large teaching hospitals, the facts.

Point three, there is nothing more conventional than a mother's desire to protect her family from chemicals that are a cause for clear concern in their effects in our bodies and our children's bodies.

Where I live in San Ramon, a suburb, is not a hotbed of green activism to say the least. So when I began to see consumer products bearing a BPA-free label in stores, I began to learn more. I learned from both scientific studies and the popular media that there are several routes of exposure, including my own breast milk. And I learned of BPA's toxicity.

During both my pregnancies, I was determined to be as healthy as possible. I used to be a labor coach for low-income pregnant women, and I saw firsthand the challenges and sometimes troubling outcomes when pregnant women did not or could not control their exposures to chemicals.

There's a lot we cannot control in pregnancy and in parenting, so the bottom line is to be able to make

informed choices about what we do consume. So maybe I'm something of an enthusiastic California citizen. I look up chemicals listed under Prop 65. And I appreciate that in this state, I can have a better understanding and awareness of my cumulative exposure to these chemicals.

Unlike my sister, who's a scientist living across the country, without access to similar information, who is experiencing now fertility challenges.

Most importantly, I am grateful that living here I can have more complete information of what my toddler and my infant daughter are exposed to. I want them to grow and live long past me, free from reproductive sorrows and grief, free from exposures to unnecessary chemicals, as they grow. And not just my children, but all children, including lower income kids who may rely on canned goods and should not be exposed to more chemicals simply by virtue of their socioeconomic status.

I must add that these babies deserve breast milk as their first food and not default to formula for sterile metal can. But if they must, again, they should not be exposed to even more chemicals simply because they're poor. Regular baby food does come in glass jars.

As a mom, I want to have the information I need to make the best choices I can for my family. Anyone who is a mother or has a mother, can relate to that. Please

remember that transparency is a hallmark of our democracy, so I ask you to please list BPA under Prop 65.

Thank you so much.

CHAIRPERSON BURK: Thank you.

MS. GORDON: Good afternoon, my name is Rivka Gordon. I am a physician's assistant, a woman's health care specialist, and the director of strategic initiatives with the Association of Reproductive Health Professionals, ARHP.

ARHP serves as the leading source of ACCME accredited trusted medical education and information on reproductive and sexual health.

ARHP was founded in 1963 and is multi-disciplinary professional association with over 11,000 members representing the full health care team, physicians, nurse practitioners, PAs, nurse-midwives, pharmacists, researchers, and educators, all with expertise in reproductive health research or practice.

ARHP and its members provide reproductive health services and education and conduct reproductive health research.

On behalf of ARHP and its members, it's my pleasure to make comment before this committee and in support of listing Bisphenol A on Prop 65. ARHP is offering comments today because we value evidence based

science and serve as the translating interface between cutting-edge science and reproductive age consumers.

We are responsible for educating health care providers with expert information, so that they can provide excellent care to their patients, safeguarding not only their health, but the health of their current and their future families.

History and science make clear that substances once considered safe have later been show to cause harm, and we all know examples of those, thalidomide, alcohol and tobacco, mercury, and DES are just some examples of those that we're familiar with.

Research informs us that a critical window of exposure may have much to do with the effect of a harmful exposure that may later play a significant effect on the woman's health or that of her child.

As a reproductive health issue, it's crucial for health care providers to learn more about the potential risks that may adversely affect their patient's reproductive health and pregnancy outcomes. It's important for women and their families to have all the information they need as they make decisions that can best support healthy lives and healthy families.

While the science is still emerging, what's presently known about BPA is worrisome. Human exposure to

BPA is widespread. It's in the seemingly inconsequential plastics and linings of metal cans that women of reproductive age babies and children come frequently into contact with and we've just discussed that over and over today.

Emerging research indicates that low levels of BPA that were previously thought not to be harmful are now associated with negative health outcomes. Research also indicates that BPA may be related to increased trends in humans and we've discussed them again. We've discussed them today, things like abnormal penile urethral development in males and early puberty in females, an increase in childhood and adult obesity, Type II diabetes mellitus, regional decreases in sperm count, many of the things that we've heard today.

Informed by research from the environmental sciences and confirmatory research in laboratory animals, who are exposed to levels of BPA that are relevant to human exposures, there's a growing concern about BPA's adverse effects on humans.

ARHP supports first-rate science in forming clinical decision making. Unfortunately, we do not always have the data we want to make absolute recommendation to our patients. But a limitation of a certain kind of evidence does not mean evidence of absence of harm.

Ethical concerns prevent us from ever being able to conduct randomized double-blinded placebo controlled studies on pregnant woman, exposing them to various levels of BPA or other endocrine disrupting chemicals.

Scientific uncertainty will therefore continue to exist. But based on the weight of the evidence from hundreds of scientific studies that we've heard about today, and the consensus of dozens of experts who have done excellent research on BPA, ARHP supports the recommendation that will decrease overall BPA exposure in our population.

ARHP recommends that this committee list BPA on Prop 65, in order to be able to protect California's public from this toxicant. ARHP and its members, many of whom are California's leading reproductive health clinicians and scientists, believe that the evidence supports listing BPA in order to protect people -- all of the people, especially women of child-bearing age, children in adolescence from the risk of exposure by adding BPA to the list Of chemicals under Prop 65.

Thank you.

CHAIRPERSON BURK: Thank you.

MS. BATISTA: This will be short. First of all, I want to thank this committee for it's important work and for looking into the chemical Bisphenol A.

My name is Elisa Batista, and among my many hats, I am a writer, a member of family organization MomsRising.org, and a mother to two small children, a five year old son and a two year old daughter. I live nearby in Berkeley, California.

At no other time in my life did I care more about the products I consume than when I became pregnant. For the first time in my life, I cared whether the food I ate was organic, whether their plastic containers had harmful chemicals like BPAs. And, yes, I read those warning labels on the walls of elevators.

I was extra cautious because all the birthing and parenting books I read, let me know that the first three months of my pregnancy were a critical time for my baby's development. I was worried, because I had already had two miscarriages, one at the age of 25. I really wanted to become a mother, so I was not going to take any changes.

I first read about BPAs in Newsweek and I was alarmed. Not only did the science around their toxicity seem real, but they are everywhere, including the plastic plates we eat from and the cups we drink from. I read that they have been found in human breast milk and even in babies.

What is frustrating about these articles is there's no way for the consumer to know which products

contain BPAs and which ones don't.

Categorizing BPAs under Proposition 65 would be helpful to prospective mothers. It would allow those of us uncomfortable with these chemicals to have the option to purchase other products. It would bring tremendous piece of mind to those of us who have suffered from multiple miscarriages or simply do not want to find out the consequences of long-term exposures to these chemicals.

Thank you for your time.

CHAIRPERSON BURK: Thank you.

MS. NOERO: Good afternoon. My name is Sophie Noero. I would like to thank the Committee for the important work you do and for the opportunity to comment today.

I work for an organization called Worksafe. We're a California-based nonprofit organization dedicated to promoting occupational safety and health through education, training, technical and legal assistance, and advocacy. We focus on eliminating all types of workplace hazards and also on workplace created toxic hazards that impact at-risk communities in California.

I'm here today in particular for those workers who can't be here to speak about their potential exposures. Often it is the low wage, non-english speaking

immigrant worker population who faces the greatest barriers in pursuing their right to know what chemicals they are working with and what their potential exposures are.

We believe that consumers have a right to know what it is in the products they use and why we are concerned about consumer exposure to toxic chemicals. Those concerns cannot be separated from the issue of worker exposure.

Workers are consumers after all, but manufacturing jobs that bring workers into contact with BPA are another important source of potential exposure to BPA.

Prop 65 listings have been very much a process that consider worker exposures. And indeed, chemicals have been listed based on scientific evidence that showed harmful worker exposures, 1-bromopropane being an example.

We are very concerned about workplace exposures to BPA, because the scientific evidence has been mounting regarding the dangers of this chemical. Workers are exposed to BPA and the chemical And manufacturing production processes. Workers usually do have higher exposures than the general population, and BPA is no exception.

Breast cancer, reproductive and developmental

health problem are very troubling issues. Occupational exposures to BPA are significantly greater than what the general adult population faces, a finding that has serious implications for both male and female workers, especially those of child-bearing age, who work in manufacturing and other industries using BPA or BPA-based products, such as thermoforming of polycarbonate and spray application of epoxy coatings.

In conclusion, we urge the Committee to follow the science, protect public health, and list BPA, so that all Californians, including our workers, are aware of their potential BPA exposure.

Thank you.

CHAIRPERSON BURK: Thank you.

MS. VENTURA: Good afternoon, and thank you for the opportunity to address you this afternoon.

My name is Andria Ventura and I'm here on behalf of Clean Water Action and our 60,000 California members. We are a national organization concerned with the environmental health of our communities, and in particular the water resources that those communities rely on.

I certainly -- and I will make this part very brief, I'd like to echo the remarks you've heard today regarding the strong body of scientific evidence that demonstrates Bisphenol A's role as a developmental and

reproductive toxicant, even at low levels, during the most vulnerable times of human development.

And we certainly entreat you to look at the most recent research that was presented earlier today. We believe it is strong and very compelling.

We've heard that the daily intake of BPA is primarily through our diet, and that that is a variable intake. Clean Water Action is concerned about another route of exposure, that is our drinking water, which can, in fact, provide a consistent dose intake over time.

Bisphenol A is being detected in water sources worldwide, and at levels that could impact human health. For instance, it appears to be a significant wastewater contaminant and is escaping through the wastewater systems into streams, lakes and even groundwater. In other words, we can't rely on treatment to adequately remove it.

