MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CALEPA HEADQUARTERS BUILDING

1001 I STREET

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

MONDAY, NOVEMBER 9, 2015

10:00 A.M.

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

COMMITTEE MEMBERS:

Ellen B. Gold, Ph.D., Chairperson

Diana Auyeung-Kim, Ph.D.

Suzan Carmichael, Ph.D.

Ulrike Luderer, M.D., Ph.D.

Aydin Nazmi, Ph.D., M.P.H.

Isaac Pessah, Ph.D.

Charles Plopper, Ph.D.

Tracey Woodruff, Ph.D.

STAFF:

Dr. Lauren Zeise, Acting Director

Ms. Carol Monahan Cummings, Chief Counsel

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

Dr. Poorni Iyer, Reproductive and Cancer Hazard Assessment Branch, Reproductive Toxicology and Epidemiology Section

Dr. Farla Kaufman, Reproductive and Cancer Hazard Assessment Branch, Reproductive Toxicology and Epidemiology Section

Dr. Allegra Kim, Reproductive and Cancer Hazard Assessment Branch, Reproductive Toxicology and Epidemiology Section

Dr. Melanie Marty, Acting Deputy Director, Scientific Affairs Division

Dr. Francisco Moran, Reproductive and Cancer Hazard Assessment Branch, Reproductive Toxicology and Epidemiology Section

A P P E A R A N C E S C O N T I N U E D

STAFF:

Michelle Robinson, Environmental Scientist, Proposition 65 Implementation Program

Dr. Martha Sandy, Chief, Reproductive and Cancer Hazard Assessment Branch

ALSO PRESENT:

Dr. Hudson Bates, Nickel Producers Environmental Research Association(NiPERA)

Dr. Julie Goodman, Gradient

Dr. Geary Olsen, 3M

I N D E X

I N D E X C O N T I N U E D

P R O C E E D I N G S

ACTING DIRECTOR ZEISE: Okay. Good morning, everyone. I'm Lauren Zeise. I'm Acting Director of the Office of Environmental Health Hazard Assessment, or OEHHA. I'd like to welcome you all to this meeting of the Developmental and Reproductive Toxicant Identification Committee.

The meeting is being webcast, so I would just ask that all of you speak directly into the microphone. You almost have to eat it in order to hear. And it's being transcribed, and a transcription will be available after -- relatively soon after the meeting.

So just before we start, a few announcements on emergency logistics. In the event of a fire alarm or evacuation, go out the door -- the exit door, walk down the steps, out the street, and we'll convene in the park across the street.

Restrooms are out the door, turn left, walk all the way down the hall, you'll see them on the right. And we'll be taking breaks throughout the meeting for our court reporter.

So first, before I turn the meeting over to Dr. Gold, I'd like to introduce the DART Committee. To my right is Dr. Ellen Gold, professor of epidemiology, Department of Public Health Sciences, School of Medicine

at the University of California at Davis.

To her right, is Dr. Ulrike Luderer, professor of medicine, School of Medicine, University of California, Irvine. To her right is Dr. Isaac Pessah, professor, Department of Molecular Biosciences, and Associate Dean of Research and Graduate Education, School of Veterinary Medicine, University of California, Davis.

To his right is Dr. Suzan Carmichael, professor in neonatal developmental medicine, Stanford University. And to right is Dr. Tracey Woodruff, professor of obstetrics and gynecology, University of California, San Francisco.

To my left is Dr. Charles Plopper, professor emeritus, Department of Anatomy, Physiology, and Cell Biology, School of Veterinary Medicine, University of California, Davis. To his left is Dr. Auyeung-Kim -- Diana Auyeung-Kim, excuse me, director toxicology and non-clinical and translational sciences study support Allergan, Inc. And to her left is Dr. Aydin Nazmi, associate professor, Department of Food Sciences and Nutrition, and Director Solutions through Translational Research and Diet and Exercise, California Polytechnic State University, San Luis Obispo.

So welcome, everyone.

Now, I'd like to introduce the OEHHA staff

starting on the end with Dr. Allegra Kim, then Dr. Farla Kaufman, Dr. Francisco Moran, Dr. Poorni Iyer, Dr. James Donald, Dr. Martha Sandy, Dr. Melanie Marty, and then our Chief Counsel, Carol Monahan-Cummings. And, Carol, you have someone that you'd like to introduce.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. I just wanted to introduce Carl DeNigris, who's sitting behind me here. He's our -- wave -- he's our newest attorney. We just hired him. This is his first day at OEHHA.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: So he gets the pleasure of coming into this meeting briefly to just see all of you and see how the meeting works.

Thank you.

ACTING DIRECTOR ZEISE: Thanks. And then from our Proposition 65 Implementation staff, Esther Barajas-Ochoa, Michelle Robinson, and Julian Leichty. So welcome, everyone.

Now, I'd like to turn the meeting over to Carol for some introductory remarks.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. I just wanted to remind the Committee of a few items. I know that you've heard this before, but since we only meet once a year or so, I try and do these reminders for each meeting. First, I'd like to remind you that in your

binder and in the materials that we provided you earlier, there is criteria that was developed by an earlier iteration of this Committee for listing chemicals under Prop 65.

And so if you have questions about the data that you're looking at for a particular chemical, please refer to the criteria which are in the back of the binder that you were given today under the tab criteria. Those are scientific criteria that were developed by the Committee. And the intent of those is to provide guidance. And there's a lot of room for judgment call in the criteria for good reason. Obviously, science moves forward and the criteria has to move with the science. And so hopefully that criteria is useful to you.

The charge for this Committee has to do with listing chemicals under Prop 65. And sometimes through some of the comments that you hear, you will be told other information that has to do with the impact of a particular listing, for example, whether or not a warning is -- might be required for that chemical, particular impacts on certain sectors of the economy.

While that information is helpful in the general sense, it isn't part of the criteria for this Committee. And so you should apply the criteria that you have available in your blinder and apply your own scientific

judgment on the questions that are put before you.

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

This Committee is also allowed, and often does, make decisions based entirely on animal evidence. The chemical that you are considering need not have been shown to be a human reproductive toxicant, and you don't need to have information about whether or not human exposures to the chemical are sufficiently high enough to cause reproductive toxicity in order to list a chemical.

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

In the event that you have -- you feel you have insufficient information or you need more time to think or discuss the questions that are before you, there is no requirement that you make a decision today on any of the questions that will be presented. You can always ask for

staff to prepare additional information, or you can ask to defer the question to another meeting.

Anybody have questions on that?

Thank you.

ACTING DIRECTOR ZEISE: Now, I'd like to turn the meeting over to Dr. Gold.

CHAIRPERSON GOLD: Thank you. Good morning. That's better. Good morning.

Before we begin today's business that is before the Committee, I'd like to take a minute to remember Dr. George Alexeeff, the immediate past Director of the Office of Environmental Health Hazard Assessment who sadly passed away four months ago.

Having worked closely with Dr. Alexeeff and having sat next to him here on this dais for the past few years, I remember as a smart, insightful, fair-minded person. So I think his family can be proud and the citizens of California can be grateful for the intelligent and even-handed manner in which he dealt with the matters brought before him in his capacity as Director. I was always impressed by the manner in which he tried to ensure that all sides had a full and fair hearing, and as he sought to make evidence based policy decisions using the best science that was available to protect all citizens of California.

So I very much appreciated the opportunity to work with him and we should all be grateful for his service to California. He will be missed.

And with that, it's more mundane instructions about public comments, unless anyone else has anything they'd like to say?

Okay. So each speaker in the public comments will have five minutes. There are blue cards available in the back. Please fill out one, if you would like to speak, and turn it into either to Esther or Michelle.

So with that, we'll turn to the business at hand. First, the consideration of -- or reconsideration of methyl-n-butyl ketone, and it's metabolite 2,5-hexanedione.

And we'll start with I believe Drs. Donald, Iyer and Moran have comments to make.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Good morning. My name is Jim Donald. I'm Chief of the Reproductive Toxicology and Epidemiology Section in OEHHA. I'm going to begin by briefly reviewing why methyl-n-butyl ketone and 2,5-hexanedione are before you today and reviewing the decisions that the Committee will be asked to make.

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DR. DONALD: Methyl-n-butyl ketone, or MnBK, was originally added to the Proposition 65 list as know to cause reproductive toxicity bases on the male reproductive endpoint in 2009 because it was identified by reference in California Labor Code Section 6382(d)

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DR. DONALD: And that section of the Labor Code captures any chemicals within the scope of the federal Hazard Communication Standard that are identified as reproductive toxicants. However, in 2012, the federal Hazard Communication Standard was amended and no longer provides a basis for listing a chemical as known to the State to cause reproductive toxicity under Proposition 65.

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DR. DONALD: For that reason MnBK was presented to this Committee in March of last year for a decision as to whether it had been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity.

At that time, the Committee deferred a decision on MnBK and requested that OEHHA attempt to procure additional information on studies of the reproductive toxicity of MnBK, in particular additional information on one study conducted at NIEHS.

At that meeting, the Committee also identified

concerns about 2,5-hexanedione or 2,5-HD, a primary metabolite of MnBK, and requested that information on that metabolite be provided to the Committee when they again reconsidered MnBK.

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DR. DONALD: So today, the Committee may decide whether MnBK has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. And to inform that decision, data on the reproductive toxicity of the metabolite 2,5-HD have also been provided to the Committee.

In addition to the decision on MnBK, the Committee may also decide whether 2,5-HD itself has been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity, and hence whether it should be added to the list.

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DR. DONALD: If there are any questions at this point, I'd be happy to address them. Otherwise, I will turn this over to Dr. Iyer who will briefly summarize the information on MnBK and its metabolic relationship with 2,5-HD. And then Dr. Francisco Moran will summarize the available evidence on 2,5-HD.

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DR. IYER: Good morning. My name is Poorni Iyer And so right now I'm going to be presenting the evidence for you in the reconsideration of MnBK for listing under Prop 65.

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DR. IYER: So MnBK is a solvent that is used in a variety of materials. The comprehensive literature search conducted previously for the March 2014 DART meeting had yielded three studies with data on the potential reproductive toxicity of methyl-n-butyl ketone in rats. And this consisted of one study on developmental toxicity, two studies with data on reproductive organs subsequent to exposure to methyl-n-butyl ketone. And as requested by the Committee, OEHHA attempted to retrieve additional information from NIEHS on the developmental toxicity study conducted by Peters et al., in 1981.

However, no additional information on this study was available from NIEHS. So Tables 1 and 2 in the HID include the same studies presented previously at the March 19th, 2014 DARTIC meeting, and they have been updated and some more information has been included for clarification.

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DR. IYER: The developmental neurotoxicity study by Peters et al., in 1981 was trying to determine if daily

exposure of the dam to MnBK would affect the developing rat nervous system in utero, and to what extent gestational exposure would pre-dispose the offspring to abnormal postnatal development.

In this study, 25 female rats per group were exposed by inhalation to MnBK at 0, 500, 1000, or 2000 ppm for 6 hours a day from gestation day 0 through gestation day 20. The endpoints examined were daily maternal weights; pregnancy outcome at birth; post-natal day 2 behavioral observations; post-natal developmental indices, at 4, 8, and 14 weeks of age, and at 18 and 20 months clinical pathology as well as gross and histopathology and the behavioral test battery was conducted.

Not all tests were conducted at all ages, and so the ages tested were newborn, weanling, puberty, adult, and geriatric.

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DR. IYER: The parental results, the findings in the parents included dose related decrease in maternal weight gain was noted with a 10 percent decrease at 1000 ppm, and 14 percent at 200 ppm; clinical signs at 2000 ppm included hair loss and incoordination.

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DR. IYER: In the offspring they found a decrease in litter size and pup birth weight significant at 2000

ppm. A decrease in post-natal growth rate of the offspring was noted with dose dependent decrease in weight gain in male offspring persisting throughout life both at 1000 and 2000 ppm with a less marked treatment effect seen in the females. The authors stated that this is -- that it was statistically significant, but details like P values were not provided in the article.

The authors concluded that exposure of pregnant rats to MnBK causes a life-long dose related reduction in overall growth of both males and females.

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DR. IYER: Some of the perturbations for the behavioral battery are presented in this slide, where changes were noted at 1000 or 2000 ppm in male and/or female for at least one age. In the inclined screen test, there was a significant increase in duration of adherence to the screen in males and females, in newborns, weanlings, and pubertal animals of both -- that is in both sexes, and in adult females, and no effect in the geriatric animals.

While the inclined screen test was designed as a means to test the muscle strength of the animals, it could also be providing information on nerve muscle activity.

For food maze behavior, pubertal animals -- the males -- pubertal males ran the maze more rapidly with

fewer mistakes, while adult offspring at 1000 ppm took longer than controls and made more mistakes. Animals at the 2000 ppm were not tested as adults.

According to the authors, maze behavior suggests an alteration in motivation, goal-oriented pursuit and/or ability to learn a simple task. Some errors in description were made in the table provided in the HID, where performance on inclined screen was reported as decreased grip strength, and shorter time to run the maze was reported as reduced latency.

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DR. IYER: Again, for some of the perturbations for behavioral battery are presented in this slide. The open field exploratory behavior showed a decreased activity in young animals, males and females, at the time 2000 ppm exposure group, but no significant difference in older animals at either treatment was noted.

For running behavior measured using the activity wheel, a significant increase in the number of revolutions run was noted in treated pubertal animals at 2000 ppm, and adult animals at 1000 ppm, but treated geriatric animals at 1000 ppm tended to be less active.

Pentobarbital sleeping time studies correlate with and are often used as an indicator of microsomal mixed function oxidase metabolic activity. However, these

could also indicate the responsiveness of central nervous system to the barbiturate.

These studies found treated male pubertal animals in the 2000 ppm group sleep longer than controls, suggesting a possible decreased metabolism, but no treatment effect was seen in male geriatric animals. Also, young male offspring of treated dams slept significantly longer than controls after a hypnotic dose of pentobarbital, but female offspring of treated dams tended to sleep for a shorter time in both age groups studied.

Another interesting observation is that older animals tended to sleep a much longer time than younger animals, as was indicated by the need to reduce the dose in the geriatric animals. Overall, the authors concluded that MnBK exposure is associated with hyperactivity in the young, which leads to a possible premature aging. Methods were well reported for the study, but data were not all reported, which is why you had asked for us to get more information if it was possible.

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DR. IYER: Attempts to quantitate the amount of MnBK and metabolites in the fetal system resulted in a qualitative identification of MnBK and metabolites like 2,5-hexanedione in fetal tissue extracts. These

observations indicated that MnBK and metabolites reached the fetal circulation and/or that MnBK is metabolized by fetal tissue.

There was some metabolites not identified in the adult tissue that were identified in the fetal tissue. The identification of these metabolites suggests that the fetal system is capable of metabolizing MnBK differently than the adult or that it tends to -- these metabolites or this metabolite tends to accumulate in fetal tissue, since it has not been identified in adult tissues.

More about the metabolism of MnBK will be presenting soon in the next few slides when we return to the topic of pharmacokinetics and metabolism of MnBK.

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DR. IYER: Moving on to the study by Katz et al., in 1980. Here five male rats were exposed by inhalation and 0 or 700 ppm for 72 hours a week for 81 days. The endpoints examined were neurotoxicity, body weights, clinical chemistry, gross histopathology of various organs including the testes.

Although, this study was designed primarily to assess adult neurotoxicity, the neurotoxic effects observed were not indicative of reproductive toxicity. The study did however report histopathological effects on male reproductive organs, namely the testes.

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DR. IYER: So as mentioned earlier, this was an adult neurotoxicity study, and all treated rats were killed at the time they developed hindlimb weakness. Tissue was then collected and prepared for histopathological examination. Systemic toxicity effects noted included markedly reduced weight gain and decreased white cell counts. Reproductive toxicity of -- what was seen was decreased absolute and relative testes weights. Authors report that the effects were significant, but P values were not presented in the article.

Atrophy of testicular germinal epithelium was described, and statistical analysis is typically not conducted for histopathological lesions. They are generally described and representative photomicrographs are included. But in this case, no data -- additional data -- no data or photomicrographs were presented however.

