

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

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Dr. Melanie Marty, Acting Deputy Director, Scientific  
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Dr. Francisco Moran, Reproductive and Cancer Hazard  
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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

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## P R O C E E D I N G S

1  
2           ACTING DIRECTOR ZEISE: Okay. Good morning,  
3 everyone. I'm Lauren Zeise. I'm Acting Director of the  
4 Office of Environmental Health Hazard Assessment, or  
5 OEHHA. I'd like to welcome you all to this meeting of the  
6 Developmental and Reproductive Toxicant Identification  
7 Committee.

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

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

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

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

1 at the University of California at Davis.

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

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

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

24 So welcome, everyone.

25 Now, I'd like to introduce the OEHHA staff

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

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

10 (Laughter.)

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

14 Thank you.

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

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

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

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

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

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

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

1 judgment on the questions that are put before you.

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

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

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

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

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

3 Anybody have questions on that?

4 Thank you.

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

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

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

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

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

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

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

11           So with that, we'll turn to the business at hand.  
12 First, the consideration of -- or reconsideration of  
13 methyl-n-butyl ketone, and it's metabolite  
14 2,5-hexanedione.

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

17           (Thereupon an overhead presentation was  
18 presented as follows.)

19           DR. DONALD: Good morning. My name is Jim  
20 Donald. I'm Chief of the Reproductive Toxicology and  
21 Epidemiology Section in OEHHA. I'm going to begin by  
22 briefly reviewing why methyl-n-butyl ketone and  
23 2,5-hexanedione are before you today and reviewing the  
24 decisions that the Committee will be asked to make.

25                           --o0o--

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

6 --o0o--

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

14 --o0o--

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

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

25 At that meeting, the Committee also identified

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

5 --o0o--

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

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

19 --o0o--

20 DR. DONALD: If there are any questions at this  
21 point, I'd be happy to address them. Otherwise, I will  
22 turn this over to Dr. Iyer who will briefly summarize the  
23 information on MnBK and its metabolic relationship with  
24 2,5-HD. And then Dr. Francisco Moran will summarize the  
25 available evidence on 2,5-HD.

1                   --o0o--

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

6                   --o0o--

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

18           However, no additional information on this study  
19 was available from NIEHS. So Tables 1 and 2 in the HID  
20 include the same studies presented previously at the March  
21 19th, 2014 DARTIC meeting, and they have been updated and  
22 some more information has been included for clarification.

23                   --o0o--

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

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

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

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

17                           --o0o--

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

23                           --o0o--

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

1 ppm. A decrease in post-natal growth rate of the  
2 offspring was noted with dose dependent decrease in weight  
3 gain in male offspring persisting throughout life both at  
4 1000 and 2000 ppm with a less marked treatment effect seen  
5 in the females. The authors stated that this is -- that  
6 it was statistically significant, but details like P  
7 values were not provided in the article.

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

11                   --o0o--

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

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

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

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

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

11                           --o0o--

12           DR. IYER: Again, for some of the perturbations  
13 for behavioral battery are presented in this slide. The  
14 open field exploratory behavior showed a decreased  
15 activity in young animals, males and females, at the time  
16 2000 ppm exposure group, but no significant difference in  
17 older animals at either treatment was noted.

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

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



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

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

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

14                           --o0o--

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

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

1                   --o0o--

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

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

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

23                   --o0o--

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

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

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

11 --o0o--

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

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

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

25 --o0o--

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

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

15 --o0o--

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

20 --o0o--

21 DR. IYER: Several studies in the rats and guinea  
22 pigs have demonstrated that MnBK undergoes metabolism by a  
23 variety of pathways. As noted in the schematic in this  
24 slide and this schematic is included in the HID as Figure  
25 1, MnBK can ultimately be metabolized to 2,5-HD either as

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

7 --o0o--

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

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

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

18 --o0o--

19 DR. IYER: Do you have any questions?

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

22 CHAIRPERSON GOLD: Just continue.

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

1           2,5-HD is used as starting reagent in the  
2 synthesis of trans-2,5-dimethylpyrrolidine and other  
3 pyrroles.

4                           --o0o--

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

11                           --o0o--

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

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

21                           --o0o--

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

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

3 --o0o--

4 DR. MORAN: For developmental toxicity, the study  
5 by Moretto et al., in '91 -- did it pass? I'm sorry. --  
6 by Moretto et al., in '91 is an in vitro study that uses  
7 the human fetal developing dorsal root ganglion cells.  
8 Cells in culture were directly exposed to 2,5-HD at 0 or  
9 2.8 millimolar for two weeks.