There are a number of studies. I'm not going to go through all of them. I will just provide three very quick examples, that the U.S. Geological Survey found.

In a 2002 study of wastewater contaminants impacting water sources, BPA was detected in 41 percent of 139 U.S. streams that they looked at.

A study of drinking water sources published in 2008 found that Bisphenol A was one of the five most frequently detected organic wastewater contaminants

impacting groundwater sites that were tested. It was found in 20 percent of those sites.

And then finally, a third U.S. Geological Service study that same year found the chemical in 30 percent of the groundwater samples collected from 47 sites across 18 states. Fifty percent of Californians, I should tell you, drink groundwater. That is their drinking water source.

In sum, Bisphenol A is entering the environment with the ultimate effect of contaminating our drinking water supplies. Wastewater treatment is not removing it adequately to protect public health, and we are concerned that levels are significant enough to have potential impacts on public health.

Given this oft unconsidered exposure pathway and the clear evidence that we believe is out there that Bisphenol A does cause harm, we urge you to add this chemical to the Proposition 65 list. And I'll leave it at that. We thank you for your consideration.

CHAIRPERSON BURK: Thank you. The next folks will be Angie Garling, Alissa Shaw, Joseph Guth, Nancy Bellen, Sarah Janssen and Gretchen Lee Salter.

And I urge you to be as brief as possible.

DR. GUTH: Okay. I've timed this out at four minutes or so. Well, we're going to take a little of a break from the science. My name is Joe Guth. I'm the

legal director of an NGO called the Science and Environmental Health Network. Besides being a lawyer, I also have a Ph.D. in biochemistry.

But I want to focus on some of the legal issues that are involved in the decision that you're making today. It's actually an interesting and complicated decision that you're being asked to make, because it involves elements of both science and the law.

You've heard that other governmental bodies have made decisions about BPA and that's true. But keep in mind that every law that governs those decisions has its own purposes, its own structure, details its own criteria, and it's own balance of interests. So some of those decisions on BPA might be helpful to you, and some might not be. I just urge you to think about that when you're thinking about what the significance of these other decisions is.

So turning then to Prop 65. As you know, it can result in placement of warnings on products. But today you're not deciding whether products should have warnings about BPA. You're not deciding whether BPA is useful, whether it's important, whether it should be regulated, whether its benefits outweighs its costs. None of that is relevant to the decision that you're making today. And many of those issues aren't even relevant to Proposition

65 at all.

You are being asked, under the proposition by the people of California, who voted for Proposition 65 simply to make a threshold decision in a process that's established by that law.

And that is to answer the question of whether BPA has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity.

But I want to focus on my remarks here on those two words "clearly shown". Those two words establish the level of scientific certainty that Californians decided is appropriate for listing a chemical under Proposition 65. But what do they mean exactly?

So laws use different standards of certainty, depending on what they're trying to accomplish. The most common standard - you will know this one - is used in -- that is used in civil cases is called the preponderance of the evidence. It means 51 percent of the evidence.

In civil cases, the party with the best case wins, even if it's only by a hair. Another standard you know is the criminal one of beyond a reasonable doubt. This is a very high standard. It requires government to eliminate every reasonable doubt in order to obtain a conviction. And a doubt is reasonable, if a reasonable

person could believe it, even if you -- even if a particular juror doesn't.

So if there is a reasonable doubt under the beyond-the-reasonable-doubt standard, then a jury shouldn't convict.

Now, "clearly shown", the standard that you must apply today, is somewhere in between. It's similar to another commonly legal standard called "clear and convincing evidence". It's a fairly high standard, but it is not as high as beyond a reasonable doubt. It admits of some uncertainty, some conflicting evidence, some doubt. It even allows a reasonable doubt to be present.

So this means that once you look at all the evidence, you can find that BPA should be listed, even if you can also see that a reasonable person could disagree. The "clearly shown" standard does not require that the decision to list BPA be the only reasonable one. So there could be good reasons for a law to list a chemical even if there's a reasonable doubt.

Proposition 65 reflects a concern that the downside of failing to act once a danger becomes clearly shown. Using too high an evidentiary standard, risks false negatives and the consequent harm to public health. Using the clearly shown standard, allows California to start a process that could protect public health, even

where there is some remaining doubt.

So in conclusion then, California is asking you to apply the legal standard of "clearly shown". It would not be appropriate for you to use a different standard, even if that standard that you would use in your own work as a scientist.

It's entirely possible for you to think that further experimentation is needed to remove all doubt about whether BPA is a reproductive toxicant, and still at the same time conclude that BPA has met the legal standard for listing under Proposition 65.

So I think it's critical that you be very clear about this standard and the question that you're being asked to answer. And if there any doubts, I'd urge you to seek clarification from OEHHA's general counsel, Carol Monahan-Cummings.

Thank you very much.

CHAIRPERSON BURK: Thank you.

MR. BELLEN: Hello. My name is Nancy Bellen. I'd like to thank the Committee for the important work you're doing. I'm a mother, a wife, a daughter, a friend. I'm also a fourth generation Californian and I'm the first person in my family to be diagnosed with breast cancer.

Like most breast cancer survivors, I did not carry the breast cancer gene. At the age of 32, I was

pregnant and diagnosed with breast cancer. My invasive breast cancer tumor was found at a prenatal check. And at that time it was the size of a nickel.

Over the next 11 days, the tumor, which was clearly estrogen fed, grew to the size of a golf ball, which could be seen across the room with my shirt off. As a survivor of an estrogen receptor positive breast cancer, I'm at greater risk over the rest of what I hope to be a very long life, at a new primary cancer or a recurrence of breast cancer.

Through my own research, I've learned how important it is to avoid certain exposures -- to avoid exposures to synthetic estrogens like BPA.

But how can I avoid BPA if I don't know which products contain it?

It has become clear to me that daily exposures to toxins like synthetic estrogens are the cause of breast cancer in women under the age of 40.

What has the exposure to synthetic estrogens cost me? My child, my breast, 13 years of biopsies and more sleepless nights than I can count.

Future generations should be spared this risk and can be spared this risk of BPA, if BPA is listed on Prop 65. Listing BPA will give families and women like me at higher risk for breast cancer reoccurrence the information

we need to avoid the chemical.

I respectfully ask you to list BPA on Prop 65.

Thank you for your time and your attention.

CHAIRPERSON BURK: Thank you.

MS. SHAW: Good afternoon. My name is Alissa Shaw, and I'm associate vice president of Planned Parenthood Mar Monte, headquartered in San Jose. Our affiliate covers 40 counties in California. We have over 500 patient visits every year in our over 30 health centers throughout the State.

Thank you for giving me the time and opportunity to speak to you today, and for the important work each and every one of you does for the residents of California. We're grateful for your commitment to the health and safety of every child and every family living in this State.

I'm here today not only as a public policy advocate for the essential community health services that Planned Parenthood provides, which includes prenatal care, primary care, childhood immunizations, cancer screenings, in addition the reproductive health services, to all that need them, regardless of their ability to pay, but also as a parent to a one year old little boy and as a breast cancer survivor. I was diagnosed at age 27.

At Planned Parenthood Mar Monte, our mission is

to provide health services, information, and resources to our clients, so that they can make life-long healthy decisions for themselves and their families.

It is this mission and commitment to the people who we serve that we urge the Committee to join us in protecting the public's health, children's health, and list of Bisphenol A, the toxic chemical, numerous unbiased scientific studies have shown it to be on the Prop 65 list. Accessing information so that families can make informed decisions about their health, and the health of their cherished responsibility, their children, should be accessible to everyone.

At PPMM we take environmental health and its impact on reproductive health seriously. With our coalition partners, we held a speaker series last year that focused solely on environmental factors and reproductive health.

And the issue of Bisphenol A was a central topic at each and every event. We currently have a program in the Pajaro Valley, near Watsonville, to work closely with farm workers and their employers to protect the farm workers and their families from harmful chemicals.

As a mother, I can tell you this issue keeps me awake at night. And the science is very, very compelling. And as a parent, I want the best for my child and all

children.

As a breast cancer survivor, my story is horribly common amongst survivors. I had no family history. And I do not know why I developed breast cancer. Now, I know it's likely that I was exposed in utero, and that it's also likely that that is a reason why I had difficulty carrying a pregnancy to term.

In closing, I urge you to consider the overwhelming scientific evidence and independent studies that have concluded that even very small trace amounts of this toxicant causes specific and harm to the developing fetus, infants and children. Children depend on their caregivers to protect them. I urge you to give them the tools to do so.

Thank you again for the opportunity for me to speak to you today and thank you for the service and commitment that you have to a healthy California.

CHAIRPERSON BURK: Thank you.

DR. JANSSEN: Good afternoon. My name is Dr. Sarah Janssen. I'm a physician, board certified in occupational and environmental medicine. And I'm speaking here today on behalf of the Natural Resources Defense Council. I also have a background in reproductive physiology and an expertise in endocrine disrupting chemicals.

I want to commend you all for hanging in there for a lot of comments, and I'm going to keep my comments brief, because many of the things that I want to talk about have already been addressed, but I want to maybe make them in some bullet points.

The first is the characterizations of the NTP process. In addition to the endpoints that were identified in the levels of some concern, which have been held up today as reasons to support your listing, I wanted to also remind you that the NTP report, which was published and finalized in September of 2008, made several other conclusions that would support a listing on Prop 65.

These include, number one, that, yes, there is widespread exposure in the human population; number two, that BPA can "possibly" affect human development and reproduction; and number three, that based on the weight of evidence, there is "clear evidence of adverse effects", for high dose developmental toxicity in laboratory animals.