In describing these effects, the authors did cite that the testicular effect of atrophy that was noted was similar to the germinal atrophy described previously by other researchers elsewhere for the metabolite 2,5-HD.

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DR. IYER: In the adult neurotoxicity study in male rats by Krasavage et al., in 1980, five animals per

group were exposed by gavage at 0 or 660 milligrams per kilogram body weight for five days a week for 90 days. And the endpoints examined in this study were body weights and histopathology of the testes and epididymides, which were processed according to standard protocol.

As is typical, representative photomicrographs for histopathology were presented. Neurotoxicity was also examined, and as with the previous study, this study was designed to assess adult neurotoxicity but male reproductive organs were examined for histopathology.

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DR. IYER: And the results are summarized here. And the systemic effects, such as reduced body weight gain was reported. The authors stated that there were varying stages of atrophy of the testicular germinal epithelium following administration of MnBK.

The histopathologic examination of testicular tissue revealed near complete atrophy of the germinal epithelium, and representative photomicrographs were included in the article.

Again, as in the previously presented study by Katz et al., in describing these effects, the author cited that the atrophy of the testicular epithelium was similar to that reported for the metabolite 2,5-HD.

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DR. IYER: Now, considering the pharmacokinetics and metabolism of MnBK, in rat following oral doses MnBK was almost completely absorbed, extensively metabolized, and rapidly eliminated in the expired air in urine. Metabolism of MnBK to 2,5-HD proceeds rapidly while further metabolism of 2,5-HD and its elimination proceed more slowly.

Peak blood level of MnBK after intraperitoneal injection was reached in 30 minutes and declined biphasically with the half-life of MnBK for the rapid elimination phase being about 10 minutes and about 7 hours in the following slow phase. In the guinea pig, the half-life and clearance time of MnBK in serum was 78 minutes and 6 hours respectively.

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DR. IYER: Three reviews provide information on the metabolism of MnBK and these include the work from the Boekelheide group, published in 2001 and 2003, as well as a review by U.S. EPA in 2009.

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DR. IYER: Several studies in the rats and guinea pigs have demonstrated that MnBK undergoes metabolism by a variety of pathways. As noted in the schematic in this slide and this schematic is included in the HID as Figure 1, MnBK can ultimately be metabolized to 2,5-HD either as

a result of the reduction or MnBK to 2-hexanol and further metabolism, or as a result of cytochrome P450 mediated omega-1 oxidation to 5-hydroxy-2-hexanone, or 5H2H, and further metabolism. So 2,5-HD can be formed from both these initial metabolites as a result of further oxidation reaction.

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DR. IYER: So from the review of the U.S. EPA, although the proportion of metabolites may defer across species, omega-1 oxidation and carbonyl reduction appear to be the initial steps in the metabolism of MnBK in several species including humans.

The metabolites of MnBK identified in the serum include 5H2H and 2,5-HD and the predominant metabolite identified in serum is 2,5-HD.

And with that, I'm going to let Dr. Francisco Moran present more information on 2,5-HD itself.

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DR. IYER: Do you have any questions?

DR. MORAN: Do you prefer questions now or I continue?

CHAIRPERSON GOLD: Just continue.

DR. MORAN: It's fine. Okay. Good morning. My name is Francisco Moran. And I'll be presenting the data for 2,5-HD.

2,5-HD is used as starting reagent in the synthesis of trans-2,5-dimethylpyrrolidine and other pyrroles.

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DR. MORAN: OEHHA found that were: Two studies on female reproductive toxicity, four studies on development toxicity, 38 studies on male reproductive toxicity. I will star by presenting a summary of the studies on female developmental and male reproductive toxicity in that order.

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DR. MORAN: The first female reproductive toxicity study is a reproductive toxicity in mice by Siracusa et al., 1992, where 15 females per group were exposed to 2,5-HD by the oral route in drinking water at 0 or 1.5 percent for 4 or 6 weeks.

For systemic toxicity reduced body weight was reported. For reproductive toxicity a decrease in protein and DNA content per ovary, fewer medium growing oocytes, and decreased litter size at 6 weeks were reported.

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DR. MORAN: The second study is a rat granulosa cells in vitro by Zhang et al., in 2013. In this study, granulosa cells in culture were directly exposed to 2,5-HD at 0, 20, 40, or 60 millimolar for 0, 12, 24, or 36 hours.

And the results were decreased cell viability with decreased dose and time, and increased apoptotic index.

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DR. MORAN: For developmental toxicity, the study by Moretto et al., in '91 -- did it pass? I'm sorry. -- by Moretto et al., in '91 is an in vitro study that uses the human fetal developing dorsal root ganglion cells. Cells in culture were directly exposed to 2,5-HD at 0 or 2.8 millimolar for two weeks.

The results were diffused modification of cytoskeletal components, enlargements in neurofilaments, decreased neurofilament density, lower cross-sectional area of the axons.

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DR. MORAN: These are two studies in rats by Ogawa et al., in '91 and '93 where 5 to 6 pregnant rats per group were exposed to 2,5-HD by subcutaneous injection at 0 or 340 milligrams per kilo per day from gestational day 12 to 19, or 680 milligrams per kilo per day from gestational day 12 to 16. Animals were sacrificed on gestational day 20. For parental toxicity, it was reported decreased body weight gain.

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DR. MORAN: For developmental toxicity results are summarized here as: Dose-related decrease in mean

live fetal body weight; degeneration in fetal sciatic nerves; dose-related morphological changes of axons, irregularly-shaped large axons, vacuoles and irregularly distributed neurofilaments, fusion of axons and axonal enlargement without aggregation of neurofilaments.

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DR. MORAN: This a chick embryo study by Cheng et al., in 2012 where 10 to 14 eggs per group were directly exposed to 2,5-HD by 100 microliters injection of 0, 100, or 1000 millimolar, and then incubated for 10 hours or 4 days. The eggs were harvested for analysis on day 6.

The results are: Various types of central nervous system deformities; increased neural tube defects; abnormal forebrain ventricle that the author described as, "...vivid disorganized structure of neural tubes..."; 70 percent embryo lethality at the highest dose.

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DR. MORAN: The scientific -- the scientific literature on male reproductive toxicity of 2,5-HD is extensive because the compound is a model chemical for testicular toxicity.

In addition, two reviews by Boekelheide group in 2001 and 2003 summarized the effects of 2,5-HD.

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DR. MORAN: The 2001 review refers to 2,5-HD as a

toxic metabolite resulting from oxidation of the commonly used solvent MnBK, and described the experimental model typically as rats exposed to 2 -- to 1 percent 2,5-HD in the drinking water for a period of 3 to 5 weeks.

The resulting toxicity is a progressive peripheral polyneuropathy, as well as testicular injury that has the Sertoli cell as a target. The most evident testicular effects are loss of germinal cells by apoptosis and testicular atrophy.

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DR. MORAN: The second review by Boekelheide, et al., in 2003 summarizes the direct toxicity of 2,5-HD in the rat, concentrating on discussing the mechanism of action that explains the toxic effect of 2,5-HD in the testes.

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DR. MORAN: As was mentioned earlier, the majority of the studies, 38 of 44, in the HID are of male reproductive toxicity. All the studies use the rat as the experimental model. And 24 out of the 38 studies for this endpoint were conducted by the Boekelheide group.

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DR. MORAN: This is a tabulation of the experimental design presented in the studies of male reproductive toxicity. Note that the number of studies in

the tables will not add up to the total of 38, as one study may have more than one experimental design in it.

First, the experimental model. As mentioned, all the studies used the rat as the animal model with this distribution of strains. The in vitro study uses testicular tissue from Fischer rats.

For route of exposure we have that 37 studies use the oral route, one study used the subcutaneous and another the intraperitoneal route.

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DR. MORAN: Regarding the concentration of dose -- or dose reported in the studies:

Five animals were exposed to a range of 0.3 to 1 percent, while in the majority of the studies, animals were exposed to 1 percent 2,5-HD. In 8 studies, the animals were exposed to a range of 60 to 2000 milligrams per kilo per day. In 4 studies were exposed to a range of 3.1 to 5.4 millimoles per kilo per day, and the in vitro study exposure ranged of 0.5 to 2. -- 20 nanomolar was used. The exposure duration ranged from a single exposure normally by gavage up to daily exposure for 12 weeks.

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DR. MORAN: Here is a summary of the systemic toxicity: Decreased body weight, peripheral neuropathy, hindlimb weakness, changes in brain tubulin assembling,

altered lipid metabolism in sciatic nerve, but not liver, decreased activity of liver lysosomal enzymes.

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DR. MORAN: For testicular effect, we have low testes weight, germ cell depletion, vacuolation, altered testicular lipid metabolism, alterations in Sertoli cells enzymes activity such as beta glucuronidase and glutamyl transpeptidase, alteration in spermatocyte markers, such as sorbitol dehydrogenase, chromatin margination, epithelial disruption, and multinucleated giant cells, intratubular cellular debris.

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DR. MORAN: Enlarged smooth endoplasmic reticulum; degenerating giant cells, electron-dense cellular debris; decreased seminiferous tubule fluid; and altered gonadotropins.

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DR. MORAN: This is a graphic representation of the distribution of the data for male systemic toxicity.

The abscissa shows the categories of effects on the -- and the ordinate the number of studies in which they were assessed. The blue bar on the left of each category, sometimes gray here, represents the number of studies where the effect was reported while the red bar on the right represented the number of studies where that

effect was not reported.

In the majority of the studies, a decrease body weight was reported while in a few it was not. In only one study an increase in body weight was reported, and that study is included with the studies reporting no decrease in body weight in the column indicated by the asterisk. In some studies, neural effects were reported.

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DR. MORAN: In the same manner, this is a graphic representation of the distribution of the data for male reproductive toxicity. Testicular atrophy or low testis weight were reported in the majority of the studies, while a few did not report such effects. One study that reported an increase in testis weight is included in the asterisked column similar to what happened to the body weight, and for the studies reporting no decrease in testis weight. The other effects are reported with lower frequency.

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DR. MORAN: And even with lower frequency, these are other male reproductive effects that were seen at least in one -- reported at least in one study, such as altered gonadotropins, enzymes activities, gene expression, and seminiferous tubule fluid.

This concludes my presentation. Thank you.

CHAIRPERSON GOLD: Thank you all three. Are there any questions from the Panel at this time of the presentations and the presenters?

COMMITTEE MEMBER WOODRUFF: I have a question.

CHAIRPERSON GOLD: Yes, Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Could you describe a little more about what reported and not reported means?

DR. MORAN: Yes. What I tried to do is summarize the frequency of the data. So I included in those figures the studies that we're looking for the effect for the endpoint. And what they found, I classified it as reported, and if they didn't see it, as not reported. But they must look for it. So the're not reporting of the studies that looked for something and they didn't find it.

COMMITTEE MEMBER WOODRUFF: Yes. No, I understand what you're saying. Did you apply any evaluation like they've just looked for it, right, not what they found?

DR. MORAN: Yes. If they looked for it and they found it, it's positive. If they look for it and they didn't find it, it is --

COMMITTEE MEMBER WOODRUFF: What does didn't find mean to you?

DR. MORAN: They didn't see it. I mean, if you're looking for instance --

COMMITTEE MEMBER WOODRUFF: It wasn't not statistically -- I guess what I'm saying is there's -- to me, reporting is we evaluated this outcome in this study, that's one question.

DR. MORAN: Right.

COMMITTEE MEMBER WOODRUFF: Then the second is what did we find, if they evaluated that outcome. And then was there an effect, and then what was the confidence limits on that effect?

DR. MORAN: It's much simpler than that is if -- I tried to tabulate just the results, you know. If they look for variations in body weight, you know, and they tendency was decrease in body weight. So all the studies that report that, you know, they look for it and they report it as decreased body weight, they say it was reported.

So if the endpoint is decreased body weight, and they look for it, and they say no change in body weight, that means it was not reported. The decrease was not reported.

DR. DONALD: Right. If I could maybe express it a different way. The tabulation was intended to indicate the occurrence of adverse reproductive effects. So when it says that an effect was reported, an effect that was generally statistically significant, or in some cases,

potential biologically significant was reported as occurring by the authors and that's what reported in this context means.

If it was not reported, it means that they -- that the data that they presented did not indicate in that study and adverse -- that adverse reproductive effect.

COMMITTEE MEMBER WOODRUFF: Okay. I appreciate that. I think that it's really useful to have these type of summaries of the data for our evaluation. I would argue that this is too wrapped up with all the -- so there's -- to me -- and we'll talk about this in the afternoon, because I have -- we have a paper in here that's in the considerations. But it should really be what was evaluated, that's one consideration, then what did the data say -- and I do not think statistical significance should be the criteria by which we necessarily say something is an adverse effect or not, because statistical significance can be highly influenced by the number of animals and the studies. And a lot of these studies are really small.

So I think it would be -- we would like to see as move -- or I would like to see is a movement towards reporting what the findings are from the multiple studies in one place, so we can evaluate it visually. I think

that will be -- because we may miss things if we just use statistical significance as our criteria by putting it into the not reporting bin.

DR. DONALD: I entirely agree with that. And that's why I mentioned that in some instances we would also report biologic -- effects that were biologically significance, even if they were not statistically significant.

The other thing I think to keep in mind is that this is intended as a very brief and somewhat superficial overview of the data. We provided a more detailed summary in the tables that were provided to you in the hazard identification materials. And, of course, all of the original data are also provided to you in the original papers that we give to you.

So we certainly, you know, consult with you about whether you would prefer a more detailed summary in this context in the future, but we have, over the years, provided summaries of different levels, and we've had feedback from the Committee about what level they preferred. So certainly this is a new committee. If you prefer a different level of detail in the summaries, we can provide that.

COMMITTEE MEMBER WOODRUFF: I'm not going to continue this point, because I know we have other things

to talk about, but I do think we did talk about this a year ago about what kind of information we -- how we like to have it reported, I think it's worth talking about if we have time at the end of the day.

CHAIRPERSON GOLD: Okay. Noted. We'll try and come back to it at the end of the day.

Any other further questions of the presenters?

At this point, then I'll turn it over to Dr. Pessah to give the -- as the lead discussant on this -- these two issues.

COMMITTEE MEMBER PESSAH: Thank you, Dr. Gold.

I want to thank Drs. Iyer and Moran for providing a summary of both MnBK. I'm just going to call it MBK, just so I don't stumble over it, and 2,5-HD, hexanedione.

In March of last year, we considered MBK and requested more information since there were only three studies. And one thing that was picked up was the major metabolite which was not part of the review back then. 2,5-HD seemed to be a missing link for biological plausibility. I think I'm going to sort of focus on biological plausibility given what I believe is the overwhelming evidence that MBK potentially could cause male reproductive toxicity. And then I'm going to talk a little bit about newer data that at least one paper that I think came out after your review was posted.

So the first thing I'd like to address is where is MBK found? In a search of the literature, clearly, at some point, it was used in a wide variety of products including solvents, especially glue and shoe manufacturing, paints, lacquer, thinners, resins, et cetera.

It was usually mixed with other solvents including methyl isobutyl ketone, which apparently doesn't -- at least from my search, doesn't undergo the same kind of metabolism. But the two were mixed. And in one case where it was mixed at a much higher rate, the MBK caused clear adverse effects on workers.

The last figures that I could find was in the National Library of Medicine 2005 report, which reported the levels of MBK production in the United States and import - they didn't separate the two - between 453 and 4,500 metrics tons.

Subsequent to that, there's no information. Apparently, manufacturing in the United States ceased, but there's no information on whether importation continues. And that may be a point that we might want to discuss.

Nevertheless, MBK is found in superfund sites, and so it is a potential exposure hazard.

What's very important and relates to biological plausibility here is that MBK is readily absorbed by

pulmonary, oral, and dermal routes. And it readily distributes to plasma, lung, and liver, and serum. And the concentration increases dose dependently regardless of route. And so exposure really, via any routes, leads to MBK in systemic tissues.

The piece that was missing last time was that, in fact, MBK is known to rapidly metabolize to 5 -- 2,5-HD, the -- via two-step oxidation, and that its precursor is actually a much higher volume chemical, hexane -- n-hexane, which I assumed was on the list, but I couldn't find anywhere.