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

14 --o0o--

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

23 --o0o--

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

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

6 --o0o--

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

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

17 --o0o--

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

22 In addition, two reviews by Boekelheide group in  
23 2001 and 2003 summarized the effects of 2,5-HD.

24 --o0o--

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

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

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

10                   --o0o--

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

16                   --o0o--

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

22                   --o0o--

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

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

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

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

10 --o0o--

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

13 Five animals were exposed to a range of 0.3 to 1  
14 percent, while in the majority of the studies, animals  
15 were exposed to 1 percent 2,5-HD. In 8 studies, the  
16 animals were exposed to a range of 60 to 2000 milligrams  
17 per kilo per day. In 4 studies were exposed to a range of  
18 3.1 to 5.4 millimoles per kilo per day, and the in vitro  
19 study exposure ranged of 0.5 to 2. -- 20 nanomolar was  
20 used. The exposure duration ranged from a single exposure  
21 normally by gavage up to daily exposure for 12 weeks.

22 --o0o--

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

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

3 --o0o--

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

12 --o0o--

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

17 --o0o--

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

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

1 effect was not reported.

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

8 --o0o--

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

19 --o0o--

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

25 This concludes my presentation. Thank you.

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

4 COMMITTEE MEMBER WOODRUFF: I have a question.

5 CHAIRPERSON GOLD: Yes, Dr. Woodruff.

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

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

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

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

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

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

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

5           DR. MORAN: Right.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 Any other further questions of the presenters?

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

11 COMMITTEE MEMBER PESSAH: Thank you, Dr. Gold.

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

15 In March of last year, we considered MBK and  
16 requested more information since there were only three  
17 studies. And one thing that was picked up was the major  
18 metabolite which was not part of the review back then.  
19 2,5-HD seemed to be a missing link for biological  
20 plausibility. I think I'm going to sort of focus on  
21 biological plausibility given what I believe is the  
22 overwhelming evidence that MBK potentially could cause  
23 male reproductive toxicity. And then I'm going to talk a  
24 little bit about newer data that at least one paper that I  
25 think came out after your review was posted.

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

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

13           The last figures that I could find was in the  
14 National Library of Medicine 2005 report, which reported  
15 the levels of MBK production in the United States and  
16 import - they didn't separate the two - between 453 and  
17 4,500 metrics tons.

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

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

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

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

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

12           It should be pointed out that n-hexane is a HPV,  
13 a high volume chemical, with more than a billion pounds of  
14 the last report in 2002. It is metabolized to MBK. Free  
15 2,5-HD concentration serves as a biomarker for exposure to  
16 n-hexane. And although we're not considering it here, I  
17 want to point out that n-hexane, MBK, and 2,5-HD are  
18 inextricably linked toxicologically.

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

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

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

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

18           And they found incidence of neuropathy or  
19 evidence for neuropathy of 22 percent relative -- compared  
20 to three percent for those that were not exposed. The P  
21 value there was 0.001. The prevalence in this study was  
22 highest among printer operators, which had an incidence of  
23 39 percent compared to non-print department employees.

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

1 printing machines, which had apparently MBK.

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

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

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

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

1 including kinesin and dynein. And it impairs microtubule  
2 assembly.

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

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

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

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

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

4 2,5-HD significantly increased ovarian and  
5 uterine malondialdehyde and hydrogen peroxide. These were  
6 statistically significant, and these are two biomarkers of  
7 adverse outcome that involve the oxidative stress.

8 Significant decreases in ovarian catalase, superoxide  
9 dismutase, glutathione peroxidase, and glutathione  
10 s-transferase. The major protective antioxidant defense  
11 mechanism occurred in all the 2,5-HD treated groups,  
12 including the lowest dose.

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

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

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

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

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

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

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

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

25           In particular, this was a mixture of solvents, so

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

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

19           So I'll stop there.

20           CHAIRPERSON GOLD: Thank you, Dr. Pessah.

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

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

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

1           No public comments.

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

5           Dr. Auyeng-Kim.

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

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

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

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

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

25           COMMITTEE MEMBER AUYEUNG-KIM: Definitely.

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

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

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

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

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

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

3 CHAIRPERSON GOLD: Thank you.

4 Dr. Luderer.

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

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

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

17 CHAIRPERSON GOLD: Any other comments or  
18 questions?

19 Okay. Are we ready to vote?

20 Dr. Luderer.

21 COMMITTEE MEMBER LUDERER: Actually, I do have  
22 one question, which is the point that Dr. Pessah brought  
23 up about the -- that this is -- that the MnBK, as well as  
24 2,5-hexanedione are both metabolites of n-hexane. And so  
25 does any decision that we make here today also have

1 implications for n-hexane as far as Prop 65?

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

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

11 CHAIRPERSON GOLD: Okay. Thank you.

12 Any more for discussion or questions?

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

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

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

22 (Hands raised.)

23 CHAIRPERSON GOLD: Eight. I see eight.

24 So no noes, and no one abstaining.

25 All right. Let's move now to female reproductive

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

5 (Hands raised.)