These same criteria have been used to list other chemicals on the Proposition 65 list in the past, including other endocrine disruptors, such as the phthalates.

I also want to come back to this question of maternal toxicity, which was brought up both this morning,

and then again this afternoon, but I'm going to mention that at the end of my remarks.

On the second point of the route of exposure in the low-dose studies, there's been a lot of discussion again about that today.

The NTP, in fact, did consider at least one dozen studies, which were identified as being of utility in their evaluation. These included eight low-dose studies and four studies that used a non-oral route of exposure. And I wanted to read to you one particular -- actually, two sentences from their report, which I think you have. They're on pages 13 and 14 of the NTP brief.

And the quote is that "Taken together, these data indicate that compared to adults at a given dose, neonatal rats, and presumably mice, metabolize Bisphenol A more slowly and suggest that differences in circulating levels of free Bisphenol A, arising from oral and subcutaneous routes of administration, as a result of first-pass metabolism, are reduced in fetal or infant animals compared to adults."

"And further, NTP concluded...", this is the second quote, "...while more research in this area is warranted, data from studies where Bisphenol A was given by subcutaneous injection were considered as useful in the NTP evaluation as oral administration when treatment

occurred during infancy when the capacity to metabolize Bisphenol A is low," end quote.

So therefore it's incorrect to say that you should discount this route of exposure as being relevant when you do your deliberations. The 12 studies I have listed here, in case you're interested in knowing what they were, but they were based on a variety of effects related to neuro and behavioral alterations, lesions in the prostate and mammary gland, altered prostate gland and urinary tract development and the early onset of puberty.

My second point is the characterization of the FDA analysis. There's been again a lot of discussion about that process today. The FDA did conduct a preliminary analysis last fall to determine whether there was an adequate margin of safety between exposures that are occurring in food and the current estimated levels of human exposure in toxicity, especially in vulnerable populations, such as infants.

The draft conclusions by the FDA that BPA was safe were sharply criticized by their scientific board of advisors, and the draft was never finalized. The key criticisms, include an over-reliance on the industry-funded guideline studies, which were the only studies used by the FDA when making their draft

conclusion. There were other criticisms for an under estimate of exposure and a too limited reading of the evidence.

Two of the bulletin points, which are from that report that I wanted to read for you, were, one, "The draft FDA report does not articulate reasonable and appropriate scientific support for the criteria applied to select data used in this assessment." And number two, "The weight of evidence provides scientific support for use of a point of departure substantially below at least one or more orders of magnitude lower than the five milligram per kilogram body weight day level selected in the draft."

And again, I'll remind you that five milligram per kilogram body weight per day level was based on the guideline studies.

In fact, FDA had a public meeting last September, which I was in attendance in. There was an invited panel of experts, many of whom are in this room from different organizations, which also included a representative from the National Toxicology Program.

That panel was asked by the Board of Science Advisors to state what they felt the dose level that FDA should be using when calculating their margin of safety exposure level. And there was an overwhelming consensus in the room or on that panel, I should say, that the

effect level should be considered to be ten micrograms grams per kilogram per day. This is on the record and you can obtain that information. Again, that level is based on the – "some concern" endpoints that were identified in the NTP report.

As a result, the FDA has gone back to the drawing board and is reevaluating the science on Bisphenol A.

My third point is, despite everything I just told you about the FDA, the question before you is not whether food is a major source of exposure or whether BPA is safe in our food supply. The other government bodies who have been held up as evaluating the evidence today also were evaluating the safety of BPA in food. And the question before you is very different.

You're being asked, as the NTP was, to decide whether or not the scientific evidence supports identifying Bisphenol A as a developmental and reproductive toxicant. NTP has reached this conclusion, and their analysis is most relevant to your deliberations today.

And then my fourth and final point is that on the topic of the generally accepted principles of experimental design for scientifically valid testing as you heard earlier, it's generally accepted by the scientific community that appropriately designed experiments used

both negative and positive controls.

And as was described in Dr. Vom Saal's presentation earlier today, many of the industry studies, which have been held up as the gold standard, have had problems with their positive control. There's also another publication, which I can give you, that was authored by a number of authors, including Dr. Vom Saal, which talks about some of the programs with the guideline studies.

In particular, I wanted to mention that, while the GLP studies are the federal gold standard for sharing laboratory credentialing, meticulous record keeping, and all of the other certifications that go along with that, they do not assure that the experiment has formed the right hypothesis, that the right questions were asked, or that the relevant endpoints were evaluated.

In this case, they did not include the more subtle, yet very important and relevant endpoints, of altered brain development, behavioral changes, and histopathological analyses of the prostate and mammary tissues using the very sensitive immunohistochemistry techniques.

On the issue of the maternal toxicity, I'd like to point you to the OEHHA draft brief. And while this is not my area of expertise, I will note that on page 31,

OEHHA staff talk about the statistical analysis of these studies. And note that there were a number of statistical outliers that were eliminated from the data sets, as well as using a one-sided rather than a two-sided group mean comparison for some of the variables, which could explain some of the reasons why there was a trend, but not a statistically significant change at the lower dose levels, which did not cause maternal toxicity. And I think maybe OEHHA staff could clarify this for you in your discussions.

So I wanted to conclude by saying that we feel the listing, based on each of the three endpoints is warranted, because of the large weight of evidence, and number of animal studies that have been done for all these endpoints in multiple species.

To disregard this large body of literature, which has demonstrated a wide variety of effects, in favor of a minority of guideline studies with design flaws and no evaluation of the endpoints that are relevant to neurobehavioral changes or the sensitive changes in the reproductive tissues of the prostate and mammary gland is not consistent with a weight-of-evidence approach.

I thank you for your attention.

CHAIRPERSON BURK: Thank you.

Last but not least.

MS. SALTER: Last in this group anyway.

Hello. My name is Gretchen Lee Salter, and I'm here representing the Breast Cancer Fund, and it's 17,000 supporters.

I thank you for examining the science on BPA. You truly do have an important job in front you. Part of that is to separate fact from fiction and relevant from irrelevant.

As Dr. Guth and others have stated, you are not being asked to ban the chemical. That is not your job today. It's merely to decide whether or not the evidence warrants a listing of the chemical.

Listening to the presentations just after lunch, I found it interesting to note that the metal can, food and chemical industry are employing the fear tactics that they promised to use at this meeting.

It was widely reported in the Washington Post and other publications last month that a meeting of these industries in Washington D.C. concluded that the best way for them to beat back regulation was to use fear tactics, such as claiming that there will be no more canned food if BPA is regulated.

It was also reported that these industries decided to make this Prop 65 meeting their test case for these tactics. I think we saw that they were true to

their word at least on that score.

Over 200 studies show exposures to low doses of BPA, particularly during prenatal period and early infancy are associated with a wide range of adverse health effects and exposures that occur before birth are particularly troubling to us as the effects on the developing fetus are irreversible and can be transgenerational.

Recently, the Endocrine Society concurred with a statement, "The Endocrine Society is an international body with 14,000 members from over 100 countries. The Society's membership represents medicine, molecular and cellular biology, biochemistry, physiology, genetics, immunology, education, industry, and other allied health fields."

This well-respected group of scientists released a scientific statement stating that endocrine-disrupting compounds, like BPA, can affect not only the individual but also subsequent generations. This statement also concluded that quote, "Exposure to estrogens throughout a women's lifetime, including the period of intrauterine development is a risk for the development of breast cancer. The increased incidence of breast cancer noted in the past 50 years may have been caused in part by exposure of women to estrogen-mimicking chemicals."

This is the first time in this Society's 93 year

history that it has released such a statement.

BPA is classified as an endocrine disrupting compound, and is often cited in the Endocrine Society statement. Its ability to mimic estrogen is not surprising, because the chemical was developed in the 1930s as one of the first synthetic estrogens. BPA was soon shunted aside as a pharmacological estrogen in favor of diethylstilbestrol, or DES, now known to cause cancer and reproductive abnormalities and is California's Prop 65 list.

In 1941, the Food and Drug Administration ignored the animal evidence of DES reproductive toxicity and approved it for use in humans and subsequent years during pregnancy and for use in cattle and poultry. Between 1941 and 1971 an estimated five to ten million women were prescribed DES. Their daughters and granddaughters paid the price, reproductive abnormalities and rare vaginal cancer that led to infertility and sometimes loss of life.

Research has shown that the daughters who were exposed prenatally had a nearly two-fold increase of breast cancer risk for women over the age of 40. And DES is a recognized reproductive toxicant and transgenerational carcinogen.

I mention DES, because we cannot continue to make the same mistakes that have been made in the past. A

number of studies in rodents have shown DES like effects, from prenatal exposure to BPA. For example, one study showed that neonatal exposure to low levels of BPA causes uterine fibroids and cystic ovaries in middle-aged female mice. In women, such effects are major contributors to infertility and most common reasons for hysterectomy.

The science is clear and it is compelling, BPA causes a wide range of developmental and reproductive effects. The materials that have been prepared by OEHHA staff, and in addition to the presentations that you've heard from Dr. Vom Saal, Dr. Woodruff, Dr. Solomon demonstrate the clear reproductive and developmental harm from BPA.

In addition, I also urge the Committee to heed Dr. Janssen's presentation that she just gave pointing out the flaws in some of those studies presented by the industry-funded study earlier today.

While these vested interests claim that BPA does not cause harm or that the science is unclear, I would ask the panel to recall that we have heard such protestations in the past from the tobacco industry as well as the lead paint industry.