It should be pointed out that n-hexane is a HPV, a high volume chemical, with more than a billion pounds of the last report in 2002. It is metabolized to MBK. Free 2,5-HD concentration serves as a biomarker for exposure to n-hexane. And although we're not considering it here, I want to point out that n-hexane, MBK, and 2,5-HD are inextricably linked toxicologically.

In terms of epidemiological and animal studies, I think the review that you did, which is included for our reference, is quite detailed. There's certainly a very large number of animal studies. Occupational exposures that pre-dominate the literature are really a study of hexane rather than MBK proper. And so those studies really are not as extensive as they should be, given the

use of MBK as a primary solvent. Nevertheless, one should assume that n-hexane is metabolized to MBK and therefore the two are linked.

There's also, in addition to occupational exposure, there have been some reports of exposure to MBK again in mixtures that individuals have used recreationally through sniffing.

In the 1970s, there was the first evidence of peripheral neuropathy. And this was associated with printers, furniture finishers, spray painters. All of these were occupational exposure. The most notable, in my mind, was the Billmaier study of 1974 who showed elevated prevalence of peripheral neuropathy among print department employees at an Ohio fabric coating operation. And they actually did a systematic study comparing employees that were in the print rooms versus executives that were distal to the print rooms.

And they found incidence of neuropathy or evidence for neuropathy of 22 percent relative -- compared to three percent for those that were not exposed. The P value there was 0.001. The prevalence in this study was highest among printer operators, which had an incidence of 39 percent compared to non-print department employees.

Those latter employees -- I'm sorry, the former employees spent about 100 percent of their time near the

printing machines, which had apparently MBK.

There is a substantial number, as you mentioned, of in vivo and in vitro animal studies that have substantiated that exposure to MBK, and, in particular, its active metabolite 2,5-HD causes dose and time dependent peripheral and sensory poly neuropathy. It can include motor involvement depending on the type of exposure, whether it's high level acute exposure or a much lower level chronic exposure.

Nevertheless, both of these neuropathies occur and now there's an understanding of how that mechanism may actually manifest. So there is biological plausibility.

In particular, reproductive impairments in the male are a hallmark of 2,5-HD exposure. Although the data on MBK is limited to the three studies that you mentioned. The Peters study in particular seems to be robust enough. And now in the framework of 2,5-D actually makes a lot of sense that, in fact, MBK can be a male reproductive toxicant.

What I'd like to focus on is a few of these papers that are more recent -- well, first of all, the biological plausibility in the male. Clearly, the targeted 2,5-HD is the Sertoli cells. It's a selective target, although not an exclusive target. It simply alters the distribution of microtubule associated proteins

including kinesin and dynein. And it impairs microtubule assembly.

It causes a change in seminiferous tubule fluid secretion and ultimately enhances apoptosis and loss of germ cells, which also promote seminiferous tubule atrophy. These occur at relatively reasonable concentration which could be relevant to human risk.

What is debated is the molecular consequences. There's some, such as the Boekelheide group that believe that 2-HD actually forms covalent bonds with lysines in target proteins within the testes, in particular the Sertoli cells. And once this happens, then they can cross-link proteins between the 2,5-HD molecules. These effects are generally thought to be progressive, and in some cases, irreversible, which also suggests potential risk.

In terms of data on females, there's much less. All the data published on female reproductive toxicity are from the perspective of n-hexanes rather than MBK. Nevertheless, one can generalize, since MBK is a major metabolite of hexane.

So, in particular, Abolaji, in 2015, this is a recent paper, investigated whether 2,5-HD itself induces oxidative stress in the ovary and uterus of exposed Wistar rats. Female rats were randomly assigned to four groups,

8 per group. They were exposed to 2,5-HD at 0, which is the control, 0.25, 0.5 and 1 percent in their drinking water for 21 days.

2,5-HD significantly increased ovarian and uterine malondialdehyde and hydrogen peroxide. These were statistically significant, and these are two biomarkers of adverse outcome that involve the oxidative stress. Significant decreases in ovarian catalase, superoxide dismutase, glutathione peroxidase, and glutathione s-transferase. The major protective antioxidant defense mechanism occurred in all the 2,5-HD treated groups, including the lowest dose.

This is contrasted with urine catalase, glutathione transferase, and GPX activities which were increased. And so there was a decrease in the target tissue and an increase in the levels in the urine.

They also measured follicle stimulating hormone in an attempt to see if there were hormonal imbalances that were produced by the exposure. And what they found was an increase in follicle stimulating hormone, but a decrease in estrogen levels in all of the 2,5-HD treated groups. They also looked at prolactin which seemed to increase in the 0.5 percent group and the 1 percent group.

The authors implied and concluded that 2,5-HD exposure disrupts hormonal homeostasis and induces

oxidative stress in the ovary and uterus of rats, and suggested that toxicological implications in women occupationally exposed to n-hexane and possibly MBK. They did mention MBK as a possible. I think they've made the link about the n-hexane to MBK metabolism.

The Zhang 213 paper that you mentioned, I won't reiterate, but they clearly found evidence for proapoptotic upregulation genes that are involved in regulating apoptosis, including BCLX and BAX and NF-kappaB. And that study seemed to be rather robust.

So there is one paper that I thought was actually quite interesting. I'm trying to find it here.

So one of the major signaling pathways in ovarian development is glutamate-nitric oxide-cyclic GMP guanylyl cyclase. Guanylyl cyclase is an enzyme that's both regulated by nitric oxide as important for the homeostasis of nitric oxide. There is already evidence that 2,4-D disrupts the system in the central nervous system in rat studies, in particular the cerebellum.

So Prieto-Castelló in 2006 published results of a chronic exposure to 2,5-HD. She used both an animal, the Wistar rat, as a model, as well as going into the field and looking at workers at a shoe factory that used solvents in the glues that were used.

In particular, this was a mixture of solvents, so

they couldn't really isolate it to any particular solvent, but a major solvent used was n-hexane. And so what they did was they treated the Wistar rats to 2,5-HD in the drinking water, and then sampled blood from the shoe factory workers and related 2,5-HD levels to altered guanylyl cyclase activity, both in the rat and in the human. And they found that both exposures in the rat and in the human, the purported exposures, seemed to dis-regulate soluble guanylyl cyclase, the same isoforms that have been shown to be important for ovarian development, again providing potential biological plausibility to female reproductive toxicity.

So in conclusion, I think there's overwhelming evidence that 2,5-HD is a male reproductive toxicant. I think this lends biological support for the MBK as a male reproductive toxicant. And I think there's emerging evidence that MBK and certainly 2,5-D is a female reproductive toxicant.

So I'll stop there.

CHAIRPERSON GOLD: Thank you, Dr. Pessah.

Any questions of the Panel -- from the Panel of Dr. Pessah?

Okay. How are we doing with -- you're okay.

So I need to check if there are any public comments at this time?

No public comments.

Okay. How about any further discussion by the Committee of the issues that have been raised by the presenters and by Dr. Pessah?

Dr. Auyeng-Kim.

COMMITTEE MEMBER AUYEUNG-KIM: Well, I agree that there's no question that MBK and 2-hexanedione causes male reproductive toxicity in rats. My question -- or the question I have is that considering that it is used as a model chemical for testicular toxicity for 20 or 30 years, why are there no reported incidences in other species?

COMMITTEE MEMBER PESSAH: Dr. Pessah, do you have anything to respond?

COMMITTEE MEMBER PESSAH: In other species, meaning other animal species or in humans?

COMMITTEE MEMBER AUYEUNG-KIM: Other animal -- both other animals, dogs, monkeys.

COMMITTEE MEMBER PESSAH: I think there are some data at least in -- there are data in multiple species that MBK can be metabolized to 2,5-HD. I can't explain why? I mean, it's possible that CYP activities may have precluded those studies, but I would imagine that negative studies would have been very useful in this case. I just don't know think that it's been examined.

COMMITTEE MEMBER AUYEUNG-KIM: Definitely.

COMMITTEE MEMBER WOODRUFF: Is there mostly rat studied or -- I mean, I didn't see very many -- I saw one rat study in here, so it could be that they just -- have other species been evaluated?

COMMITTEE MEMBER PESSAH: There have been some studies in mice.

CHAIRPERSON GOLD: Dr. Plopper, did you have a comment or question?

COMMITTEE MEMBER PLOPPER: Well, I tried to address that issue. And I think one of the concerns here is that this is a wonderful model for looking at processes that require functional tubulin systems. And what has happened is that the impact that this might have on health has been lost. But it seemed to me that from looking through the literature that I could dig up that there's no question that the same process occurs in rats, cats, dogs, guinea pigs, and humans. And the problem is it hasn't been documented clearly in everyone, but I think Dr. Pessah gave us a nice overview of all the metabolic processes here.

And I know, just to tell you, I once used this chemical to attack cilia. So I know it works and it's a ubiquitous toxicant for tubulin related processes. I think Dr. Pessah's outlined all of the other metabolic parts of it. So I think it's correct that there isn't a

lot of literature on other species, because it's such an excellent model to use for other studies.

CHAIRPERSON GOLD: Thank you.

Dr. Luderer.

COMMITTEE MEMBER LUDERER: I think it's also important to highlight something that Dr. Pessah mentioned, which is that although there aren't published studies of testicular toxicity in humans that I'm aware of, clearly it has pronounced peripheral neurotoxicity. It causes peripheral neuropathy at high rates, and that was also found in the rats.

So it seems to me that there would be no reason to expect that it would cause peripheral neuropathy in both species but not the testicular toxicity.

COMMITTEE MEMBER PLOPPER: I would agree with that, yes.

CHAIRPERSON GOLD: Any other comments or questions?

Okay. Are we ready to vote?

Dr. Luderer.

COMMITTEE MEMBER LUDERER: Actually, I do have one question, which is the point that Dr. Pessah brought up about the -- that this is -- that the MnBK, as well as 2,5-hexanedione are both metabolites of n-hexane. And so does any decision that we make here today also have

implications for n-hexane as far as Prop 65?

CHAIRPERSON GOLD: I'll turn that over to the staff, but I suppose we can make a recommendation, but Dr. Donald.

DR. DONALD: We would welcome any recommendations you'd like to make, but the short answer is no. Listing a metabolite of an unlisted chemical does not have repercussions for the listed chemical, except perhaps to raise concerns about whether it should come before you as a candidate.

CHAIRPERSON GOLD: Okay. Thank you.

Any more for discussion or questions?

Seeing no more, I think we're ready to vote.

So we will vote on these separately. I have two separate votes here.

So the first one is for methyl-n-butyl ketone. And the question before you is has methyl-n-butyl ketone been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? So all those voting yes, could you raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Eight. I see eight.

So no noes, and no one abstaining.

All right. Let's move now to female reproductive

toxicity. Has methyl-n-butyl ketone been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: One, two, three, four.

Dr. Carmichael, is your hand up?

PANEL MEMBER CARMICHAEL: No, it's not.

CHAIRPERSON GOLD: No, okay.

Three, four, five. I see five.

Those voting no?

(Hands raised.)

CHAIRPERSON GOLD: Two -- three.

And no abstentions, correct?

Okay. So let me just announce the vote for the male reproductive it was 8 yes and 0 noes and no abstentions. And for female reproductive toxicity, it was 5 yes, 3 no, and no abstentions.

And finally, for methyl-n-butyl ketone, we will talk about vote -- on developmental toxicity. So has methyl-n-butyl ketone been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Is that a yes? Okay, one, two, three, four, five, six.

Those voting no?

(Hands raised.)

CHAIRPERSON GOLD: One, two.

And no abstentions.

And so the result is that we have 6 voting yes, and 2 voting no, and no abstentions.

Okay. We'll turn now to 2,5-hexanedione. And the question before you is has 2,5-hexanedione been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Unanimous at 8, 0 noes, and no abstentions. So we have 8 voting yes that the chemical has been shown to cause male reproductive toxicity.

Turn now to female reproductive toxicity. Has 2,5-hexanedione been clearly shown through scientifically valid testing, according to generally accepted principles to cause female reproductive toxicity? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: I see one, two, three four.

Voting no?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three, four, and no abstentions. So we have 4 voting yes to cause female reproductive toxicity, 4 voting no, and no abstentions.

Next developmental toxicity. So has 2,5-hexanedione been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON GOLD: Three.

All those voting no?

(Hands raised.)

CHAIRPERSON GOLD: You're going to change yours to yes?

So we now have four -- can I see a show of the hands for yes?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three, four.

Okay. Those voting no?

(Hands raised.)

CHAIRPERSON GOLD: One, two, three.

Abstentions?

(Hand raised.)

CHAIRPERSON GOLD: We have one. Okay. So for developmental toxicity, 2,5-hexanedione, we have 4 voting yes, 3 voting no and 1 abstention.

Okay. I think that concludes our voting. Do we need to take a break?

You're good.

Okay. So the next item on the agenda is we have a series of items concerning prioritization of chemicals. So the staff is coming to the Committee for guidance about prioritization.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes, I just wanted to follow up on Dr. Ulrike's point about asking for the listing for the consideration of n-hexane. Did -- was that --

CHAIRPERSON GOLD: All right. Can we take that up.

COMMITTEE MEMBER WOODRUFF: Did that get resolved?

CHAIRPERSON GOLD: No. So let's take that up, if we can take a minute on that.

Anyone wish to comment on that?

COMMITTEE MEMBER WOODRUFF: I think we should have the staff -- would we ask you to look at it, is that the next step, if that would be a recommendation?

CHAIRPERSON GOLD: Yes, that's pretty much what we did with 2,5-HD. And so is the Committee in agreement that we should ask the staff to look at n-hexane?

Yes.

Okay. Good. Thank you for reminding us.

All right, now we can move to prioritization. And the first item is nickel. And Dr. Iyer, are you going to make a presentation? Sorry, Dr. Donald, I apologize. You're starting.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Yes, I'm -- okay. I'm going to briefly review the process we use for prioritizing chemicals, and then describe the epidemiologic data screen that we applied in this iteration of that process.

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DR. DONALD: The document process for prioritizing chemicals for consideration under Proposition 65 by the State's qualified experts that was adopted by OEHHA in December of 2004 was included in the materials that were provided to you prior to this meeting.

That process was developed in consultation with members of this Committee and members of the parallel Carcinogen Identification Committee at that time.

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DR. DONALD: And the purpose of the process obviously is to identify chemicals for evaluation by the Committee. And our goal is to focus the efforts of the Committee on chemicals that may pose significant hazards to Californians.

One thing I'd like to emphasize is that prioritization is only a preliminary appraisal of the evidence of hazard. It's based entirely on review of abstracts of studies and not on review of entire study reports.

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DR. DONALD: The process was previously applied in 2007. At that time, we applied it to a broad range of chemicals that had been identified from literature searches, as well as chemicals suggested by this Committee, or by other State agencies, the scientific community, or the general public.

And the chemicals that we identified were those that had at least some data suggestive of the potential of the chemical to cause developmental or reproductive toxicity. In this iteration of the process, we applied -- we applied it to 19 chemicals. And those were chemicals that had been identified in 2007 as having relevant data, which did not have sufficient human data available at that time to pass our epidemiologic screen.

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DR. DONALD: And this just lays out the entire process. We start with a pool of candidate chemicals. We apply a screen, a focused literature review to identify some chemicals for Committee consideration. Those chemicals are released for public comment at the same time as they're provided to the Committee.

And this is the stage, of course, that we're at today. We're consulting with you about which chemicals may go on for further review. And this meeting also provides an additional opportunity for oral public comments. And at the end of this meeting, or after this meeting, OEHHA will select the chemicals for which hazard identification materials will be prepared. And then below the line is the brief outline of the subsequent process that those chemicals will go through.

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DR. DONALD: So as I said, we applied our epidemiologic data screen to a pool of 19 candidate chemicals. We began with an on-line literature database search, primarily of TOXLINE and PubMed. Our goal was to identify epidemiologic studies that reported or investigated an association between exposure to the chemical in question and an increased risk of any relevant adverse developmental or reproductive outcome. And once

we identified those chemicals, we looked specifically for those that reported such an association.

The criterion for passing this epidemiologic data screen were that we identified two or more epidemiologic studies of analytic design that were considered to be of sufficient quality, and that reported a statistically significant association between the exposure to the chemical and an adverse outcome.

Descriptive epidemiologic studies or case reports alone were not considered sufficient to satisfy this screen.

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DR. DONALD: In addition to the search for epidemiologic studies, we also conducted a literature search to identify experimental animal studies and other relevant data, such as data and mechanisms of action of the chemical, metabolism, pharmacokinetics and so forth.

And again, I'll emphasize that this preliminary toxicological evaluation of the overall evidence was based entirely on abstracts of studies and not complete study reports.

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DR. DONALD: The chemicals that were identified by application of this screen were nickel and nickel compounds, pentachlorophenol, tetrachloroethylene,

perfluorooctanoic acid, or PFOA, and perfluorooctane sulfonate, or PFOS. And those are the chemicals before you today.

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DR. DONALD: For each of the chemicals, we -- you were provided with the compiled abstracts of the epidemiologic studies we identified, as well as the experimental animal studies and other relevant data that we found during this preliminary toxicological evaluation.

Those were provided to you 45 days before this meeting, and were also released for public comment at that time. And all of the comments that we received were provided to you again prior to this meeting.

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DR. DONALD: So today, we're asking for your advice on which chemicals might possibly proceed to the developmental of hazard identification materials, and consideration by this Committee for addition to the Proposition 65 list.

The other purpose of the meeting today is that it does provide an additional opportunity for public comment on these chemicals.

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DR. DONALD: So I will stop there and take any questions you have.

CHAIRPERSON GOLD: Any questions for Dr. Donald?

Dr. Carmichael.

COMMITTEE MEMBER CARMICHAEL: Yes. Could you just summarize the process -- or the criteria for saying that something was an adequate study or who and -- was involved in how the process occurred.

DR. DONALD: I'll actually delegate that question to Dr. Farla Kaufman, who is one of the epidemiologists in our group and can better describe that than I can.

DR. KAUFMAN: Good morning. Because this is a screen and because we are only looking at the abstracts, it's not as strict a criteria as we have for development of HID materials. So it is, as Dr. Donald mentioned, restricted to studies -- the ones that pass the screen are restricted to studies that are of more analytical design, not so much descriptive or case studies.

We try and find evidence of case control or cohort, but in many abstracts people don't really outline the design as well as they really do in the studies most of the time, not always.

In addition, we look for, but don't always find, evidence of control of confounding or models that control for other variables. Some do, some don't. So it is a judgment call. It is -- and winds up, you know, not -- as I mentioned, not as strict a criteria, but those are the

general guidelines.

COMMITTEE MEMBER CARMICHAEL: Thank you.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So just to clarify, you -- chemicals can be considered for Prop 65 listing through other processes besides this process we're discussing, is that correct?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. There's four separate methods for listing chemicals under Prop 65. And this Committee is one of them, and there's three others that are administrative processes that we manage.

COMMITTEE MEMBER WOODRUFF: Do you take -- I'm sorry, if I don't remember this. Do you guys take nominations? Do you have a nomination period during the year for people to nominate chemicals from the public?

CHIEF COUNSEL MONAHAN-CUMMINGS: Not a particular period, but we do take proposals from the public for chemicals that they believe we should consider for listing. And the Committee certainly has the ability to recommend that as well. Obviously, we just did that on the last chemical you talked about.

COMMITTEE MEMBER WOODRUFF: Oh, right, yes, we did recommend that. I realize.

So now I have a question about this prioritization process. My first -- actually, before I

ask my question, you said there were 19 chemicals that were considered. Do we -- and also, I -- did we get a copy of your presentation? I don't -- I couldn't find it in here. If you could tell me where it is, that would be great.

DR. KAUFMAN: It's in a separate folder.

COMMITTEE MEMBER WOODRUFF: Oh, in a separate folder. Okay. Can you tell me what the other -- I mean, can we get a list of the other chemicals that you considered in this process that were not --

DR. DONALD: I'm sure. Yes, we could provide you with that list. I'm afraid I don't have at the hand at the moment.

COMMITTEE MEMBER WOODRUFF: That's fine. After lunch, maybe?

DR. DONALD: Yeah, certainly.

COMMITTEE MEMBER WOODRUFF: Okay. I wanted to see if there were going to be a time that we could talk about this prioritization, because I'm concerned that the prioritization we're going to identify chemicals only based on human evidence. And so the last chemical that we just evaluated we evaluated it only based on animal evidence. So what are we -- I think we should think about this criteria and whether it's sufficient to capture the range of chemicals that we might want to consider as a

Committee.

DR. DONALD: I probably didn't make it very clear in the presentation, but the -- this is an iterative process. This epidemiologic data screen was the first screen that was specifically recommended by the members of this Committee and the CIC when the process was adopted. We have subsequent to that applied a different screen based on animal data. And then it was decided, again in consultation with the prior iteration of the Committee, that we would once more apply the epidemiologic data screen.

It is not intended to identify chemicals that are only of concern, because of human data. That's why we include all of the data from animal studies and related studies. It was intended to reflect the concern of the Committee, at that time, that they wanted, first of all, to look at studies where there were some data, or perhaps a substantial amount of data in humans. But in the future we will apply other screens, probably again based on animal data, or if you have recommendations for screens, that we would apply, we would be happy to consider those.

COMMITTEE MEMBER WOODRUFF: So the -- because I read -- this document then the August 2015 document that you wrote then -- which you're applying the epidemiological screen, there's actually another screen

before that for other data, is that right?

DR. DONALD: No. In this case, the criterion for chemicals proceeding through the process was based on the availability of epidemiologic data. But once chemicals pass that first criteria we assembled all of the relevant data that we could identify. And that's the basis for this preliminary toxicological evaluation that I mentioned.

So I suppose you could think of it as sort of a 2-step process. We apply an initial screen to narrow down the range of chemicals, and then we look at the entire body of data. And on that basis decide which ones will come before you as potential candidates.

COMMITTEE MEMBER WOODRUFF: Okay. I mean, I think it makes sense to start with the ones that have a lot of human data, if they haven't been considered by this committee. But I think then after we've done that, we should look at the ones that have animal data, because we may be -- you know, there's a lot of chemicals that don't have studies into humans. And also, just -- do you consider the ubiquity of exposure in the California population as a criteria? I know you're not supposed to consider that for the hazard ranking, but just in terms of prioritization?

DR. DONALD: Yes. In the document that we

provided to you, this is laid out. But we have to establish, at least to our satisfaction, that there is a potential for exposure to the chemical in California. We do not attempt to quantify that exposure, so it is a relatively general screen. But if we find evidence that the population of California can be exposed to the chemical, then that is sufficient to pass that level of this process.

CHAIRPERSON GOLD: Any other questions or comments?

Dr. Sandy.

DR. SANDY: If I may just clarify a little bit. So in the December 2004 process document, it explains that to be a candidate chemical, the chemical must have some potential for exposure in California. So that's a base screen that we do. And then we do iterative -- as Dr. Donald said, we do repeated screens. So I believe it was in 2007 that there was the first epidemiologic screen applied to the pool of chemicals with developmental reproductive toxicity concern, and those were brought to you.

And then I think it was in 2011, we applied an animal data screen and brought you another set of chemicals. And now, we've applied an epidemiological data screen a third time. So as we need to, we apply new

screens.

CHAIRPERSON GOLD: Thank you.

Any other comments or questions?

I have one comment before we get started, which is I just want to underscore that we are not making a decisions today about whether to list a chemical. And therefore, we will not be taking any votes. We're just trying to advise the staff about the priorities in terms of these chemicals that they brought before us.

So we'll try and get a sense of the Committee, but we won't be taking a formal vote, okay?

Are we read now to move to the first item, which is nickel?

Dr. Iyer, is that correct?

(Thereupon an overhead presentation was presented as follows.)

DR. IYER: Okay. So today, I'm going to be presenting the evidence available for prioritization of nickel and nickel compounds. And I looked at the animal studies and Dr. Kaufman worked on the epidemiologic evidence for human data.

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DR. IYER: Uses for elemental nickel is primarily for alloy and stainless steel. Nickel compounds can also be used in stainless steel itself. And other uses include

batteries, jewelry, coins, and industrial plumbing. Elemental nickel is also used in high performance batteries, such as those that start jet engines or power satellites.

Elemental nickel is also used in jewelry, coins, and industrial planning, as I mentioned earlier. And nickel compounds have been used in nickel plating, batteries, ceramic pigments, and as a catalyst for chemical reactions.

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DR. IYER: Exposure to nickel in occupational settings mostly occurs in nickel processing industries. Exposure from consumer products comes from food, nickel-containing jewelry, coins, stainless steel cooking and eating utensils, and also exposure from tobacco.

Environmental exposure sources include contaminated air from oil and coal combustion.

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DR. IYER: The human data included seven epidemiologic studies reporting adverse developmental or reproductive outcomes associated with nickel and nickel compounds. Three of these studies were analytical studies of adequate quality. And they reported increased risk of low birth weight, decreased birth weight, decreased gestational age, and one study reported increased risk of

adverse developmental or reproductive outcome with findings that were not statistically significant.

Eleven studies reported no increased risk, 21 related studies and four studies with no abstract.

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DR. IYER: Looking at the animal data, 35 studies reported reproductive or developmental toxicity, which included alter -- either altered hormonal levels or ovarian histopathology, significant alterations in milk composition or decreases in mammary RNA content, decreased number of live fetuses, or embryotoxicity, fetal loss, or increased frequency of both early and late resorptions. Also, there was teratogenicity or decreased sperm motility and sperm concentration or count.

The other parameter was induced lipid peroxidation in testis or testicular damage or degeneration. And histopathology of seminiferous tubules and infertility was noted, but there was some species variation for that.

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DR. IYER: Continuing on with the animal data, five studies reported no reproductive or developmental toxicity, 61 were related articles, and there were 18 studies with no abstracts, just titles, indicating reproductive or developmental toxicity.

And that's all the information for nickel.

CHAIRPERSON GOLD: Thank you. So, at this time, I'll see if there are any -- first of all, let me see if the reporter needs some time?

THE COURT REPORTER: Yes.

CHAIRPERSON GOLD: Okay. Ten minutes. So let's reconvene at 11:40

(Off record: 11:30 AM)

(Thereupon a recess was taken.)

(On record: 11:40 AM)

CHAIRPERSON GOLD: Can we please reconvene.

Can we please take our seats and reconvene.

I just want to check in with the Committee one more time to see if they have any questions of Dr. Iyer before we proceed with the public comments?

Any questions for Dr. Iyer?

Hearing none.

We'll proceed with the public comments. And the first person is Hudson Bates.

DR. BATES: Thank you very much for this opportunity to address you. My name is Hudson Bates. I'm the executive director of an organization known as NiPERA. It's the Nickel Producers Environmental Research Association. We are an industry funded association. We're a not-for-profit organization and we fund academic

research around the globe on human health and environmental effects of nickel compounds. I'm also a toxicologist.

One of the reasons why I came here today was to talk to you about the very issue of prioritization. One of the assumptions that comes out of this exercise in the nomination nickel and nickle compounds is the assumption that we are moving towards the direction of saying there is conclusive evidence of human reproductive toxicity as a result of exposure to nickel or nickel compounds. And I think that's one of the areas that I would like most to be able to address.

But before I do that, I did want to mention, when we look at all the places that we see nickel exposure from, and when we look at the fact that we have public exposure from the air, I think we need to put that into context.

Nickel is an element, and as such it's different than many of the compounds that you're dealing with today. Right now, nickel compounds exist everywhere here. I see public with coffee cups. Nickel is in coffee and it's there because plants require it. It's essential for plants.

And, in fact, even here in California, nickel augmentation of soils has to occur for almond orchards in

order to be able to produce adequately.

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DR. BATES: So that is a consideration. And what that means is we have to consider not only whether something -- an effect could be caused but at what level it could be caused and whether that level can ever be achieved in the human population.

There is no question that nickel and nickel compounds can cause animal reproductive toxicity. We've seen this for a very long period of time. And, in fact, the 2011 REL here in California for the chronic oral REL is based on animal reproductive toxicity. In fact, it's based on a study that I ran in 2000.

So that is absolutely not the question. The question is whether or not the data for human exposure to nickel and human effects from nickel have significantly changed since this was last reviewed in 2007.

And during that period of time, there have been a few epidemiology studies, but the biggest epidemiology study was one that we commissioned on behalf of the European Commission and the Danish EPA back in the early 2000s. We were looking at the effects of nickel on the highest exposed occupational cohort we could find anywhere in the world. This was a cohort that existed in Russia using technology that existed from -- previous to World

War II. It was in the Kola peninsula.

And to make a long story short, this study showed no risks of nickel exposure associated with observed reproductive impairment in the human population in that refinery in that town. I think this is very important.

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DR. BATES: And the reason this is very important is I try to summarize here on the graph. If we look at the top and we convert all of the exposures for various studies into an absorbed dose, which is, of course, the important dose for reproductive toxicity. We can see the top, the animal NOAEL that was used for the RELs. We can see the REL as the second bar coming down from the top. And then we can see the worker exposure in the Kola peninsula. Remember, that study showed no correlation with exposure to reproductive -- exposure to nickel causing reproductive toxicity.

So what does that tell us? When we look at the remaining epidemiology studies that have been published since 2007, and we see that air is represented in this graph, the reason why you don't see red up there is that it's in the nanogram range. These are all microgram concentrations. There is so little contribution from the air to the absorbed dose that it can't even show up on this scale.

And when we compare it to the high level from the animal study, we can see that the air exposure that these studies are purporting to show a correlation with human reproductive effects are a tiny, tiny proportion of what we get in our diet every day.

And remember, what we get in our diet is because plants require nickel. It has to be there. So when we talk about burning oil and things like that, causing nickel in the air, it's not because it was put there anthropogenically. It's there because oil is decayed plant matter, and that's how the nickel gets in oil and petroleum products. And we burn those things, that's what gets into the air.

So about 30 percent of urban air comes from natural sources. Okay. This is wind, dust, and stuff like that picking up dust. The rest of it we're putting up there mostly through burning of fossil fuels.

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DR. BATES: So in concludes, I'd like to say that if we look at this, OEHHA has actually already gone through the person of evaluating the nickel data, most recently in 2011, coming up with a chronic oral, and acute oral RELs, and the inhalation exposure values also. And they are -- the REL is 100 times higher than -- I'm sorry, the animal data, the threshold that we see these effects

at in animals is 100 times higher than the REL.

And if we look at the human population, that threshold is about 200 times higher than what the public could be exposed to from drinking coffee and things like that. So I think that nickel should be considered as a low priority for evaluation.

Thank you.

CHAIRPERSON GOLD: Thank you.

Any questions for Dr. Bates?

Okay. Thank you very much.

DR. BATES: Thank you.

CHAIRPERSON GOLD: Julie Goodman.

(Thereupon an overhead presentation was presented as follows.)

DR. GOODMAN: Thank you very much for the opportunity to speak today. I'm Julie Goodman, an epidemiologist and board certified toxicologist at Gradient, which is an environmental consulting firm in Massachusetts. And I'm here today on behalf of the American Chemistry Council.

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DR. GOODMAN: So as was discussed earlier, OEHHA requires two or more analytical studies of adequate quality reporting an association to pass the epidemiology screen to be considered for listing, and OEHHA has

identified seven studies reporting associations and concluded three of adequate quality. And as I provided in written comments and hope to go over in the next five minutes, none of these seven studies are of adequate quality. And also of 21 studies identified, three don't actually identify or evaluate associations.

Of the remaining 18, 16 of them are low quality. And even among them, results are inconsistent. And the final two can be considered higher quality and these studies have null results.

I also just want to briefly mention that the CAS number listed is for nickel metal, and these epidemiology studies are not evaluating nickel metal. You actually can't tease out which form of nickel, but it's unlikely to be metal, because it's the oxides in the nickle sulfate are most likely to be in air pollution. So, if anything, this CAS number should be changed.

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DR. GOODMAN: So how did we determine adequate quality? Well, looking in the OEHHA guidance, it's not very specific. It just says to look at type of study, study population, exposure situation, endpoint, but it doesn't really give anything prescriptive exactly, what's high, what's low.