These industries wanted to continue using their products that scientists knew were harmful, and therefore manufactured their own science to support their aims

causing unwarranted doubt, uncertainty and inaction on the part of regulators that led to needless harm of Californians and the American public.

It is clear this pattern is being repeated. We must not allow industries who stand to gain financially from your decision to confuse and cloud the issue.

Given the evidence of the multi-system transgenerational hazards of BPA, it is essential that this chemical be legally defined as a developmental and reproductive toxicant. Failing to do so would knowingly put the public's health at risk.

Thank you very much.

CHAIRPERSON BURK: Thank you.

How is our court reporter doing?

THE COURT REPORTER: I am fine.

CHAIRPERSON BURK: Do you need five minutes?

THE COURT REPORTER: No, I'm good.

CHAIRPERSON BURK: Okay. We will begin our committee discussions now.

In order to facilitate this, I have sort of pre-assigned people to take the leads on the three main endpoints here. And so I'm arbitrarily going to start with the male reproductive system. And I guess for that we have Dr. Ken Jones and Calvin Hobel, so which one of you would like to -- shall I choose?

Well, why don't you start, Dr. Hobel, and then we'll get the discussion going.

COMMITTEE MEMBER HOBEL: Yeah, I think you wanted me to focus on male reproduction --

CHAIRPERSON BURK: Could you move closer to the mike.

COMMITTEE MEMBER HOBEL: You wanted me to focus on male reproduction.

CHAIRPERSON BURK: Yes.

COMMITTEE MEMBER HOBEL: And, you know, I find this very difficult, because if I focus on sort of what I spent most of my time looking at, I reviewed very carefully all the information. I looked at the NTP and the CERHR monograph. And I really liked the way they looked and ranked the risk.

I think they did a very good job in giving some parameters to look at. But if I look at their assessment of reproductive effects, they indicate there's negligible concern about exposure to BPA.

However, in that same paragraph, they mentioned that it's mainly in reference to non-occupational exposure. And when you look at occupational exposure, they add additional risk by saying it's minimal risk. So that at least points out to me that there are, you know, two groups of people you're looking at, in terms of

reproductive toxicology.

So I'd like to just step back for a minute and sort of let you know how I look at this issue. I think there are really four different issues. One is the timing issue. In perinatal biology, I think that what we're now doing is looking at the life-course perspective over time. And when you do that, you begin looking at sort of reproduction and pre-conceptional events. Clearly, in reproduction medicine today, it's very clear that with IVF, for example, there's been identified effects of the environment on sperm and eggs. And the epigenetic phenomena that's been described is quite remarkable, that there are effects on sperm and the unfertilized egg, leading to changes in the genetics. And some of it has to do with imprinting of genes that goes from generation to generation.

So I think that then when you move into after fertilization, and with the development of the fetus, and then the fetus then with implantation is exposed to the mother. And then to the effect of the transfer of the substance to the fetus increasing the risk. And, you know, it's very clear that there's a very big difference between levels in the fetus and in children.

And clearly, that identifies an area of risk, but then that risk decreases as the child gets older, and then

during adulthood.

But then when you even go toward the end of life, the recent article published showing that there is a relationship between BPA and diseases, like cardiovascular disease and diabetes. So clearly, there's a difference over time, and that makes it very difficult to, you know, point your finger at one area of this continuum and say that's an area of concern when other areas may not -- there may be less risk.

Then we already talked about the difference between the consumer and workers exposed to BPA. Then there's a difference in the models that are used to study this, whether you're looking at animal experimentation or human exposure. And there are really very big differences between metabolism and the turnover rates of BPA in terms of animals compared to humans.

So trying to put all that into perspective has been -- is a bit difficult, but I felt that what I mentioned about the National Toxicology Program assessment, I think they did really quite a good job.

But I think that as I begin to identify the areas that are of concern, I think there are areas, and especially in the more recently published data, which I think is very important for us to consider. The primate studies in the monkey recently published by Nakagami, and

showing this behavioral sexual dimorphism. So this suggests that it doesn't only affect the reproductive system. It affects the brain. And so this is an area of major concern in perinatal biology today because of the high incidence of autism and all these issues with children, behavioral problems.

So I think that then as you go into other areas. The area -- the recent publications by Hugo on the effect of obesity, and the effect of BPA on some of the hormones that play a very important role in insulin sensitivity.

So I think that there are things that are beginning to develop that clearly points to me that there are areas of risk. And so I think that as I look at this, clearly there's more studies that need to be done. They need to be carefully designed. And as you probably know, in the United States, there are plans to have a national children's study. I'm very involved in that in Los Angeles. In Los Angeles, we're going to follow a 5,000 women over five years and their children for 20 years. And we're collecting all kinds of samples, urine samples, blood samples, samples from the carpets, samples from the walls, samples from the yard.

And, you know, I think a study like that over the next many years would give us important answers. But do we wait 20 years? I'll be 90 years old.

(Laughter.)

COMMITTEE MEMBER HOBEL: So clearly I think there are issues. And the way I presented it to you, it's going to help me decide how I'm going to vote.

And so that's the end of my comment.

CHAIRPERSON BURK: Okay. Well, maybe I'll -- actually, before Dr. Jones starts, I did ask, just to be thorough here, Ellen Gold to look at all the human studies. So maybe you want to comment on -- and let's stick to male first so we can be more systematic here and then we'll go to the animal.

COMMITTEE MEMBER GOLD: I think in the interests of time and the lateness of the hour and the fact that OEHHA's staff did such a good job reviewing this morning, I don't need to go into the details of the studies. And so maybe I'll just jump to sort of my summary at the end.

So I just have two sentences.

CHAIRPERSON BURK: Perfect.

COMMITTEE MEMBER GOLD: I mean, they did summarize -- there are seven studies published on the topic that are human studies, four of which were in vitro and then there were a couple of small cross-sectional studies.

So in summary, just jumping into it, I think the data on human male reproductive toxicity are largely

cross-sectional and derived from very small studies with inadequate control of confounding variables. And therefore even though some of the positive -- even though some positive associations were reported with gonadotropins and so forth, the evidence seems inadequate to determine if BPA -- so this is the human evidence -- to determine if BPA has an adverse effect on human male reproduction.

CHAIRPERSON BURK: Okay. Are we all pretty much in agreement that we're not certainly going to be able to identify BPA as a male reproductive toxicant on the basis of sufficient human data?

So that brings us to the animal.

COMMITTEE MEMBER JONES: Right. So I will just start off by saying that my comments here are based, to a great extent, as were yours, on the NTP, CERHR expert panel report, as well as the DART Committee report, both of which I think were incredibly good and very complete.

And I'll just also sort of cut to the chase here. I think that Bisphenol A at low concentrations that would be expected for the majority of people in the State of California, and by that I mean those who are not occupationally exposed to BPA over long periods of time.

I think it is my estimation here that BPA has not been clearly shown to be a male reproductive toxicant.

Secondly, I would say that for men who are exposed for prolonged periods of time at high concentrations, concern has been raised, primarily based on animal studies. And I would bring that up as you did.

However, at this point, I don't believe there is sufficient scientific evidence that BPA is a male reproductive toxin. And I think obviously that there is a need for further studies on this. And I would await them in terms of like National Children's Study and others. And I know that there are studies going on now in humans looking at this.

But at this point, I don't think we have enough evidence to say that this drug is a reproductive -- or this chemical is a reproductive toxin.

CHAIRPERSON BURK: Male reproductive?

COMMITTEE MEMBER JONES: Yes.

CHAIRPERSON BURK: The highest level of concern by NTP was for the prostate endpoints. What's your thinking on that?

COMMITTEE MEMBER JONES: Let me be specific here.

CHAIRPERSON BURK: I know you gave kind of a general. I do want to make sure that we -- if anyone has anything to say about any of those that they have a chance to say it. And I know you tend to be relying on them. But that was the one that got the greatest level of

concern.

COMMITTEE MEMBER JONES: Yeah. The way I read this data, primarily from the DART Committee's summary is that BPA leads to primarily non-significant effects in some studies using advanced molecular and or cellular approaches, but not using traditional methods, such as organ weight or routine histopathologic evaluation.

And the way I read this was that there was statistically significant in one of three studies in which molecular and/or cellular studies were done in mice. And that there was a lack of statistical significance as far as the prostate in rat studies, but I may be wrong here.

Does anybody from the Committee want to comment on that?

CHAIRPERSON BURK: I think a staff comment would -- to make sure we're on the right page here.

DR. LI: So are you asking for clarification of the prostate studies?

COMMITTEE MEMBER JONES: I am, yes.

DR. LI: I actually have a slide of the five studies that used the quantitative Or immunostaining method, if you want to look at it, the data will --

CHAIRPERSON BURK: I think we have it in our handouts here, so we can just refer to it.

DR. LI: Yeah. And talking about the statistical

analysis of each individual studies, I don't remember the details.

CHAIRPERSON BURK: Well, I think the bigger issue is --

COMMITTEE MEMBER JONES: If you look at page 142 here in this chart, I think that the changes in dose ranges that were significant are in bold. You can't hear me -- are in bold. And I don't see too much here that's in bold, except perhaps this adult exposure study on the bottom.

DR. LI: Okay. As much as I can remember the details, if there is a statistical significant analysis, if it is not significant, I would report it as not significant. I mean you see a change, but it's not significant. If you see anything that I've said that increase the volume that means what's also reported, okay.

If they did the analysis, it's significant. If they did not do analysis, that's what they say.

If you look at -- if you look at the prostate this in mice on the screen, you have the Y uses the quantitative immunostaining. So those are the five studies. I don't think most of them are histopathological studies. They don't routinely do statistical analysis.