So what we did was came up with a system based

largely on U.S. EPA's risk of bias framework and others to come up with what we thought would -- are good criteria for judging the quality of studies.

And we divided it into three tiers. And essentially tier 1 and tier 2 are deal breakers. So if a study did not use appropriate statistics, the results are not reliable. There's a high risk of bias. It's low quality. If there's no personal exposure measurements, you can't be sure to what a person was exposed, so you -- again, results aren't reliable. It's low quality. And then in tier 3, we looked at aspects that we felt could impact study quality, but maybe not as much. And so as long as three or four were met, then a study had a low risk of bias.

And so looking at the three studies that -- now granted, it was based on abstract review, and I did read the whole study, but still I think it should be considered.

The Guo et al. study was a cross-sectional study in China, that did not look at associations. It just looked at correlations. No way to look for confounding. So again, this doesn't pass tier 1. It doesn't use appropriate statistics.

And then there's the Bell et al. 2010 study and the Ebisu and Bell 2012 study. The second study being a

follow-up of the first with an expanded cohort. And these studies did not look at personal exposures. They used central air monitors, so it cannot be known exactly what people's exposures were.

As well as some other limitations, including issues with potential confounding for things like maternal weight and socioeconomic status.

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DR. GOODMAN: And just to put this in perspective. We did this for all of the studies. Those three I just mentioned that CalEPA called adequate quality in purple on the left with the other 18. And essentially, green means a criterion was met, pink means it doesn't, and what you can see is a lot of pink.

As I said, all three -- you know, the statistics in tier 1. And then the exposure measurement and study design in tier 2 all have to be green for adequate quality. And there's only these two studies at the bottom, which were the -- both studies of the Russian cohort met the tier 1 and 2, and then going on to tier 3, one of them met all 4, and one of them met 3 out of 4, so we classified them as a low risk of bias.

And so essentially, your -- OEHHA required two things, statistical associations and high quality. And overall, the studies are not of adequate quality. And the

two that could be considered were null. And I also would argue that it's not enough just to have a few studies. You really want to have, you know, the overall epi suggesting an association consistency among all studies, which you don't.

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DR. GOODMAN: So taken together, no epidemiology studies of adequate quality report associations, so nickel metal should not be listed for prioritization.

Thanks very much.

CHAIRPERSON GOLD: Thank you. Any questions from the Committee for Dr. Goodman?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yes. I don't have a question. Well, I do. I don't know if this is really a question, but I just wanted to clarify, because the risk of bias term has actually very specifically been defined within the clinical literature, and does not include those elements that you included.

So I just want to clarify that if you looked at the risk of bias elements that have been developed via Cochran or the Grade methodology, which have been tested in the clinical literature for over 20 years, they're really methodological features that would have been shown to empirically influence the study outcomes in one

director or another, so -- and they include things like was there blinding to where people went in to in terms sequence generation, was there randomization in the process, was there blinding to outcome?

And in the case here for looking at environmental exposures studies, because there has been an adaptation of the systematic review methods into environmental health, you didn't mention NTP, the OHAT's approach, which they actually have a whole risk of method and an tool that they've developed, which also would include an evaluation of the exposure assessment.

So I think that is one way to evaluate studies, but I just want to clarify that the risk of bias term you're using is not what has been defined or used in the clinical literature.

DR. GOODMAN: Yeah, thank you. I would mention this came from, as I said, U.S. EPA IRIS, NAS looking at IRIS, and that's where I took it from. So, I'm sure it's -- the definition has changed, but I think what's key is whatever we call it -- and I'm happy to call it something else, if you'd be more comfortable. These are factors that impact the interpretation of results. I mean, if the statistics aren't correct, you can't -- the results aren't reliable.

And so these are things that do impact how you

interpret results and really we should be paying attention to them. It's the first thing and the second thing. I think it's important to have a set of rules, because otherwise you're not going to -- it's almost impossible to look at each study the same way, because you don't -- whether you have different people looking at studies or you're looking at them at the beginning versus the end, by establishing criteria for what you're going to consider high and low quality, that's going to help you make sure you're consistent in how you look at all the studies, and give you a more consistent, transparent review of the state of the literature.

Thanks.

CHAIRPERSON GOLD: Okay. Thank you. Any other burning questions at this time? Because I've asked Dr. Auyeung-Kim to sort of be lead discussant on the nickel.

COMMITTEE MEMBER AUYEUNG-KIM: Thank you for the summary, Dr. Iyer, and as well as the public comments.

And so, you know, while I agree that there are some limitations to the studies that were presented, I think that by looking at the abstracts that we do need to look at, more in detail about -- of -- we need to look more in detail about the study design, et cetera, to make a decision.

And the other item that I'd like to bring up is

that currently, we are looking at both nickel as well as nickel compounds. We're not just looking at the metallic nickel. And currently, nickel carbonyl is listed for developmental -- as a developmental toxicant. And so that I think needs to be taken into consideration as far as making a decision, because I believe what we -- what bringing this forward would also -- we would need to reevaluate the listing for nickel carbonyl as well, is that correct?

CHAIRPERSON GOLD: I think we need clarification from the staff.

CHIEF COUNSEL MONAHAN-CUMMINGS: You wouldn't need to reevaluate an existing listing for that --

COMMITTEE MEMBER AUYEUNG-KIM: Okay.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- that particular chemical, no.

CHAIRPERSON GOLD: Dr. Sandy.

DR. SANDY: Maybe I can clarify that we are proposing that the term or the scope of the document, if we were to write a -- provide you with hazard identification materials would be on nickel and nickel compounds, and that would allow the Committee to decide what of those -- among those many compounds you felt were appropriate, but we would not be relooking at anything that was already listed.

COMMITTEE MEMBER AUYEUNG-KIM: Okay.

CHAIRPERSON GOLD: Do you have anything else to add?

COMMITTEE MEMBER AUYEUNG-KIM: No, that's all that I had to add.

CHAIRPERSON GOLD: Okay. Any other comments or questions from the Committee?

I have one question for the staff, are you asking us to sort of rank the priority or just say prioritize or not?

DR. DONALD: Given the small number of chemicals, you know, if you choose to rank them, that's entirely up to you, but we're not requesting specifically that you do so.

CHAIRPERSON GOLD: So you're just saying prioritize or not prioritize, is that what you're looking for from us?

DR. DONALD: Essentially, yes.

CHAIRPERSON GOLD: Okay. Dr. Carmichael.

COMMITTEE MEMBER CARMICHAEL: And so I realize this was base -- started with the epi -- epidemiologic screen, but our decision of whether we recommend to move forward with a compound can be based on the results of that or the animal data, is that correct, not -- I mean, it could either/or or both?

DR. DONALD: Yes, in short. The relevance of the epidemiologic screen was simply to narrow down the range of chemicals that we would bring before you, but what we're requesting is your advice about which ones should go forward from this stage in the process based on the entirety of the data.

CHAIRPERSON GOLD: Dr. Plopper.

COMMITTEE MEMBER PLOPPER: So if I'm understanding this correct that all of the studies that you provided us related to nickel and those compounds are for compounds, and they're not -- have already -- they are not being -- they're already being -- they are -- what am I trying to say?

Some of them, nickel carbonyl has already -- some of them have already been listed. So the ones that are there are the ones that are not listed. And so it was a little confusing to me just exactly what you wanted.

DR. DONALD: The only nickel compound that is currently on the Proposition 65 list as known to cause reproductive toxicity is nickel carbonyl. So the extent of the recommendation you make could include nickel or all nickel compounds or both.

CHAIRPERSON GOLD: Dr. Auyeung-Kim, do you have a recommendation to the Committee or should we just pole the Committee?

COMMITTEE MEMBER AUYEUNG-KIM: My recommendation for the Committee is that we do consider it for prioritization, but it would not be of high level.

CHAIRPERSON GOLD: Thank you. Anyone else want to make any comments?

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: So we can -- but you said that we put it in this group, the group that we're thinking about -- or that you recommended to us as a prioritization, you're going to sort through them, is that right?

DR. DONALD: That's correct. OEHHA, under the defined process, makes the decision ultimately about which chemicals come before you based in large part on your recommendations, but, you know, we also have practical considerations about resources and balancing the workload for the Committee. So the order in which the chemicals that you recommend come before you are influenced by those considerations.

CHAIRPERSON GOLD: So I wonder if I might restate my conclusion that it was to prioritize or not to prioritize. Could it be maybe just high or low priority, would that -- because I think the issue is should it be taken off the table entirely or is it a higher or a lower priority?

DR. DONALD: We're looking for your advice, so if that's what you'd like to advise us, we will certainly take that into consideration.

CHAIRPERSON GOLD: Okay. So is the Committee ready to advise?

We're not taking a formal vote.

(Laughter.)

CHAIRPERSON GOLD: We're trying to -- trying to reach some sort of sense of the Committee. I'm not even sure if we'll get consensus. I'll aim for that, but I don't know. Let's start at this end this time and just got a sense of -- Dr. Nazmi, do you want to weigh in on this at all?

COMMITTEE MEMBER NAZMI: I would agree with Dr. Auyeung-Kim that nickel is a medium priority listing.

CHAIRPERSON GOLD: That's good. Thank you.

Dr. Kim, you're sticking with that?

COMMITTEE MEMBER AUYEUNG-KIM: Yea, I'd like to stand that it be a medium level priority, simply because we also do have animal data that substantiates that it is a reproductive toxicant.

CHAIRPERSON GOLD: Than you.

Dr. Plopper.

COMMITTEE MEMBER PLOPPER: Yeah, I would go along with that. If we're going to include more than just

elemental nickel, yes, it's medium priority.

CHAIRPERSON GOLD: Okay. Dr. Luderer.

COMMITTEE MEMBER LUDERER: Yes, I would also agree with that, compared to some of the other chemicals that perhaps I would make it a -- consider it a lower priority.

CHAIRPERSON GOLD: Dr. Pessah.

COMMITTEE MEMBER PESSAH: Medium to low priority.

CHAIRPERSON GOLD: Okay. Dr. Carmichael.

COMMITTEE MEMBER CARMICHAEL: Medium priority.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Medium.

CHAIRPERSON GOLD: Okay. And I would agree to a low to medium, so does that help.

DR. DONALD: Yes, certainly.

CHAIRPERSON GOLD: I'm trying to get a sense of how go forward with the others as well.

DR. DONALD: Yes. And just for the record, could you clarify that the recommendation is for nickel and nickel compounds?

CHAIRPERSON GOLD: Yes, I think that's our understanding.

DR. DONALD: All right. Thank you.

COMMITTEE MEMBER WOODRUFF: Can I ask, has this been considered by the cancer group as a carcinogen?

DR. DONALD: Nickel and nickel compounds are already listed for cancer.

COMMITTEE MEMBER WOODRUFF: Oh, okay. Okay. Thank you.

CHAIRPERSON GOLD: Okay. Are we ready to move on. Maybe we could fit in one more before we take a lunch break, does that sound okay with everyone?

So the next presentation concerns pentachlorophenol. And I believe Dr. Kaufman is going to provide a presentation.

(Thereupon an overhead presentation was presented as follows.)

DR. KAUFMAN: Hi. This body of evidence was compiled by myself and Francisco Moran, who's sitting to my left.

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DR. KAUFMAN: So pentachlorophenol or, as I'll refer to it PCP, is an organochlorine compound. It's -- in 1984, it was classified as a restricted use pesticide and it's currently only used for industrial -- for industrial uses as a wood preservative for utility poles, railroad ties and wharf pilings.

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DR. KAUFMAN: Occupational exposure to PCP can occur during treatment of wood products. The general

population can be exposed to low levels of PCP in contaminated indoor and outdoor air, food, drinking water, and soil.

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DR. KAUFMAN: The epidemiologic literature included nine studies reporting statistically significant increased risk of adverse reproductive or developmental outcomes. Four of these studies were of analytical design and adequate quality. The reported findings include adverse neurobehavioral development. With increased -- increases in coordination -- sorry decreases in coordination, sensory integrity, attention, and visuomotor integration, also increased risk of spontaneous abortion, presence of PCP in breast milk which impacts the quality of the milk, as well as changes in hormone levels in males with increased sex hormone binding globulin and decreased inhibin B. Two studies reported no increased risk and there were also five related studies with -- and three studies that had no abstract

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DR. KAUFMAN: The animal data consists of 19 studies reporting reproductive or developmental toxicity. These include increased testes weight, increased seminiferous tubule, atrophy, reduced epididymal sperm density, reduced percentage of moving sperm, decreased

Sertoli cell viability, decreased fertility, increased resorptions, reduced litter size and fetal body weights, increased malformations, reduced T4 concentration, reduced number of corpora lutea, and increased severity of oviductal intraepithelial cysts, as well as delayed sexual maturation.

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DR. KAUFMAN: The animal data included also one meeting abstract reporting reproductive or developmental toxicity, three studies reported no reproductive or developmental toxicity, and there were also 20 related studies, and 11 studies with no abstracts.

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DR. KAUFMAN: That concludes the presentation for PCP. I'll take any questions.

CHAIRPERSON GOLD: Thank you. Any questions from the Committee for Dr. Kaufman?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: I just want to clarify I understood correctly. So there are several studies from the human epidemiological literature that shows a positive risk or adverse outcome, and all of the animal studies showed no outcomes. That's a little --

DR. KAUFMAN: I'm sorry. This -- I'll go back to this slide. Sorry, I didn't make it clear. These studies

showed adverse outcomes in the animal data. Subsequent to that, the slide after that, these are additional studies, but the 19 studies did show adverse effects.

CHAIRPERSON GOLD: Thank you. Any other questions from the Committee?

So I don't have any public comments?

No public comments.

So we'll move the Dr. Plopper who I've asked to take the lead on discussing pentachlorophenol.

COMMITTEE MEMBER PLOPPER: Okay. Well, I'd like to thank Dr. Kaufman for that summary. That took about 90 percent of what I was going to say, and did it already, so that helps.

I would point out that one of the four studies that OEHHA has identified as one of statistical strength actually doesn't have any health outcomes in it. That's the one, but it's the very detailed study. I can't pronounce the name, Guvenius, 2003, that looked at levels in maternal blood and cord blood and breast milk and found significantly high levels in all three, but didn't make any judgments as to what impact that would have. But the fact of the matter is that there are high levels. There are high enough levels anyway.

Most of the 19 animal studies that were done here that showed some sort of a response were at levels that

were probably an order of magnitude higher than the ones that were identified in the breast milk. But the thing that was striking to me is that this is one of these compounds that has been studied in a wide range of species, rats, mink, sheep, rabbits, and bovine sperm. And they all found exactly the same types of negative reproductive outcomes that were mentioned in the slide.

So I'm not going to go through them all, unless somebody wants to hear about them all, but essentially it's almost every species, it's almost all been provided by some -- by the digestive tract in some form either in water, or in food or by gavage.

And the responses seem to be about the same regardless. Some of the statistical significance or strength is low, but the fact that there's more than one study in every species, and they all find the same things I think is very -- was -- in my opinion, that made it raise the flag, because you just go through these and they almost say all the -- they're only going to look at one or two different sets of outcomes, and they all find the same things.

And I want to point out that the industry is emphasizing that this is only used to preserve telephone poles, and the cross bars, and now for fence posts. And the other thing is that posts it's also the principal

preservative for railroad ties. And every time -- every -- I haven't been around one of these garden stores in a few years, but these are being sold to be used for landscaping. And my understanding of these compounds is that once they get mixed with water, then they end up in plants. And that would be something it would be worth looking at.

But the fact that people are using these by their -- with their hands to put them into areas where they're going to put material that they're going to consume or their children are going to play on, I think, sort of says, just in my opinion, that what would likely be a very low exposure level otherwise, the fact is this chemical lives forever. As a former soldier, I will tell you that in the 1970 -- early 1970s every piece of ordinance that was shipped to Vietnam was soaked in this material. And in the 1980s, I don't know many of you know this, but the army never let you go away. They tried to decommission all this material in Kentucky and it poisoned about 400 of the employees there.

And it's never been discussed and maybe they're going to come after me now, because I was told this was very top secret, but they called me up to say what are we going to do about this. And I said I told you it was a toxicant in 1970. It does not go away.

So I think that it -- I'm not saying it should be a high priority, because I don't know how many people are exposed. I was quite shocked to see how high the levels were in this one population. I think it -- my opinion is it's certainly worth considering, because whatever -- even if they change all the ties out and put them in with concrete, those -- they're going to sell those ties, and they're selling them now. In fact, two of my neighbors have their entire gardens built with these, and I haven't decided what to tell them, but now I don't have to worry about it, because you will.

(Laughter.)

COMMITTEE MEMBER PLOPPER: So that's my comments, unless you want to go paper by paper. I've got plenty of comments on these papers.

CHAIRPERSON GOLD: Well, I just was -- wanted to ask you what your recommendation would be with regard to prioritization, then we'll open it up to the Committee.

COMMITTEE MEMBER PLOPPER: Well, I would say medium to high. It would be medium just because -- if it weren't for the fact that the people who use -- who commercially generated these and sell them don't worry about them once they go away, but they don't go away. They just go somewhere else and other people use them. So that would be my concern is that it's out there.

CHAIRPERSON GOLD: Thank you.

Any comments or questions by the Committee?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: I was just wondering, are there any restrictions on resell of CPC[sic] containing products like railroad ties or...

CHAIRPERSON GOLD: Anybody know the answer to this question?

Dr. Kaufman.

DR. KAUFMAN: Not that I know of. I know you can't buy the chemical outright. It's restricted use. But as Dr. Plopper has noted, they're selling railroad ties, and they all have PCP in them.

CHAIRPERSON GOLD: Dr. Luderer.

COMMITTEE MEMBER LUDERER: Yeah, kind of a related question, how long has it been restricted for residential use?

DR. KAUFMAN: Since about 1984 is when EPA ruled on that.

CHAIRPERSON GOLD: Other questions or comments from the Committee?

So the recommendation was sort of medium to high priority. Anyone want to disagree or suggest something else?

We're all sort of in agreement, medium to high.

Is that good for the staff?

Okay. Thank you.

I wonder if we can fit one more in before lunch? Is everybody up for that?

So we're at tetrachloroethylene now. And Dr. Kaufman you're making that presentation as well

(Thereupon an overhead presentation was presented as follows.)

DR. KAUFMAN: I am. Thank you.

These materials were prepared by myself and are Yassaman Niknam who's in the audience, if you have a question.

So this is the evidence for prioritization of tetrachloroethylene. Tetrachloroethylene, also known as perchloroethylene, or perc, is a volatile synthetic chlorinated solvent. It is used in textile processing and dry cleaning. However, the use of perc in dry cleaning in California is being phased out and will be completed by 2023.

Perc is also used in metal degreasing operations, in paint strippers, and water repellants, and as a chemical intermediate.

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DR. KAUFMAN: Occupational exposures can come from dry cleaning, and metal degreasing operations.

Exposure from consumer products include dry cleaned clothes, fabric finishes, spot removers, and glues used in arts and crafts. Environmental exposure is from contaminated air and water.

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DR. KAUFMAN: The epidemiologic literature includes 13 studies reporting statistically significant increased risk of adverse or adverse developmental or reproductive outcomes. Five of these studies were of analytical design and of adequate quality that reported results in offspring exposed prenatally.

The reported adverse outcomes include increased risk of stillbirth, mental illness, schizophrenia, risky behavior, as well as subclinical visual dysfunction in adults specifically related to color discrimination.

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DR. KAUFMAN: Ten additional studies reported increased risk of adverse developmental or reproductive outcomes with findings that were not statistically significant. Five studies reported no increased risk and five related studies were also identified.

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DR. KAUFMAN: The animal data consists of four studies reporting reproductive or developmental toxicity. Outcomes of these studies include behavioral changes, such

as autistic-like behaviors, decreased fetal body weight, reduced oocyte fertilizability and teratogenicity, specifically micropthalmia which is an eye abnormality.

No animal studies or meeting abstracts were identified reporting no reproductive or developmental toxicity. There was one study with unclear findings that was found and 10 related studies as well as four studies with no abstracts.

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DR. KAUFMAN: That concludes this presentation.

CHAIRPERSON GOLD: Okay. Thank you. First of all, any Committee questions for Dr. Kaufman on this tetrachloroethylene?

Dr. Carmichael.

COMMITTEE MEMBER CARMICHAEL: You said it's being phased out. Was that only for dry cleaning related uses?

DR. KAUFMAN: Yes, exactly.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Is this listed as a chemical carcinogen by Prop 65 already?

CHAIRPERSON GOLD: Yes, it is.

COMMITTEE MEMBER WOODRUFF: Okay. Thanks.

CHAIRPERSON GOLD: Other questions of Dr. Kaufman by the Committee?

I have no public comments, is that correct?

That's correct. Okay. So Dr. Luderer is our lead discussant on this chemical.

COMMITTEE MEMBER LUDERER: Okay. Well, as Dr. Plopper said, Dr. Kaufman has already, you know, well summarized the literature. I just wanted to add kind of some of the major things that I thought were interesting about the database that led -- would lead to my recommendation of also making it medium to high priority for tetrachloroethylene.

So it is a widely used chemical as we heard, although it's being phased out for dry cleaning in California, not being phased out for other uses. It's well absorbed via inhalation, oral, and dermal routes. And I think my understanding is that one of the -- it's a frequently found chemical in Superfund sites, of which there are quite a few in California unfortunately.

So one of the things that I found compelling that made me put this into the moderate to high category was that among the epidemiological studies, there were a few kind of categories of outcomes that there were several studies supporting those adverse outcomes as being related to tetrachloroethylene. I'll just say PCP, because that's quicker.

There were several studies looking at I'd say fetal losses. So one study found increased -- significant

increased odds ratio for stillbirth. And then there were several studies that found increased spontaneous abortion rates, so -- and in addition for the spontaneous abortion and stillbirth, that was consistent with one of the few animal studies that were provided to us in abstract form of increased full litter resorptions with exposure during prenatal development in rodents. That was the Nartosky and Kavlock study.

The other kind of broad category of endpoints that came up in multiple of the epidemiological studies. Although, I will add that many of these were from the same cohort, which is a cohort in Cape Cod that was exposed via the drinking water. But that is a very well characterized cohort where extensive exposure -- individual level exposure modeling was done for those individuals. So I think that those -- the exposure modeling in those studies is very -- a great strength of those studies.

And so the category that I'm referring to is neurodevelopmental, so adverse neurodevelopmental outcomes. So we heard about the increased risk of bipolar disorder, schizophrenia, post-traumatic stress disorder that was in the Cape Cod cohort that I mentioned. But there was another study from Jerusalem, actually from Israel, that found increased risk for schizophrenia with parental employment in dry cleaning were one of the main

exposures is also PCP.

There were some additional studies. Again, the Cape Cod cohort found increased risk for risky behavior, such as smoking, alcohol, and drug use with prenatal exposure, and the subclinical adult vision changes particularly to color vision. As well as one study that looked at air pollution exposure to PCP that found an increased risk for autism. But as with all the particulate matter air pollution exposure studies, the problem there is that the PCP exposure was highly correlated with other compounds that are found in air pollution.

So there were multiple other endo -- epidemiological studies, and I won't go through what all the outcomes were. Those were kind of the ones that jumped out at me, because it seemed as though there were multiple kind of lines of evidence pointing in that same direction.

So, in summary, I think that there's enough -- that there are enough epidemiological studies that some of these are supported by the few animal studies that seem to be available that this should be moved forward for prioritization, and I would say in a moderate to high level.

CHAIRPERSON GOLD: Very good. Thank you.

Questions for Dr. Luderer from the Committee?

Comments, questions?

None. I'm hearing none.

So are we in basic agreement with her assessment of medium to high priority?

Any disagreements?

Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I wouldn't disagree, but for the reasons that you've highlighted, and also for the fact that there's such broad exposure to consumers, to the average public, through a route like dry cleaning -- my suit has been dry cleaned. I don't know how many of you all go to dry cleaning, but I know a lot of -- I know there's going to be a lot of risk, even though it's being phased out in California. It's -- until 2020, is that the phase-out period?

DR. KAUFMAN: The final deadline is 2023. It's being phased out gradually, so they've -- they have conditions about older machines can't be replaced with ones that -- if they're replacing machines, they can't be ones that will use perc. And there's some other caveats within that. But the final deadline is all dry cleaners have to not be using perc by 2023.

COMMITTEE MEMBER NAZMI: Right. So I guess my thoughts are that because of the broad exposure through

that common means to the general public, I would go a little bit more towards the high priority versus medium high.

CHAIRPERSON GOLD: Okay. Any other comments?

So we're seeing medium to high -- to high priority for this one. Does that sound about right?

Okay. My suggestion is we take a lunch break and we'll come back and complete the list and the rest of the items on the agenda.

Should we reconvene -- what?

Okay. Well, I'll thank the Committee for that.

How does 1:15 sound? Is that too long, too short?

COMMITTEE MEMBER WOODRUFF: Let's do it at 1:00, then we might end early.

CHAIRPERSON GOLD: Fine.

COMMITTEE MEMBER WOODRUFF: I know, I'm --

CHAIRPERSON GOLD: 1:00 or 1:15, preferences?

CHIEF COUNSEL MONAHAN-CUMMINGS: 1:15, please.

CHAIRPERSON GOLD: 1:15.

CHIEF COUNSEL MONAHAN-CUMMINGS: Please.

CHAIRPERSON GOLD: 1:15. Staff has some work to do, yeah.

CHIEF COUNSEL MONAHAN-CUMMINGS: I just want to remind the Committee -- just remind the Committee that you

still have issues that are to be decided, so don't discuss those among yourselves or with others at your lunch break.

Thank you.

CHAIRPERSON GOLD: We'll stand adjourned until 1:15

(Off record: 12:23 PM)

(Thereupon a recess was taken.)

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

(On record: 1:30 PM)

CHAIRPERSON GOLD: Okay. I think we're ready to reconvene. I understand that we have the 19 chemicals that were selected for screening and that we have to read those into the record.

These were requested. They should be in front of each place at the Committees chairs. And Dr. Donald are you going to read them in?

DR. DONALD: Yes. So the 19 chemicals that were screened by application of an epidemiologic data screen for this meeting were carbon tetrachloride, chlorine dioxide, diazinon, endosulfan, methoxyflurane, methyl ethyl ketone, mirex, nickel and nickel compounds, palm oil, pentachlorophenol, perfluorooctanoic acid, perfluorooctane sulfonate, propoxur, styrene, tetrachloroethylene, thallium, trichlorfon, trichloroethane, and vinyl chloride.

CHAIRPERSON GOLD: Very good. Thank you.

Anything else?

No. Okay. So I think we're ready to begin with the next prioritization item, which is the perfluorooctanoic acid. And Dr. Kim is going to provide us with a presentation, correct?

(Thereupon an overhead presentation was

presented as follows.)

COMMITTEE MEMBER WOODRUFF: Yes. Can I just say, I just wanted to put on the record that we have done a systematic review of the relationship between prenatal exposures to PFOA and birth weight. And I do think they're in the references, so just so that everyone knows.

CHAIRPERSON GOLD: Okay. Thank you.

Dr. Kim.

DR. KIM: Okay. This is the evidence available for prioritization of perfluorooctanoic acid, also know as PFOA or C8. Dr. Yassaman Niknam screened the animal studies.

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DR. KIM: PFOA is used to manufacture most pluoro[sic} -- fluoropolymers -- excuse me -- which impart fire resistance and stain, oil, and water repellency, and are used to make non-stick cooking surfaces, stain repellent treatments, and waterproof breathable membranes for clothing.

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DR. KIM: PFOA can result from the breakdown of some fluorinated telomers, which are used to make products for surfaces resistant to soil, stains, grease, and water, or for high-performance surfactants used in firefighting foams or semi-conductor manufacturer.

The most recent data from Biomonitoring California showed that PFOA was detected in serum of 100 percent of firefighters tested in 2010 to '11 and 99.9 percent of teachers tested in 2011 forward.

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DR. KIM: Thank you. Now I'll turn to the evidence available for prioritization. The epidemiologic data included 34 studies reporting adverse developmental or reproductive outcomes associated with PFOA. Nineteen of these were analytical epidemiologic studies and contributed to passing the human data screen for presentation to this Committee.

These analytical studies reported effects on development, including fetal growth restriction, altered hormone levels, neurobehavioral effects, lower anti-body levels, shorter gestation, brain defects, delayed menarche, and overweight and obesity.

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DR. KIM: Reported female reproductive effects included gestational diabetes, pregnancy induced hypertension, and possible decreased fecundity. Male reproductive effects included lower sperm count and concentration and increased luteinizing hormone and follicle stimulating hormone.

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DR. KIM: There were nine additional epidemiologic studies with findings of developmental or reproductive toxicity, but these findings were not statistically significant. Forty-one studies reported no increased risk of adverse developmental or reproductive outcomes. They were four studies with unclear findings and 57 related human studies.

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DR. KIM: There were 20 animal studies reporting reproductive or developmental effects. Developmental effects included lower pup weight and decreased liver metabolism, delayed or absence of vaginal opening, compromised lung function due to airway inflammation, and delays in mammary gland growth and development.

Female reproductive effects included lack of estrous cycling and histopathologic changes in the cervix, uterus, and vagina.

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DR. KIM: For the male reproductive toxicity endpoint, testicular dysfunction was observed. There were also two animal studies reporting no DART effects, 36 studies reporting on related information, and one study with no abstract.

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CHAIRPERSON GOLD: Thank you. Does the Committee

have any questions for Dr. Kim?

Dr. Auyeung-Kim.

COMMITTEE MEMBER AUYEUNG-KIM: So for the Biomonitoring California reports, did they report any -- if there was any exposure in non-teachers and non-firefighters?

DR. KIM: Those were studies actually specifically of firefighters. It was a firefighters exposure study and a teachers study. And they were -- I believe they're both in Southern California. And the Teachers study was all females.

CHAIRPERSON GOLD: Thank you. Any other questions at this time?

Okay. I have one public comment. Are there any others before?

So Geary Olsen.

DR. OLSEN: Thank you to the Committee. Thank you, Dr. Gold, for chairing the Committee and to OEHHA.

My name is Geary Olsen. I'm an epidemiologist with the 3M company. I have had the good fortune, or lack of good fortune sometimes I think, about studying these PFOA and PFOS for a long time. And I like -- appreciate the opportunity just to mention a couple comments.

And my comments are going to be somewhat off-the-cuff, but we've given an extensive -- extensive,

20 some odd pages quick review of some of the issues that are -- you have to deal with PFOA and ultimately with the compound that will follow this compound. These are chemicals that are basically attached to proteins. And so with that in mind, you have to think about where they traverse from the body standpoint.

And there's a paper written by Longnecker a number of years ago talking about the advent -- or advance of modern analytical chemistry and being able to measure things at very, very low concentrations. And these are measured at nanograms per ml, or parts per billion.

And Longnecker stated basically that it allowed you to for a -- to examine a great proportion of the variation measured could be accounted for by differences in subject's metabolism and excretion. And PFOA is not metabolized besides the compound you're seeing itself. So it's a long-chain fluorinated compound.

And then Longnecker opined that the concentrations measured may be a reflection of the byproduct of the underlying pharmacokinetics, systems biology, and the pathogenesis. Several of the epidemiological associations that have been discussed or reviewed here via the screening process that are statistically significant may be actually a reflection of this underlying pharmacokinetic process.

And those associations could include such things as time to pregnancy, birth weight, delayed menarche, decreased breast feeding duration, early onset menopause, and even endometriosis.

A lot -- there's a lot in the literature that now discusses this kind of reflection of the literature. And it clearly can't be reflected in just screening abstracts themselves.

And Dr. Woodruff here, and her team, did an extensive review looking at one of these associations, which is between birth weight and PFOA. But the question becomes, because PFOA is excreted primarily renally, although it could also be through bile, that the glomerular filtration rate may affect the association with PFOA, as it's related to birth weight. So it gets a little bit complicated to try and understand what's going on.