CHAIRPERSON BURK: Are you saying they don't use statistical analysis on the results of immunostaining?

DR. LI: Not often. I mean, you know, people do that academic research studies and they report the slides and look at -- review the tissue sections to find out what is representative, you know, of the lesion then we report it.

But we can go back to look at each individual study to see which one did analysis and which one didn't.

COMMITTEE MEMBER JONES: And how about on Table D6.

DR. LI: D6. So what's the question?

COMMITTEE MEMBER JONES: The question is the significance of the studies? These are not the -- these are just the histopathology and other changes in dose ranges. I don't think they're --

DR. LI: For the studies by Timms et al., I believe that was from a group associated with Dr. vom Saal. I think he can speak for their study better than I do.

And for the studies of Ogura et al., and I don't believe that study did a statistical analysis.

Yeah.

CHAIRPERSON BURK: Okay. Yeah, I just wanted to make sure that we addressed -- essentially, what I've heard is that the quote "guideline studies" don't look at these in great detail, but some of these others have. And

I think the big question is, is that clear indication of male reproductive toxicity? In other words, can we reasonably expect that to go on or not?

COMMITTEE MEMBER JONES: Translate into problems?

CHAIRPERSON BURK: And we don't really have the kind of data that we would like to see that would show male reproductive toxicity in a -- maybe more from the fertility point of view or more from -- you know -- but, you know, you have to be concerned about these things. They probably mean something, but it's just hard for us I think to --

COMMITTEE MEMBER JONES: It would seem to me that we're still --

CHAIRPERSON BURK: -- say that it's clear.

COMMITTEE MEMBER JONES: Right, I agree with you.

CHAIRPERSON BURK: I don't know, any other comments on that?

DR. LI: I just wanted to clarify table D6 is just studies in mice. Also, you have one, two, three studies in rats that is another slide, you know, a PowerPoint slide.

So if you're looking at table D2 on page 142, it's just studies in mice.

CHAIRPERSON BURK: So it's a combination between that and what's on our screen?

DR. LI: Yeah. Then you should look at Table D7 as well. That is on page 144.

CHAIRPERSON BURK: Well, I think the bottom line was, again, what we've heard is, if you use more sensitive techniques, you may see something, but again --

COMMITTEE MEMBER JONES: We don't know what the true endpoint is.

CHAIRPERSON BURK: It's hard to know what the true outcome of that is going to be.

DR. LI: If you think about the long-term study, that one study on the slide is by Dr. Ho et al., '06. That study treated animals against SD rats neonatal, then wait until the animals grow into adulthood, give combined injection of T and estrogens and they found it increased the incidence of -- what is it called at PIN, which is cancer.

So if you question is about the meaning of the effect, there is at least one study that found that effect.

CHAIRPERSON BURK: Okay. So you consider that's outright cancer and that it was initiated prenatally.

DR. LI: Neonatally.

CHAIRPERSON BURK: Neonatally.

DR. LI: I'm not saying it's initiated. What I'm saying is the neonate was treated with Bisphenol A by SC

injection at a level, if I remember, it's about ten micrograms per day -- per kilogram per day of injections into the neonates. They let those animals grow into adulthood, then give an injection T & E, then those animals develop, you know, neoplastic lesions, which is also investigated through epigenetic mechanism, because you are asking the meaning of the effects. That's one study that found that effect.

CHAIRPERSON BURK: Do you know, and I think this was in the documents somewhere, if BPA has been evaluated as a carcinogen?

DR. LI: That's not in the topic of our review, but there are review papers on that issue.

CHAIRPERSON BURK: All right.

Go ahead.

COMMITTEE MEMBER ROBERTS: Carol, for clarification, would neoplastic lesions that are attributed to exposure neonatally be under the DART Committee or under the Carcinogen Identification Committee?

CHAIRPERSON BURK: I know if it's transplacental carcinogenesis, meaning prenatal, then it would be in our domain, otherwise I'm not sure.

DR. DONALD: That's an issue that we've never actually formulated a position on. It could be argued

that it does fall under the province of the cancer committee, unless you consider the lesion to impact the reproductive potential of the animals, but I think it's probably an issue for you to determine rather than us.

CHAIRPERSON BURK: Because I think on page 23 of the HIM, there is a little thing on carcinogenicity, but interestingly, it seems like the only thing you're -- it says the European Union stated the evidence does not suggest carcinogenic activity of BPA in rats or mice, but now it says maybe a modulator.

DR. LI: Yeah. One of mine personal opinions for you to consider -- to think about how to address this issues is to think about the clinical. You know, doctors, you know, who treated the prostate disease or cancer, usually go to the American Society of Andrology meeting. So it's a male repro effect. So I don't know whether that will carry any weight or not, but, you know, it's a male repro issue. Again, that's from my personal opinion again.

(Laughter.)

CHAIRPERSON BURK: Well, what about the legal, did you have any comment on that?

CHIEF COUNSEL MONAHAN-CUMMINGS: Boy that's really sensitive.

Maybe you could frame the question for me a

little differently, so that I could see where the legal question is, whether you can consider something that may cause cancer later to be a male reproductive effect, is that what you're asking?

CHAIRPERSON BURK: Yeah, I think we're just trying to distinguish between the cutoff between it being a developmental effect and a male repro effect, I guess.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. So it would seem that the cancer could have to affect the male reproductive system or process, right?

CHAIRPERSON BURK: Um-hmm.

CHIEF COUNSEL MONAHAN-CUMMINGS: So, you know, it's probably not as clear as it could be, but it is somewhat in your area of expertise whether you think that is an effect or not. It wouldn't necessarily be a legal question, per se.

DR. DONALD: One other thing you might perhaps consider is the histopathological effects on reproductive organs are typically regarded as reproductive effects. So a neoplastic lesion could be interpreted as a histopathological effect.

CHAIRPERSON BURK: That's true, but then we're back to the not seeing anything in the sort of typical histopath observations. And then these indications here with changes in the epithelium, the proliferation and so

forth, but one of them showing increased neoplastic lesions.

COMMITTEE MEMBER ROBERTS: How old were the rats when they were --

COMMITTEE MEMBER JONES: Mice.

COMMITTEE MEMBER ROBERTS: No, this one says rats -- when they were evaluated for neoplastic lesions?

DR. LI: If my memory is correct, I think they also injected the Bisphenol A on Day 1, 3, 5.

COMMITTEE MEMBER ROBERTS: And when they looked for the neoplastic lesions, they were how old?

DR. LI: That should be the adulthood. It should be at least 90 to 120 days old. I don't remember the -- it's the adult.

COMMITTEE MEMBER ROBERTS: You said how old?

DR. LI: At least 90 days old. I don't remember clearly, but we can go back to the study, described in Appendix too, there should be a description for that study.

COMMITTEE MEMBER ROBERTS: The reason I'm asking, is that I'm comparing it to the age of animals from reproduction studies, and those are typically around six, eight weeks old when they get started on exposure. They have to go for ten weeks in advance. The don't typically get sacrificed until -- well, obviously until the breeding

part is over, sometimes a little bit later, so they would be within that age range. They would not be two year old rats?

DR. LI: No, certainly is not two years old. That's what I remember.

COMMITTEE MEMBER ROBERTS: Thank you.

CHAIRPERSON BURK: Okay. Well, we've got to keep moving. Are there any other comments about male reproductive toxicity?

DR. LI: Twenty-eight weeks. The animals were 28 weeks.

CHAIRPERSON BURK: Twenty-eight weeks.

DR. LI: So it's about half a year, six months old.

CHAIRPERSON BURK: Tough one. Any other comments?

I think -- you know, I hate to rush this, but I know we want to be able to discuss the others endpoints.

Any other -- anybody else want to make a case for these more sensitive changes and/or carcinogenicity?

If not, are we ready to vote?

We can vote now or we can wait till the end and vote on all of them? Which would you prefer?

You want to vote on all of them at the end. That's probably wise. I don't want to rush anybody on

anything.

So let's move on to the female reproductive toxicity. And for that I have asked Dr. La Donna White and Dr. Gold to take the lead. So would you like to go first, Dr. White?

Dr. Gold, would you like -- which color do you prefer, gold or white?

(Laughter.)

CHAIRPERSON BURK: Take it away.

COMMITTEE MEMBER GOLD: I'm going to take the same strategy as I did before, which is not to summarize again all the studies that were summarized this morning, and also in the handouts so effectively by the OEHHA staff.

Just briefly, there were seven studies, six of which were cross-sectional and four of which were very small. And so then with without going into the particulars, let me just go cut to the chase, which is my summary.

The human evidence regarding female -- I'm doing human, right?

CHAIRPERSON BURK: Sure. It's a good place to start.

COMMITTEE MEMBER GOLD: I think that's what you asked me.

So this is the human evidence regarding female reproductive toxicity is largely cross-sectional with inadequate control of confounding variables making the determination of the likelihood of any causal relation almost impossible. And the three studies with potentially adequate samples size and some control of confounding were also cross-sectional and found no associations.

Therefore, the human evidence seems inadequate to support a causal relation of BPA to adverse effects on female reproduction in the human.

CHAIRPERSON BURK: Okay, do you think any of those studies would lend support to any of the animal studies? Or maybe can I ask Dr. White if she has --

COMMITTEE MEMBER GOLD: Let me think about it for a minute.

CHAIRPERSON BURK: Okay. Think about it and let's hear what you came up with.

COMMITTEE MEMBER WHITE: Well, I think for me the thing that was most interesting and compelling with respect to the data, of course, is the high dose. The high doses in the animal models. And I know we're talking about humans, and you had mentioned the animal model.