And Dr. Woodruff concluded, and their review said at that point in time, that there was not an association -- or it was not classifiable I think is probably the correct language that you used.

COMMITTEE MEMBER WOODRUFF: (Shakes head.)

DR. OLSEN: No. Okay. Well, you'll have the opportunity to correct me.

But the issue becomes is some of the associations

confounded through -- by this underlying pharmacokinetics, which creates the confusion that we have.

So our comments are -- were provided to you. I do want to just reiterate a couple final points. PFOA is restricted in its importation and use through the U.S. EPA Product Stewardship Program. My company, 3M, no longer manufactures or uses PFOA whatsoever.

Two, there are declining residues of PFOA in the general population. Okay. It's down about 60 percent since the 2000 time frame. And three, that there is, if you look at the toxicological data, especially as you look a birth weight for example, there's an ample margin of safety between the concentrations measured in the pups and the dam that gave the pup the concentration, and that which would be measured in the general population.

So that would conclude my comments for PFOA.

CHAIRPERSON GOLD: Thank you.

Are there any questions for Dr. Olsen from the Committee?

Very good. Thank you.

DR. OLSEN: Thank you.

CHAIRPERSON GOLD: Okay. So we've asked Dr. Carmichael to lead the discussion of PFOA.

COMMITTEE MEMBER CARMICHAEL: Okay. Well, thank you for the review that's already been given. As has been

stated, there have been quite a few -- relative to some of these other chemicals that we've looked at, there are quite a few epidemiologic studies, and quite a few that have found a positive association with a reproductive outcome. And many different outcomes have been looked at, but one in particular that has been studied the most frequently is fetal growth. And as was mentioned there, Dr. Woodruff is one of the co-authors one of the recent reviews, and there's another one by Bach that was just published this year. And both of them concluded that there was sufficient evidence for an association with fetal growth.

And then there's also a review by -- with Dr. Woodruff as a co-author where they looked at the synthesis and the consistency of the animal and the human evidence, and again concluded that there was sufficient -- there was evidence for an association.

So given this level of evidence, I think definitely it's important to -- I would recommend moving forward with considering this compound for listing formally. And given the amount of evidence and the persistence and the ubiquitous exposure, I would recommend towards a higher -- a high level priority.

CHAIRPERSON GOLD: Thank you. I've also been asked to ask you if there's a particular set of endpoints

that the staff should focus on? It's okay if you say no. I just -- if there is, that would help focus their work.

COMMITTEE MEMBER CARMICHAEL: Well, it's an interesting literature, because there's so much on fetal growth that they're even, very systematic, very thorough, very well done reviews. So on some level, I mean, that's definitely an important outcome to think about, but it has -- fortunately, it has been thoroughly reviewed and that's very helpful.

And as far as other outcomes, it was interesting, it seemed like there were -- they were quite varied and definitely not anywhere near the balance, lots on fetal growth, and then just a variety of outcomes come to mind. So I'm -- out of all of those, none come to mind that I would focus on in particular, not that I would exclude any either, but none.

CHAIRPERSON GOLD: Okay. Thank you. Any comments or questions, discussion by the Committee on this compound?

Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I'd like to hear what Dr. Woodruff has to say about her study.

CHAIRPERSON GOLD: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Sure. So in terms of the -- there was a question about exposures. So in the

United States -- this is from data from NHANES from a paper we published in 2011, which is -- the date is probably 2008 or '09, but PFOA has ubiquitous exposure among pregnant women in the United States, so about 99 percent, and -- but that being said, and we actually have been doing a study, which was a collaboration with the Biomonitoring Program, in a pregnant population at UCSF.

And the maternal and fetal exposures are more in the at least detectable, somewhere between the 50 to 70 percent range. So we're seeing exposures to PFOA, but it is true 3M did -- they outphased -- sold the -- right, got rid of it and are not manufacturing, and there's been a phase-out, and that EPA entered into a voluntary phase-out with the chemical manufacturers back in 2000. And we're seeing declines in PFOA exposures. Nonetheless, it's very persistent and found in -- measured in many people as was presented.

So we did a systematic review of the literature -- the animal and the human literature looking at prenatal exposures to PFOA and effects on gestational growth. And we -- I had alluded to this earlier during the day, but we used a method that we've adapted from the clinical literature. So we use the methods that have been developed over the last 20 years via Cochran and the GRADE methodology, which does a -- has a systematic approach to

literature identification, evaluation of the quality of the -- individual evaluation of the quality of the studies and then evaluation of the overall quality of the body of evidence, and then comes up with a summary rating about the state of the evidence.

And so that method has been published and is available for people on-line. It's very similar to the method that's been produced by the National Toxicology Program the Office of Hazard Assessment and Toxicology.

So our conclusion -- we also published a protocol, so part of a systematic review is to publish the method that you're going to use to evaluate the literature before you do the literature evaluation, which we also have on-line.

And after doing a documented search, search extraction -- data extraction, and evaluation of the study quality, and overall study evaluation, we found that there was sufficient evidence in animals, as well as humans, to conclude that exposure to PFOA -- higher exposure to PFOA lead to decrements in birth weight at birth.

And there's another thing, I did want to say that we have looked at this issue about the reverse causality, which has been proposed. I know Matthew Longnecker has been an author on some of those papers. And it works essentially like this, that the glomerular filtration

rate, which is active during pregnancy, that the -- that also metabolizes the PFOA and -- or gets it into -- so it can go into the urine. And that if you have -- that it can have an effect of looking like -- that the higher levels of PFOA are actually a result of the -- of less -- or higher -- less glomerular filtration instead of indirectly being -- the birth weight effect.

So we looked at that literature, because, of course, if the PFOA birth weight literature could be explained by changes in glomerular filtration rate happen that happen during pregnancy, then we have to evaluate that literature and see what's the level of evidence for that relationship between GFR and birth weight. So we actually did a systematic review of that as well.

And so you were right, we did conclude from that that there wasn't sufficient evidence to conclude that there's a relationship between GFR and birth weight. So therefore, it's hard to -- our conclusion is that the finding that we had between prenatal PFOA and birth weight was robust.

And also, while that GFR reverse causality might explain some of the associations seen between PFOA and birth weight in human studies, it doesn't explain the observations in the animal studies which were directly experimental studies, in terms of their similarity --

they're a little bit like randomized controlled trials and that animals are deliberately dosed, and then the outcomes are observed after that. So that's what we found.

CHAIRPERSON GOLD: Okay. Thank you. Questions?

Dr. Pessah.

COMMITTEE MEMBER PESSAH: So I was just wondering the relationship between the animal studies and exposures in humans, what are the doses? Are they relevant?

COMMITTEE MEMBER WOODRUFF: So we have two underlying principles. And one is that effects that are observed in animal species are related to -- that those are indicators of effects in humans, and that's based on a National Academy of Sciences report that was done on reproductive and developmental toxicants.

And then we also assumed that based on other reports that -- by the National Academy of Sciences that you -- there's a consistent dose response and that unless there's data to the contrary, you -- there's no threshold.

The findings -- the doses in the animal studies were higher. We actually did something too that's not been done in the toxicological literature, which I highly recommend, because I think it gets to this issue about non-significant findings in animal studies, because if you look at the individual animal studies, that is true, but we actually put them all on the same scale and did a

meta-analysis, just like you would for human studies.

And what ends up happening is that you increase the statistical power of the findings. And so the meta-analysis found a robust effect that was statistically significant, even though the individual studies, because they were smaller, the confidence limits crossed the null.

And so we -- when we did the analysis -- and this -- we looked at human -- we looked at mammalian animal studies. It turns out the PFOA has been valuated in zebrafish, salmon, fruit flies, and chickens. So it's a pretty well studied chemical.

We didn't actually figure out the dose -- we didn't determine the dose response from the higher end exposures, because they were so much higher than the range of exposures and used the lower ones, though albeit, they are higher. I think maybe 10 to 100 times higher than the human exposure studies, I want to say, but I'd have to go back and look.

CHAIRPERSON GOLD: Okay. Thank you.

Any other questions or discussion by the Committee members?

So the recommendation was a high priority. Do I hear any sort of differences with that opinion on the Committee?

Everybody sort of in agreement this is a high

priority for prioritization?

Thank you.

Okay. So the next one the perfluorooctane sulfonate. And Dr. Kim is going to make the presentation on this one.

(Thereupon an overhead presentation was presented as follows.)

DR. KIM: This is the evidence available for prioritization of perfluorooctane sulfonate, also known as PFOS. Dr. Marlissa Campbell screened the animal studies.

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DR. KIM: PFOS is a synthetic, fully fluorinated organic compound with a long carbon chain and has lipid and water-repellent properties. PFOS was used to produce a wide range of products, including fabric stain repellents, coatings for leather and paper products, firefighting foams, and mist suppressants for acid baths.

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DR. KIM: PFOS resists typical environmental degradation processes, and therefore persists in the environment. It can also be formed by environmental degradation or metabolism from many precursors. PFOS is no longer manufactured in the U.S., though a few limited use are allowed, and it is still produced outside the U.S.

The most recent data from Biomonitoring

California show that PFOS was detected in serum of 100 percent of firefighters tested in 2010 to '11, and in 99.8 percent of a sample of female teachers tested in 2011 forward.

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DR. KIM: The epidemiologic data included 31 studies that examined PFOS and reported increased risk of developmental or reproductive toxicity. Fifteen of these were analytical studies and contributed to passing the human data screen. Developmental effects following prenatal exposure to PFOS included effects on fetal growth, neurodevelopment, anti-body concentrations, postnatal weight, waist to height ratio, and hormone levels. These were effects in offspring, just to be clear.

In addition, maternal PFOS exposure was associated with pregnancy induced hypertension and miscarriage.

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DR. KIM: There were also four studies reporting findings of developmental or reproductive toxicity that were not statistically significant.

There were 29 epidemiologic studies reporting no increased risk of adverse developmental or reproductive outcomes. Three studies had unclear findings, and there

were also 56 related human studies.

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DR. KIM: Turning to the animal data, 29 animal studies reported that PFOS was associated with developmental or reproductive toxicity, including decreased viability, increased malformations, developmental neurotoxicity, deficits in organ function, and altered hormone levels in adult males.

There was also one developmental study reporting no effects of PFOS. Thirty-two additional studies reported on related information. These were mechanistic, pharmacokinetic, and in vitro studies, and studies that examined effects of postnatal exposure on development.

CHAIRPERSON GOLD: Thank you, Dr. Kim.

Any questions or comments from the Committee of Dr. Kim's presentation?

No. Okay. And, Dr. Olsen, are you going to make another presentation? And are there any other public comments?

That's it.

MS. ROBINSON: That's it.

CHAIRPERSON GOLD: Dr. Olsen.

DR. OLSEN: Thank you, again, Committee. Just a couple comments to make sure we have some clarification with PFOS versus PFOA, and a comment on Dr. Woodruff's

statement. And I'll do this comment first.

There was a paper just recently published by Morken et al., looking at the relationship between glomerular filtration, okay, and birth weight or fetal growth. And it's a very large paper that was not included in Dr. Woodruff's analysis of the data set.

And that paper definitely concluded that there's a strong association between GFR and fetal growth okay. Okay. It was published in PLOS 1 just a few months ago. After the series of papers by Dr. Woodruff's team, as well as the analysis of the fetal growth GFR analysis that they also did that was published also in 2015. So it's like ships passing in the night as far as these papers go.

The other paper I wanted to make the Committee aware of is PBPK modeling done by NIEHS and Hamner Institute, one on -- and they both looked at PFOS and PFOA as it related to birth weight. These papers are also -- this paper is also published in EHP. Let's see here it was published here -- well, actually, the paper will be in the December issue, but it's been on-line access since November -- or since May of this year.

And what they concluded for PFOA and PFOS was that about 50 percent of association in epidemiology studies was attributed likely to be confounding by the GFR. That was their conclusion. And I'm -- so just aware

-- make you aware of other literature.

Now, to get back to a couple final points regarding PFOS. Once again, just to let the Committee know that PFOS -- 3M was the only manufacturer of PFOS in the United States. And we phased out of this chemistry announced is 2000, and pretty much were phased out by 2002 to 2004 time period. It does have a few significant new use -- it comes under significant new use rules, and primarily by the federal government kind of a restriction activity that the government uses, or a selected couple of industries.

Second, there's declining residues of PFOS in the general population. Compared to 2000, it's about an 80 percent reduction in the chemistry found in PFOS in the general population. Again, those graphs are in our comments.

And three, I'll go back to, it has an ample margin of safety. When you look at these margins of safety, again, you're looking at a benchmark dose lower concentration 10 percent response. Usually, as you're -- your number you're using for the toxicological data and taking that number, okay, which is a NOEL below a NOEL, because you're doing a benchmark dose modeling exercise and you're comparing that to either the mean of the population or like the geometric -- or the 95th percentile

of the general population. And that ample margin of safety, when you look at birth weight as an example, comes in between two and three orders of magnitude.

So those are my comments. Thank you.

CHAIRPERSON GOLD: Thank you. Any questions for Dr. Olsen by the Committee before we go on?

DR. OLSEN: Thank you.

CHAIRPERSON GOLD: Thank you.

So, Dr. Nazmi, I think is going to lead the discussion of this chemical.

COMMITTEE MEMBER NAZMI: All right. Thanks, Dr. Kim and Dr. Olsen for your comments. So I think it's important to reiterate two issues that we've -- some of us have mentioned, number one, that exposure to PFOS is ubiquitous in the U.S. population. So as Dr. Kim mentioned, firefighters, teachers, nearly all pregnant women from other data, other studies. And number two, that it is a persistent organic pollutant, which means it's going to remain in the environment forever.

And those are relevant, whether or not population exposures are -- might be decreasing or population levels might be decreasing, the fact is they're not going to disappear.

So given everything that we've read, and I just want to highlight three studies that I was able to locate

that were not in the documents that were more recent studies than since 2014. And certainly in 2015, there's been an explosion of PFOS studies.

One -- these are three studies that are high quality that I'd like to highlight, one of them from Environmental Health Perspectives, June 2015, by Toft et al. that looked at amniotic fluid and biomarkers of fetal Leydig cell function, and concluded that environmental PFOS exposure was associated with steroid hormone and insulin-like -- insulin-like factor of 3, concentrations in amniotic fluid: One related to male reproductive toxicity and human cell quality from the life study. Also, in EHP from 2015 by Buck Louis et al., concluding that PFOS was associated with altered sperm quality, lower percentage of sperm with tails.

And a final one by Tsai et al. from 2015 from the International Journal of Hygiene and Environmental Health that concluded that PFOS was or wasn't negatively associated with serum, levels of sex hormone, binding globulin, FSH, and testosterone in young adult -- adolescents, 12 to 17 years old.

And I think that is germane to the larger conversation. And based on this weight-of-evidence approach, considering those and other studies, and the documents that we received in considering the compelling

and consistent evidence, I think it's important to reiterate that everything that we're seeing -- that I have seen, at least with PFOS, is very consistent. The large number of human studies in males and females examining various development and reproductive outcomes, many of them in a range of populations around the world, with concordant findings, my recommendation is that PFOS be categorized as a high priority listing in this committee.

CHAIRPERSON GOLD: Okay. Thank you. Can I just ask you if you think there are any particular outcomes that the staff should focus on?

COMMITTEE MEMBER NAZMI: Yeah. You know, I was just looking at that from the previous conversation. And it seems like -- I highlighted -- I highlighted mostly developmental outcomes, low birth weight, low birth outcomes, alterations in neurobehavioral gross motor development. But there were also some really compelling studies from a male reproductive point of view, predominantly sperm quality, sperm morphology, and some from female reproductive outcomes.

So I guess I would prioritize developmental outcomes, but not by much.

CHAIRPERSON GOLD: Okay. Thank you. Any questions or further discussion by the Committee? First, any questions of Dr. Nazmi?

Any further discussion?

So he has suggested a high priority for PFOS. Is there anyone who disagrees, thinks it should be a lower priority?

I'm not hearing any. High prioritization.

Okay. So that concludes the prioritization portion of the agenda.

I think we'll move to staff updates, but I do want to come back to the couple of things that we raised this morning. So unless somebody feels like we ought to do those before we do staff updates, I think we'll do staff updates first and then come back to it.