There was insufficient evidence for me to feel like we could actually say that there is an effect with respect to female developmental and reproductive toxicity.

I'm not so sure that can be extrapolated on -- the animal model can extrapolate into the human model, because the doses were so incredibly high. They were very high doses that we would not expect humans to be exposed to.

So looking at the weight of the uterus, looking at possible mammary lesions in the mice and possibly rats, a lot of the data said possible, maybe has the potential. But I didn't quite feel like there was conclusive and clear evidence to be able to say that in doses where humans would normally be exposed, there would be an adequate toxicity to affect development and reproduction. I didn't see it.

I suppose it could be there. But the thing that really made me think that I was very interested in would be the BPA -- the level of BPA and the structure of the BPA in the amniotic fluid. I think that would be something to really take a look at, because the endpoint, of course, would be any effects that it could have on the fetus, and then, of course, the newborn. That to me is most interesting at this point.

There's not enough information to say that -- with respect to females and reproduction, that there is a problem at low doses. Everything is just really confusing in the literature with respect to low doses.

High doses, we know that. We have information

there. But I'm not exposed and I don't think anyone here is exposed to greater than 600 milligrams per kilogram per day of BPA. If we are, then we need to see the studies. We need to see the human data on that to make it compelling. It's not compelling for me with respect to female reproduction. I just can't see it.

And I can't see the extrapolation of the animals into human data. I can't see it, primarily because of the physiology -- well, not the physiology, but the biochemistry and the bioavailability of BPA after it's actually been -- after humans have been exposed, it actually converts to an inactive form. But in that inactive form, if it's at high-dose levels, anything -- particularly with meds, as we know, the higher you go with respect to dose, then you're going to start to see some effects.

But I'm not convinced that the data is clear with respect to the inactive form that we tend to see in humans more so than we do in rats or mice. I'm not clear. It's just not clear. I mean, if it is, somebody please tell me that it's really clear, because I have not -- I've heard clear evidence. I'm still looking for it.

CHAIRPERSON BURK: Well, we all have our, as we heard before, probably our own definition of clear. So I want to make sure that we address some of these things.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, could I just make one clarification in terms of what the Committee is doing today. One of the considerations is not what the current dose is that people are receiving. And so I understand that you don't believe that people are currently receiving a particular dose or we don't have evidence of that.

But the dose that a person would be receiving or, you know, those kind of things are not considerations for today, because it's a matter of identifying the chemical as causing the effect or not in animals or humans. And we deal with those at a different point in the Prop 65 process.

So I just want to clarify that. And I'm not saying that you were incorrect, but I just want to clarify that if you're basing your -- hold on. Wait.

COMMITTEE MEMBER WHITE: No, I'm not basing my decision.

CHIEF COUNSEL MONAHAN-CUMMINGS: I understand that. And certainly the dose is something that you do need to consider when you're looking at the difference between animals and humans. And so that's why I just want to clarify that at the point where you make a decision about whether it causes an effect or not, you can consider the evidence in animals, even if there's no evidence at

all in humans.

COMMITTEE MEMBER WHITE: Right. Right. I understand that. I'm speaking in respect to the NTP brief and what was mentioned with respect to the high doses verse the low doses in animals, as well as with humans.

CHAIRPERSON BURK: I think I understand what Carol is trying to say though, is that we are performing just the hazard identification step of a risk assessment --

COMMITTEE MEMBER WHITE: Right. No, I understand that.

CHAIRPERSON BURK: -- and we don't have to determine a dose. What we have to do is sort of weigh the evidence of the studies we've seen --

COMMITTEE MEMBER WHITE: Yeah, that was sort of an aside with respect to the human concentration.

CHAIRPERSON BURK: -- to make a determination if we can say that it's known to be, you know, one of these endpoints at any level I suppose. I think maybe the bigger issues here are more with the fertility and so forth, the role of maternal toxicity, and so forth, as just a way to understand those kind of things, but --

COMMITTEE MEMBER WHITE: Right, and those things are still not clear.

CHAIRPERSON BURK: -- it still doesn't dismiss

the more sensitive endpoints and the lower dose things. So I think we have to consider them.

Did you have any thought on the mammary gland, which was, I think, mentioned by NTP as --

COMMITTEE MEMBER WHITE: Right. Based on the higher doses -- or the doses in the rats that there were the possibility of mammary gland alterations and lesions. I mean, that can be significant when you're thinking of breast cancer lesions, et cetera. I mean, that is significant. I think that's very significant. And so, yeah that did impress me. I did see that and I thought that was pretty significant.

CHAIRPERSON BURK: Linda.

COMMITTEE MEMBER ROBERTS: Are there any life -- did anybody in the room, please raise your hand, are there any lifetime exposure studies with Bisphenol A?

DR. HENTGES: Are you talking cancer studies?

COMMITTEE MEMBER ROBERTS: Yes, I'm talking two year bioassay type of studies.

DR. HENTGES: Yeah, there are lifetime studies -- these are NTP -- sorry, Steve Hentges -- lifetime bioassays by NTP rats and mice, male and females. Those were probably published around -- or reports around late eighties or so. And they concluded -- I don't remember the terminology they used, but basically they didn't find

any compelling evidence that BPA was a carcinogenic risk.

CHAIRPERSON BURK: Yes. And one second -- I mean, please go ahead and then Lauren will speak after.

DR. vom SAAL: I just wanted to briefly mention that Dr. Huff from the National Cancer Institute has actually written an article - that I have, that I'd be happy to give to your staff - that draws the conclusion that if Bisphenol A were evaluated using current standards, it would be deemed a carcinogen, based on the studies that Dr. Hentges just mentioned to you. And that is a National Cancer Institute scientist who's written that.

I'd be happy to give those reports to you.

DR. ZEISE: Yeah. We didn't evaluate the carcinogenicity studies. And I would like to point out there has been a good deal of work looking at some of the developmental effects on the mammary gland. And we did see some discussion earlier today, but we didn't evaluate those studies. There are many studies exploring both effects on breast cancer as well as prostate cancer.

CHAIRPERSON BURK: All right. Well, so I think as far as it goes, we may be able to sort of defer that, because we really don't have the information that we would need to have.

Any other comments on female reproductive

toxicity?

Let's move on to developmental tox. And I've asked Linda Roberts and Carl Keen to take the lead on that, and I'll chime in myself.

I'll let Linda go first.

COMMITTEE MEMBER ROBERTS: Thank you.

CHAIRPERSON BURK: Always.

COMMITTEE MEMBER ROBERTS: I tried to limit myself -- although there are a huge numbers of studies, what I tried to limit it to --

CHAIRPERSON BURK: Get closer to the mike.

COMMITTEE MEMBER ROBERTS: Better?

Although, there are a huge number of studies, what I tried to limit myself to are where the exposure in the animal studies occurred in what would be considered equivalent to prenatal exposure in the human, which is pretty much the gestational period in a rodent, plus maybe a few days afterwards.

And because we're looking at clearly shown, I focused upon the manifestations that the consensus of manifestations of developmental toxicity that have existed for a long period of time, which is the prenatally, the malformations, the growth and the functional changes.

And, of course, in the functional changes, that's one of the areas of teratology that is really still in

progress and always will be in progress. And so there are new bits of evidence about that, that may be becoming stronger with time.

We referred to high dose studies. The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other.

And when you have situations where the animals are either losing weight or gaining very little weight or they're described as emaciated, that to me can be a cause of something like an increase in resorptions prenatally. Surprisingly, even when there were some fairly strong forms of maternal toxicity, it did not cause malformations. So it doesn't seem that that particular endpoint out of the four is of concern.

When there is maternal toxicity, it does have a decrease in fetal body weight. It has an increase in prenatal loss. Those are both endpoints that are more commonly associated with severe maternal toxicity than others.

And a decrease in ossification does not -- as long as it is a decrease in ossification, and not a structural change, it tends to go along with decrease in

fetal body weight.

There were some less common endpoints that were evaluated in some studies. Those included changes in gene expression, lung -- the retinoic gas receptors, which are known to be affected for things like retinoids which are known to have developmental effects, but they change the receptor expression, and they end of up having malformations, so there is something different here between whatever Bisphenol A is doing and whatever retinoid gases are doing.

There was a prenatal study that founded a change in the -- a decrease in the number of splenic lymphocytes. One study was just prenatal. It was supported by a study that was both pre- and postnatal. We don't have an actual immunotox follow up to review with that. There was a change in sheep in the amplitude of the luteinizing hormone surge. The N was 11. I should say also I tried to look for studies that have group sizes at least in two digits. I don't tend to put a lot of strength in N of 2 or 3 or 4.

And there were changes in anogenital distance of -- in mice there was one that was longer in females and longer in males. That didn't seem to be consistent with what I would be expecting.

You know, I'm -- that's pretty much where it

comes to. There are clear effects from the high-dose levels. At least, in my perspective, there are not clear effects on the low-dose levels, because we have seen situations where some studies are positive and some studies are negative. And when you do have very small numbers of animals in groups, that does increase the variability within a group.

And it either makes it harder to statistically find something. It also puts a lot more variability in it. So if anything, when I've come through this entire binder of information, one of the strongest most compelling things, that I hope some of you who do research in here come away with is please put adequate numbers of animals into it, so we have clearer evidence whether a study is negative or positive.

CHAIRPERSON BURK: Carl.

COMMITTEE MEMBER KEEN: My reading of the binders was remarkably similar to what you read. As is usually the case, I'd like to really compliment OEHHA for bringing a lot of these together, because I think the materials that we got were -- I'll use the word "overwhelming", but in a positive sense of the word. It gave a pretty good comprehensive view of what the state of the literature is. I just want to iterate some of the points so it's clear that we're pretty much on the same page.

As I look at the literature, I see very little evidence that there is an increased risk, absence of maternal toxicity, of fetal or neonatal mortality. I don't see any clear trends for malformations or specific birth effects. No clear evidence of reduced birth weight or growth.

In the occasional paper, and there's over 70, which I went back and read each of the individual papers, you'll find a sporadic report of something. But where I get a little concerned or actually quite concerned is the lack of consistency as you go across the reports. Part of this is because the doses which are used in the different studies are all over the board. And sometimes -- I don't want to use the word "deceptive", but it is not helpful, because you'll read one thing in an abstract and then later you'll find out well, that's not quite what they meant. As an example with the Nakagami paper, which has been referred to, which I think is very provocative.

This is the very recent non-human primate Rhesus monkey study. You'll look at the abstract, and it says the dose was ten micrograms per kilogram. One gets very excited at that point or a concern and excited sort of fashion, when they say there's behavioral abnormalities, but that was done by -- deep in the paper it says well, this really translates into a dosage of five milligrams

per kilogram. I appreciate that we're not supposed to be focused on doses here, but that is in the same range where one does see signs of maternal toxicity, so one cannot completely ignore it.

My own sense is that the literature is confused, because you almost have to construct tables as to what is the real dose which is being administered to the mother and how might maternal toxicity be differentially expressed when it's given internally by intraperitoneal injection or perhaps my mini pump relative to when it's taken orally.

I was -- I found very persuasive that the classical or conventional animal test studies, I think the two- and three-gen studies have a bit of a bright line that say that if you see evidence of maternal toxicity, even using old conventional methodologies, that seems to be about where the trigger point is for seeing some fetal and embryonic damage.

I think it's worth noting that as we use more sophisticated techniques or what defines potential neonatal pathologies, we should apply the same logic for looking at maternal toxicity using things a little more cleaner than reductions in body weight, reductions in food intake, et cetera. If we go into that criteria, it depends where do we say maternal toxicity should be a

major driver or not.

I was impressed that there's clearly some effects at relatively low levels on some immune parameters with the low dose. The difficulty is knowing how to interpret that. One interpretation is it was an improvement in some of the parameters of the immune system. You see an increase in antibody production. That's not necessary -- so are we asking the question is there any evidence that BPA is just having an effect or is the evidence that it's having a deleterious effect.

As I read the papers where the immune system has been looked at, I could not pull that out of there. The same thing with the gene effects, which has already been alluded to, the fact that one sees alterations in the expression of gene A, gene B, gene C, it's difficult to know what to do with that information till you see some level of consistency across studies, and you ask the next question, whether or not the alteration in gene expression ultimately translates into changes in protein.

We can get big changes in genes routinely. I was a bit disturbed some of the things that were reported are 30 or 40 percent changes. Typically, we don't get excited by a 30 or 40 percent change in the expression of a gene, unless what you mean by that is you're actually seeing changes in the protein. So a lot of what I'll use the

word is "provocative" information, but that's where I kind of see it standing.

I need to comment that I think, again one of the very provocative observations that's out there, that was only briefly touched upon in one of the presentations today, and I don't think was actually captured in the monographs we had, though I may have missed it, and that was the recent paper, the journal paper was in PNAS, where it suggested that BPA -- not that it suggested, but at very high levels can affect some gene methylation patterns.

That was interesting. But the real value or impact of that paper, was that if they then proceeded to give some of those mouse strains high single carbon donors, such as folate, they effectively blocked the effect of the BPA or masked the effect of BPA on gene expression.

That throws in an entirely new equation. It says that perhaps different sensitive populations are going to have very -- will respond differentially to BPA, and that could be anything from the amount of methionine in the diet to folate in the diet to B12 in the diet. And that kind of reshifts for me how I would even want to look at the human data, because looking at a person who has an MTHFR abnormality, that is they have a problem with folate

metabolism, they may indeed may be more sensitive.

So it's those sorts of questions that I think we have to be open to. But as I read the literature now, it's confusing, and it doesn't, by any criteria, meet my definition of clear. So I'll stop at that point.

CHAIRPERSON BURK: Very good.

Are there any comments on the brain and behavior studies?

I know that was the one that -- at least one of the ones that NTP thought had some concerns. So I looked at that and I found it really intriguing and with some consistency. But again, most of the studies are not our generally accepted sort of things, due to the numbers, as you mentioned, and the, you know, single dose and all those kind of things.

But there is a pattern there. And the truth of the matter is, testing right now for behavioral toxicity, I think, is still relatively rare. And so we don't have those typical kind of studies that we'd like to see.

COMMITTEE MEMBER ROBERTS: Actually, Dotty, in this case, a guideline developmental neurotoxicity study would not have been a help to us, because you have extensive postnatal exposure, as well as the prenatal, so we couldn't have used it as we would have liked.

CHAIRPERSON BURK: So you're saying in a

guideline study, you have prenatal and postnatal exposure.

COMMITTEE MEMBER ROBERTS: Yes.

CHAIRPERSON BURK: Would that -- I just have to know this, because I went through and just picked out the prenatal ones for the animals. But I still find that troubling legally, that, is it true we can only look at prenatal exposure in a rat, even if the rat's brain is developing the equivalent to -- that the postnatal time, that's it's equivalent to still prenatal in a human.

DR. ZEISE: Right.

CHAIRPERSON BURK: That's fine, right. So what you're saying is how long do they do the -- well, it doesn't really matter, since we don't have one, but I mean --

COMMITTEE MEMBER ROBERTS: I think it goes -- and I'm doing this from memory and I haven't looked for -- been involved with one for a couple of years. I believe they go on further postnatally than we would be able to -- from what I recall.

But there may be somebody in OEHHA that would be much better at the neurobehavioral aspects.

DR. DONALD: We had prepared a slide on

CHAIRPERSON BURK: Thank you

DR. DONALD: Well, the good news is we prepared it. The bad news is we can't find it.

(Laughter.)

DR. DONALD: This slide is too help elucidate the relative developmental stages that occur in various different species. The reason we prepared this slide was we anticipated this may become an issue.

And the short answer is that there is -- certainly, there are developmental stages neurobehavioral developmental stages that occur postnatally in rats, that occur prenatally in humans. So our feeling is that is perfectly valid to consider postnatal effects on rodent models, if they correspond to what's clearly a prenatal development period in humans.

CHAIRPERSON BURK: Yes. And quite a few of them were designed, I think, with that in mind, if you look at the exposure days. And I think -- because a number of these were looking at specific nuclei in the brain and they know when those develop and they know when they develop in humans and so forth. I think they're an intriguing model that I find very interesting. And the fact that, you know, there's a reduced volume in number of cells in the locus coeruleus and all that.

Whether this is enough at this point for me to say it's clear, I don't know.

What page?

I will tell you the studies that I'm on start on

B7 and go through about B12, I think. So what they are is there's Wistar rats are B7 and 8, SD rats are B9. I think Fischer rats are B10. Mice are B11. And then we add in, a long with this, the prenatal exposure in the -- to the non-human primates in the Nakagami study.

All I'm saying is that they're all -- oh, sorry. Start on page 47. There's a certain pattern in there that I think may be of concern. I'm not sure yet it meets our standard of clarity.

But did anybody else have any thoughts on that? Unfortunately, there's different behaviors tested in different ones. But the sex --

DR. DONALD: Hopefully, it's not too late to be of value, but this is the slide we were looking for.

CHAIRPERSON BURK: Wow. So tell me in the rat -- okay.

DR. GOLUB: So they're standardized to the rat. And it's showing where the rat is and then it's showing where birth and where -- on development of different areas in Macaque and human come relative to that.

And you can see that the -- and there's several different species there. And the birth comes at different times relative to rat development in some of the different species.

And then moving over into Macaques and humans,

it's the development of the limbic areas and cortical areas is much later. And it occurs before birth rather than after birth as in the rats and the mice.

Even this is confusing, but I think you very well stated the general principle that the brain development that takes place prenatally in humans takes place postnatally in rats and mice.

CHAIRPERSON BURK: And some of these studies, I think, were designed to hit certain developmental points, particularly the ones that evaluated specific nuclei in the brain, because they know when those develop in humans and so forth.

DR. GOLUB: Right, with the locus coeruleus being earlier than that.

CHAIRPERSON BURK: Being earlier. And then you know -- anyway, I don't know how anyone else feels about those, but I just felt that I had to point out. There are quite a few studies coming along there. Again, whether they're our kind of studies if that has a meaning, you know, in terms of the number of animals, and the way they do the statistics and all that.

I know that NTP picked out certain ones that they thought were adequate studies. So among all those tables that you see, they liked Kwon, Negishi, Della Seta, Palanza, and Ryan, and Vandenberg. So at least NTP

thought that some of those studies were useful for them.

One of the other more intriguing things is the looking at the dopamine system too. I thought that was -- again though, I have to say some of these I think are just perhaps what they truly call hypothesis-generating type of studies, and they're not the traditional type of neurotox that we want to see.

COMMITTEE MEMBER KEEN: But I think it's also worth noting those as when they did signal some out as being, what they thought I guess were, the more robust studies, I see females no effect, males no effect.

So the ones that they identified as perhaps some of the higher tiered studies by their criteria, seemed to be the studies that actually had less effects reported or observed than the ones which they found to be weaker studies.

COMMITTEE MEMBER ROBERTS: I'm looking at the NTP brief on page 20. And on the left-hand column, it says, "Overall the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health", which implies that they think that something may come of this in the future, but they are not there yet.