(Thereupon an overhead presentation was presented as follows.)

MS. ROBINSON: My name is Michelle Robinson, Environmental Scientist in the Prop 65 Implementation Program.

Since your last meeting, as you can see, we have added two chemicals administratively for causing cancer, and seven for reproductive or developmental toxicity. For cancer we have teriparatide and CMNP, also known as pyrazachlor. For developmental toxicity, we have ethylene glycol. And for development and female reproductive toxicity, we have the six triazines. Their effective listing date is pending.

Carol will discuss this shortly.

--o0o--

MS. ROBINSON: On the next slide we have a list of chemicals under consideration, and the issue date of the Notice of Intent to list. There are seven in the cancer endpoint category and one in developmental toxicity endpoint category.

For cancer, we have sedaxane, 1-bromopropane, furfuryl alcohol, and -- let's see, sorry -- tetrachlorvinphos, parathion, malathion, and glyphosate. And for development toxicity, we have topiramate.

--o0o--

MS. ROBINSON: We've also proposed one safe harbor level that's shown on this slide. It is for the Maximum Allowable Dose Level for the six triazine -- triazines. It was proposed on June 12th, 2015.

Now, I'll turn things over to Carol.

Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thanks, Michelle.

So my presentation is on current pending litigation against the Office of Environmental Health Hazard Assessment. We have three -- actually, we have seven pending cases right now against the office, and three of those were filed by Syngenta Crop Protection.

On the previous slides, you saw that OEHHA had listed the, what we call, the triazine chemicals, the class of chemicals and their breakdown products. That listing was challenged during the listing process. And so currently, we have determined that they meet the criteria for listing, but the listing date has not been determined because we're in litigation.

So we actually have a hearing on the merits that is scheduled for this Friday in the trial court here in Sacramento. And we expect to have a decision from the trial court this year. Depending on the outcome of that case, my guess is it will go up on appeal by one side or the other, and we'll have an update for that for you next year at your next meeting.

Related to that, that's why the safe harbor levels for the triazine chemicals haven't been adopted yet, because we won't finish the regulatory process for the safe harbors until the listing of the chemicals is actually complete.

The other two cases that were filed by Syngenta, one has to do with -- is a related case on the triazines. And that is they made a request under the Public Records Act for records from OEHHA, and have challenged our production of records saying that they -- it was insufficient. So we'll see how that case plays out,

depending on the outcome of the base case.

The other case has to do with the chlorothalonil, which is actually listed under Prop 65 as a carcinogen. We have a no significant risk level, safe harbor level for that, which was challenged by Syngenta. And that case is currently stayed until February the 26th, pending the outcome of a potential safe use determination by OEHHA regarding the use of that chemical on a number of food products.

We have another case that was filed by Mateel Environmental Justice against OEHHA that is challenging our current safe harbor level for lead. And that case was -- is -- they had a hearing last week -- I think it was the 3rd. It was last week. I don't know. It all runs together -- and were unsuccessful in asking the court to stay the proceeding while we were in the middle of a rule-making. So we are still defending that case. Our answer is due in December.

At the same time, we received a petition from the Center for Environmental Health requesting that we change or repeal the current MADL for lead, which we are in the process of doing. So we just recently had a hearing on that petition, and we have a pre-regulatory draft of potential set of MADLs for lead that would actually be the first time we would establish a level for an exposure,

other than for one day. Our levels, as proposed, would be for intermittent exposures to lead. And so there would be different levels for different time frames between the exposures. So, for example, a daily level, a level for one to ten days, a level for up to 116 days, I think, is the max.

Your Committee will, at some point in time, be peer reviewing that -- those decisions. And so you'll see that when we get to the actual regulatory phase, as, you know, you see the documents, the scientific basis for our safe harbors before they're adopted. And so you'll have a chance to comment on that individually.

Before I get to the two that are on appeal that we have one other case that isn't related to Prop 65, and that is a challenge to our public health goal for the chemical perchlorate. We were recently sued by the California Manufacturer and Technology Association for our public health goal. The answer in that case is due in December.

We have two cases that are up on appeal right now, both of them filed by the American Chemistry Council. The first one is appealing the trial court decision upholding the listing of the chemical BPA, bisphenol A, which you may remember has a long storied past with this Committee.

But it was -- it was listed by OEHHA for developmental toxicity, and that listing was challenged. And so we currently have a briefing schedule from the court of appeal. We have to file our brief in January, so we're hoping that sometime during 2016 we'll have a final opinion in that case.

The other ACC case has to do with the Carcinogen Identification Committee listing of DINP, which is a phthalate as a carcinogen. That listing was challenged. We were successful at the trial court level, but we're up on appeal in that case as well with a brief due in March. And so hopefully, we'll have a decision in that case next year also.

So based on all of that and a couple of more cases that were anticipating at any time, you understand why I introduced our newest lawyer this morning, who is actually assigned to working on PRAs and litigation.

So any questions?

CHAIRPERSON GOLD: Thank you. Any questions for counsel?

Okay. Hearing none. I wanted to turn back to two things that came up this morning. I think one might a little bit quicker than the other. I don't know.

But a couple of you raised the question about whether you can recommend chemicals to OEHHA for

prioritization. A couple people said they might want to mention some, so I'm going to ask, at this time, if you have anything that you want to tell the staff in that regard? Otherwise, you can communicate with them, I think, in the future.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: I was going through the list, and I had a question. So are polybrominated diphenyl ethers not on the Prop 65 list? I didn't see them, but --

DR. DONALD: That's correct. They are not.

COMMITTEE MEMBER WOODRUFF: Oh. Well, I would like to nominate PBDEs for the list then, based on neurodevelopmental effects. And then you mentioned perchlorate, is that on the list?

DR. DONALD: No. Perchlorate was considered by this Committee and they declined to list it.

COMMITTEE MEMBER WOODRUFF: Oh, what year did they consider it?

DR. DONALD: I'd have to look it up.

COMMITTEE MEMBER WOODRUFF: There's so much more new science to think about.

DR. DONALD: I think it was 2008.

COMMITTEE MEMBER WOODRUFF: Oh. So there's been a lot of studies since 2008.

DR. DONALD: Well, chemicals that have been considered by the Committee previously can be brought back to the Committee.

COMMITTEE MEMBER WOODRUFF: Oh, you mean like BPA.

DR. DONALD: Among others.

CHAIRPERSON GOLD: Are you suggesting perchlorate?

COMMITTEE MEMBER WOODRUFF: Perchlorate and then chlorpyrifos.

These are all chemicals -- well chlorpyrifos and PBDEs have been chemicals that have a lot of new data, because they've been studied by a lot of the Children's Environmental Health Centers that EPA and NIEHS fund, so I know there's a nice set of epidemiological evidence on them.

DR. DONALD: Yeah. Just so the Committee is aware, chlorpyrifos is another chemical that was previously considered by the Committee and not listed.

COMMITTEE MEMBER WOODRUFF: Oh, what year?

DR. DONALD: Again, I don't know off the top of my head, but I can get that.

COMMITTEE MEMBER WOODRUFF: Well, there's been -- because there's been a number of studies published recently, so...

DR. SANDY: So --

CHAIRPERSON GOLD: Dr. Sandy -- Dr. Donald.

DR. DONALD: Okay. As you're probably aware chlorpyrifos is being reviewed by U.S. EPA. So there is a possibility that there may be an opportunity to consider listing through an administrative mechanism.

COMMITTEE MEMBER WOODRUFF: I thought they were proposing to take it off the market.

DR. DONALD: Well, it wouldn't be the action they took, so much as the reasons why they took it that would provide the basis for listing.

COMMITTEE MEMBER WOODRUFF: I see. Okay.

CHAIRPERSON GOLD: Okay. Any others that we want to suggest?

Okay. If you think of any, I'm sure the staff will be happy to hear them.

So the other issue that came up was sort of the presentation of either associations or differences that are found. And I'd like to separate this into two things, sort of presentations that are given here orally versus what we receive in our packets, which are much more detail.

So I'd like to open it up for the Committee to make some suggestions to the staff about what they'd like to see. The point was made that statistical significance

alone shouldn't guide everything that we do, that sometimes you see large differences that aren't significant, just because the sample sizes are very small.

And I think we're all pretty much in agreement with that. So the question is how should that be presented both orally and in our detailed things, and more broadly how would we like associations and differences to be presented to us? I'm recognizing that in these oral presentations it's really sort of a brief overview and summary. It's not really possible to go into the kind of detail that we receive in our packets.

So that's why I'd like to separate the discussion of oral presentation versus what we receive in our packets. And I'll open it up to the Committee to provide some suggestions.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Well, I think it would be really helpful to -- I think it would be useful to have us review some of the tools that have been -- that being developed -- have been developed over the last several years to look exactly at this issue. And I was -- I think this came up maybe a year ago, that the National Toxicology Program has been doing a lot of work in this area, and that perhaps we could ask them to come in and show us what they've been putting together. And then that

would be a good guidepost for us to look at, in terms of these types of methods of data extraction and data evaluation, because I think the thing that's most challenging is that we want to have the data put on the same scale, because you'll have studies that will -- I mean, this was our experience in looking at PFOA and birth weight.

And I just want to say that when we went in to do this evaluation on the epidemiological evidence, it was my opinion before I went into the evaluation that we wouldn't really see that much. And I think it was because the individual studies were in themselves not big enough, and also because people had published them in so many different ways, that you couldn't really see what they looked like until we had put them all using the same type of relationship, using the same scale and the dose response.

So I think that -- I know that the National Toxicology Program has been thinking a lot about this in terms of developing analytic tools to improve our ability to collect and look at the data. And I think it would be useful to talk with them and then come back to us and show us some of the -- or have them come and present to us some of the things that they've been doing.

CHAIRPERSON GOLD: Would the staff like to

respond to this? I mean, have you received input, for example, from the NTP, and so -- or been in communication with them?

DR. SANDY: We have been following what NTP has been doing, but we haven't received direct input from them, but we will take this into consideration, these suggestions.

CHAIRPERSON GOLD: Okay. Thank you.

Anything else?

Okay. I personally feel like the oral presentations really are just a summary of the more detailed information that we have, and it's really not possible to go study by study. It might be possible though, if it's within the purview of say the NTP guidelines to provide sort of -- I don't want to call it a meta-analysis, but where we get some sense of what the differences or associations, what their magnitude looks like, sort of a summary of that might be helpful.

But that also has to consider the sample sizes, because again some things will not be significant, but they might be large differences, for example. Small numbers, they wouldn't be significant.

Dr. Luderer.

COMMITTEE MEMBER LUDERER: Yeah, I'd just actually -- because I think what Dr. Woodruff was just

referring to has to do more with the detailed assessments. And then we were having some discussion this morning about these screens. And so I had two -- I mean, I actually think that the way that you presented them, where you separated out the epidemiological studies that had -- that found evidence of adverse effects that were statistically significant. But then also highlighted those that had some evidence of adverse effects that were not statistically significant.

So I thought that is a helpful way of, you know, pointing out kind of what you were just talking about, and as well as Dr. Gold, that, you know, affects may be important that are not -- do not meet statistical significance in an individual study.

But then this morning I think there was still some confusion, even after we asked for clarification among the panel members including me, about the process for these screens.

So my understanding from what you told us was that you do two kind of screens, and they don't necessarily go -- you screen epidemiological literature first. And only if that's positive, do you screen the animal literature. You have also done screens where you start with the experimental literature as the first step of the screen. And sometimes one is done and sometimes

the other, was I understanding that correctly?

DR. DONALD: That's correct. And those are not necessarily the only screens we will apply. Those are the screens we've applied to date. We're considering other screens that we might apply in the future.

DR. SANDY: This is Martha Sandy. I'd like to clarify though that ones we've identified that a chemical passes the screen, whichever screen we're applying, epidemiology or animal data screens, then we look at all the evidence and do this preliminary toxicological evaluation. And that's why we did present to you the number of studies and the findings from animal data and then other relevant data.

CHAIRPERSON GOLD: And I think we found that helpful. Okay. Any other comments on this point or this issue?

COMMITTEE MEMBER WOODRUFF: I agree with you that I think that the details are very -- are more useful in the written material, and that it's the oral study by study of -- oral explanation is not as useful.

CHAIRPERSON GOLD: Okay. Hearing nothing else, I think we can move to a summary of the Committee's actions.

ACTING DIRECTOR ZEISE: Okay. So the Committee deliberated on two chemicals, methyl-n-butyl ketone and 2,5-hexanedione. And the Committee decided on whether

methyl-n-butyl ketone had been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity.

They considered female reproductive toxicity and developmental toxicity. For male reproductive toxicity, there was a unanimous vote. So in methyl-n-butyl ketone will be added to the list for that endpoint. For female reproductive toxicity, the vote was 5 yeses to -- and 3 noes, no abstaining. For that endpoint to be included, there would have had to have been a vote of 6, so that one will not -- that particular endpoint will not be added for that chemical.

And then for developmental toxicity, there were 6 yeses, 2 noes, with no abstaining. And with 6 yeses that endpoint, developmental toxicity will be added for methyl-n-butyl ketone.

For 2,5-hexanedione for the male endpoint, there was a unanimous vote that it had been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity. So for that endpoint, it will be added to the Proposition 65 list. For the female endpoint, there were 4 yeses, 4 noes, and no abstentions, so it will not be added for that endpoint.

For developmental toxicity, there were 4 yeses, 3

noes, and 1 abstaining, so it won't be added for that endpoint either.

So coming out of the discussion for those two chemicals, we heard from the Committee that they'd like to see n-hexane.

CHAIRPERSON GOLD: Can I interrupt for one minute. Dr. Kaufman, did you have a point to make?

DR. KAUFMAN: I'm sorry. I think -- I believe it was 5 yeses, 2 noes, and 1 abstention for the vote on developmental.

CHAIRPERSON GOLD: For developmental I have 4, 3, and 1.

DR. KAUFMAN: Oh, I'm sorry.

CHAIRPERSON GOLD: Four, 3, and 1.

ACTING DIRECTOR ZEISE: Four, 3, and 1.

DR. DONALD: If I can make just a very minor clarification for the record. MnBK is already on the list on the basis of male reproductive toxicity, so it will actually remain on the list, and will not be added to the list on the basis of that endpoint.

CHAIRPERSON GOLD: Thank you for that clarification.

ACTING DIRECTOR ZEISE: Thank you for that clarification, Jim.

Okay. So again, the Committee asked us to

look -- asked us to bring in n-hexane to them for their review.

And then for prioritization, nickel and nickel compounds were given a priority of sort of medium low to medium. The Committee for pentachlorophenol advised us that the priority would be medium to high. For perchloroethylene or tetrachloroethylene or perc, the Committee recommended medium high to high. For PFOA, perfluorooctanoic acid, the Committee gave that a priority of high. And for PFOS, perfluorooctane sulfonate, the Committee gave a priority of high.

So for -- in discussion about our oral presentations and our written documentation, the Committee recommended that we either look at the NTP systematic review literature and report back to them on that or bring in NTP to present on that literature. So we'll look at that.

And then I think that was the summary in terms of recommendations for that discussion.

Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: And then we had the three additional chemicals that Dr. Woodruff is suggesting.

ACTING DIRECTOR ZEISE: Yes. And so we also had the three additional suggestions for the Committee review,

and that was PBDEs, perchlorate, and chlorpyrifos.

And so I guess to conclude, I'd like to thank the Committee for all the hard work. We know that this takes a lot of your time to go through that, and so we really appreciate the work and the donation of your time to the State of California.

We'd also like to thank the staff for all your hard work. These meetings take a lot to put on from the -- that you've seen the high quality of documents coming from the scientific staff. And then from the implementation side and the legal side, it also takes a lot of effort to put these on, so thank you.

And I'd also like to thank all the participants in the audience and on the web for participating in our process. We really appreciate your coming to the meeting, testifying, giving the Committee information to consider in making their decisions.

So thank you all and safe travels.

Ellen.

CHAIRPERSON GOLD: Okay. If there's nothing further, I'd like to call this meeting into adjournment. And thank you all for your participation.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 2:26 p.m.)

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

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 24th day of November, 2015.

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