CHAIRPERSON BURK: Okay. We're getting near the end of our legal time, I guess, so -- we can do till close

of business, what does that mean? How long is that?

Oh, okay. Well, anyway are there any more comments?

Ellen.

COMMITTEE MEMBER GOLD: Can I just say that in the NTP report just to go along with what you were saying, they do express some concern about neural and behavioral effects. So, you know, their level of concern is raised compared to some of the other things we've been talking about.

COMMITTEE MEMBER ROBERTS: There was a comment made about the change in how we evaluate going from the 20th century to the 21st century. And I think this particular chemical is a good example of where - I hate to say it - we may need to revisit it at some point, because there may be additional information that comes out that strengthens one area or another. The neurobehavioral is one aspect of it. I think the immunological is potentially another. And even more with, you know, the gene expression could be an area as well. The functional changes are, I think, where we're seeing -- and long-term health effects from the prenatal exposure are where we may be seeing the science develop.

CHAIRPERSON BURK: Yes, I totally agree. And I want everyone to realize that it's always possible for the

Committee to revisit when more evidence surfaces. And it seems like there's a trajectory. There seem like a lot of people interested in BPA right now and looking at it. So maybe some studies will come that will be, what can I say, provide clearer evidence for us, more sufficiency. I don't know now. I'm not saying how anyone is going to vote though, so I'm just --

(Laughter.)

CHAIRPERSON BURK: I don't want to make it sound like it's pre-determined.

But I did want to make a point though, that we have been known to revisit a chemical. One comes to mind after a number of years, which was, I think, environmental tobacco smoke. We thought there was something there in the beginning, but there wasn't enough evidence, and more studies came out and we looked at it again and there was.

All right, are we ready to --

DR. ALEXEEFF: Dr. Burk, I just wanted to make a point, since you mentioned about the revisiting. We could -- and you raised -- there are several issues that were raised, the behavioral, the breast cancer, sort of thing like that. So we could keep a look at that and to see if there's maybe something that might be of interest that we could bring back to the panel to look at more specifically on some of these endpoints you mentioned.

CHAIRPERSON BURK: That would be very nice. What would we like to put on their list to keep a look out for?

COMMITTEE MEMBER KEEN: I think it's a high probability that there will be future work probing this issue as to whether or not the single carbon status or folate status alters the susceptibility, because that seems to be a message that could be pulled out of that paper. And if that's the case, then suddenly one can talk about target populations that could change considerably the ability to actually detect BPA effects, assuming that they're there, with a high level of precision.

CHAIRPERSON BURK: Lauren.

DR. ZEISE: The other issue, while we didn't look in detail at the cancer endpoint, there are number of early-in-life studies and in utero studies that show precursor lesions. And we could, again, look at that very carefully and come back to the Committee on that point.

COMMITTEE MEMBER WHITE: That sounds wonderful.

CHAIRPERSON BURK: Dr. Hobel.

COMMITTEE MEMBER HOBEL: Yeah, I think there's also this issue of nutrition. The cancer people are becoming very interested in nutritional supplementation to address issues that lead to cancer. And it's all related to folic acid -- or some of it's related to folic acid. So I think that that literature should be looked at very

carefully.

CHAIRPERSON BURK: I would ask for any neuro and behavioral tox studies.

Also, maybe from what Carl said earlier, maybe Epi studies are never going to be helpful, but I still think that if there are any good ones, we would sure want to see those.

COMMITTEE MEMBER KEEN: Yeah, I would hesitate to ever want to be accused of saying Epi studies have no value here. I think the difficulty might be that it's going to be -- if indeed we have not even a bimodal, but a trimodal type of response, that really screams to me that that means there needs to be prospective studies and a fair amount more attention paid to what the serum concentrations or blood concentrations are in the metabolite profile, which is largely absent right now.

You know, I do have a fear. My fear is, is that we are -- because we're looking at the data the way we're supposed to, and it's as a whole that, you know, we may be under -- not underestimating but we could be missing a clear and present danger. It's a real possibility.

And I think that that though could be cleaned up pretty quickly with getting some more information in these areas. These are not daunting studies. They shouldn't take years and years and years. And they could be

published very quickly.

The second-hand smoke was referred to just a few minutes ago, that was pretty -- for those unfamiliar with it, I want to make you maybe feel a level of comfort. The Committee went from an almost unanimous no, the evidence isn't strong enough. I'm remember distinctly one member who said yes, he thought it was, because it was literally only about a month later, that a key publication came out that we all said, that's what we were waiting for.

You know, so things can change very quickly. We just need the appropriate data, I think, to marshal that way. It's not like it's decades.

CHAIRPERSON BURK: All right. Any further comments from the Committee?

I think this, again, just like you said, is something -- this has happened to me many times on here. It's not an easy decision, because there are things that, you think, oh, there's something there, but is it clear enough.

So that's what we'll find out right now. So I will read these verbatim. We require five positive votes, five "yes" votes to list, and that's a majority of the Committee members.

So, has Bisphenol A been clearly shown, through scientifically valid testing, according to generally

accepted principles, to cause developmental toxicity?

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

(No hands raised.)

CHAIRPERSON BURK: All those voting "no", please raise you hand.

(Hands raised.)

CHAIRPERSON BURK: So that's all.

And I guess we have nobody abstaining.

Okay. So, secondly, has Bisphenol A 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: I see none.

All those voting "no", please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: Okay, seven.

And no one abstaining.

And finally, has Bisphenol A 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?

(No hands raised.)

CHAIRPERSON BURK: Zero.

All those voting "no", please raise your hand?

(Hands raised.)

CHAIRPERSON BURK: So again seven.

So the Committee has not voted to list Bisphenol A.

Okay. On the agenda now we have staff updates.

We'll wait.

(Thereupon there was a pause in the proceedings.)

CHAIRPERSON BURK: Okay, so we'll have two staff updates. First Cynthia Oshita.

MS. OSHITA: This will be very quick here.

As you will recall, the Committee last met in November of 2008. And since that time, there remain two chemicals that was mentioned at the last meeting. They are 4-methylimidazole and methanol that are under consideration for administrative listing as known to cause cancer and reproductive toxicity respectively.

Each chemical has progressed to the Notice of Intent to List phase and the review efforts continue on both.

In addition, in December of 2008, OEHHA announced the possible administrative listing of four other chemicals, and they include carbaryl, metam potassium, metofluthrin, and spirodiclofen as chemicals known to the

State to cause cancer. And comments have been received on these chemicals as well and are under review.

And last, since last November, a Maximum Allowable Dose Level for di-n-hexyl phthalate has been adopted at 2,200 micrograms per day oral. And that level became effective January 1st, 2009.

Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Hi. This is Carol Monahan-Cummings. Just real quickly, I was thinking that Cindy was going to mention also that we have some current chemicals up for listing under the Labor Code Provision of Prop 65. We have 30 chemicals that have been proposed, and they're fairly evenly split between repro and cancer chemicals.

The public comment period closed on Monday the 13th, July the 13th. And on Tuesday -- yes, yesterday -- we got a third lawsuit that is related to Labor Code listings.

And so that's the lead into the fact that we have three cases pending currently against the Governor and/or OEHHA and the Agency. I think I mentioned to you before, there was an action that was filed by the Sierra Club as the lead plaintiff, but it's a coalition of environmental and labor groups that filed that case. It doesn't concern this group directly. The CIC members individually are

sued in that case, but not the DART members.

It indirectly affects you, because it has one component that's related to prioritization for Committee listings. And it also deals with authoritative body listings and listings under the Labor Code mechanism.

A related case was filed in November, I believe, or December by the Chamber of Commerce related to the Labor Code listings as well. It was consolidated with Sierra Club case. And it has actually been decided the issues in that case, and it's up on appeal currently.

And then the third case that I mentioned that was filed yesterday was filed by the styrene -- a styrene trade group. And it is also related to Labor Code listings. In particular, the proposal to list styrene as a chemical known to cause cancer. So the majority of the litigation is really focused on cancer, but with the exception of the prioritization process for committee listings. Does anybody have questions?

DIRECTOR DENTON: I'll just take a few minutes to summarize the action of the Committee today.

The Committee unanimously decided not to list Bisphenol A as a developmental and reproductive toxicant. The Committee would like us to follow up with further evaluations. And you might double check me on this to make sure that I accurately captured what it is that you

would like to see.

But I see that there are three different areas that you would like us to follow up on. One is the Bisphenol A and nutritional status, specifically regarding folic acid, but there could be others.

Well, actually four, the nutritional status, susceptibility. There may be susceptible populations or target populations, which could be more susceptible to Bisphenol A.

The third is the issue of the cancerous lesions, which could potentially be a result of Bisphenol A exposure. And then finally, the further review of the neurobehavioral studies.

And the fifth is the immunotox function. The immune function, so those five areas you would like us to investigate more fully and bring back to the Committee.

So my closing remarks that, first of all, that I would really like to -- well, I want to thank the panel for taking such a deliberative approach to this chemical. It's a very high profile chemical. It's a very important chemical. And I think that you did your job today and I really appreciate your attention to this matter.

I'd also like to thank my staff, who have spent an incredible amount of time, many months, on this chemical, many hours preparing for this meeting. Once

again, the OEHHA staff are just an incredible group of scientists. And I know that all of us appreciate that. I do.

I'd also like to thank the audience, most of which have left.

(Laughter.)

DIRECTOR DENTON: But for those of you who are remaining, we also appreciate your input. I think your input is critical to making this a public and transparent process.

And so with that, I guess we're in adjournment.

Thank you very much.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 5:16 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 3rd day of August, 2009.

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