6 CHAIRPERSON GOLD: One, two, three, four.

7 Dr. Carmichael, is your hand up?

8 PANEL MEMBER CARMICHAEL: No, it's not.

9 CHAIRPERSON GOLD: No, okay.

10 Three, four, five. I see five.

11 Those voting no?

12 (Hands raised.)

13 CHAIRPERSON GOLD: Two -- three.

14 And no abstentions, correct?

15 Okay. So let me just announce the vote for the  
16 male reproductive it was 8 yes and 0 noes and no  
17 abstentions. And for female reproductive toxicity, it was  
18 5 yes, 3 no, and no abstentions.

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

25 (Hands raised.)

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

3           Those voting no?

4           (Hands raised.)

5           CHAIRPERSON GOLD: One, two.

6           And no abstentions.

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

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

15           (Hands raised.)

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

19           Turn now to female reproductive toxicity. Has  
20 2,5-hexanedione been clearly shown through scientifically  
21 valid testing, according to generally accepted principles  
22 to cause female reproductive toxicity? All those voting  
23 yes, please raise your hand.

24           (Hands raised.)

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

1 Voting no?

2 (Hands raised.)

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

6 Next developmental toxicity. So has  
7 2,5-hexanedione been clearly shown through scientifically  
8 valid testing, according to generally accepted principles  
9 to cause developmental toxicity? All those voting yes,  
10 please raise your hand.

11 (Hands raised.)

12 CHAIRPERSON GOLD: Three.

13 All those voting no?

14 (Hands raised.)

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

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

19 (Hands raised.)

20 CHAIRPERSON GOLD: One, two, three, four.

21 Okay. Those voting no?

22 (Hands raised.)

23 CHAIRPERSON GOLD: One, two, three.

24 Abstentions?

25 (Hand raised.)

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

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

6 You're good.

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

11 Dr. Woodruff.

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

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

18 COMMITTEE MEMBER WOODRUFF: Did that get  
19 resolved?

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

22 Anyone wish to comment on that?

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

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

4 Yes.

5 Okay. Good. Thank you for reminding us.

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

10 (Thereupon an overhead presentation was  
11 presented as follows.)

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

16 --o0o--

17 DR. DONALD: The document process for  
18 prioritizing chemicals for consideration under Proposition  
19 65 by the State's qualified experts that was adopted by  
20 OEHHA in December of 2004 was included in the materials  
21 that were provided to you prior to this meeting.

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

25 --o0o--

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

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

11 --o0o--

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

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

1                   --o0o--

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

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

17                   --o0o--

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

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

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

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

12                           --o0o--

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

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

22                           --o0o--

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

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

4 --o0o--

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

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

14 --o0o--

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

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

23 --o0o--

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

1           CHAIRPERSON GOLD: Any questions for Dr. Donald?  
2           Dr. Carmichael.

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

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

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

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

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

1 general guidelines.

2 COMMITTEE MEMBER CARMICHAEL: Thank you.

3 CHAIRPERSON GOLD: Dr. Woodruff.

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

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

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

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

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

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

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

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

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

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

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

16 DR. DONALD: Yeah, certainly.

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

1 Committee.

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

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

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

1 before that for other data, is that right?

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

9 So I suppose you could think of it as sort of a  
10 2-step process. We apply an initial screen to narrow down  
11 the range of chemicals, and then we look at the entire  
12 body of data. And on that basis decide which ones will  
13 come before you as potential candidates.

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

25 DR. DONALD: Yes. In the document that we

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

9 CHAIRPERSON GOLD: Any other questions or  
10 comments?

11 Dr. Sandy.

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

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

1 screens.

2 CHAIRPERSON GOLD: Thank you.

3 Any other comments or questions?

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

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

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

14 Dr. Iyer, is that correct?

15 (Thereupon an overhead presentation was  
16 presented as follows.)

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

22 --o0o--

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

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

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

10                   --o0o--

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

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

18                   --o0o--

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

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

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

5                           --o0o--

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

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

20                           --o0o--

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

1           And that's all the information for nickel.

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

5           THE COURT REPORTER: Yes.

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

8           (Off record: 11:30 AM)

9           (Thereupon a recess was taken.)

10          (On record: 11:40 AM)

11          CHAIRPERSON GOLD: Can we please reconvene.

12          Can we please take our seats and reconvene.

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

16          Any questions for Dr. Iyer?

17          Hearing none.

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

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

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

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

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

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

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

1 order to be able to produce adequately.

2 --o0o--

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

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

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

18 And during that period of time, there have been a  
19 few epidemiology studies, but the biggest epidemiology  
20 study was one that we commissioned on behalf of the  
21 European Commission and the Danish EPA back in the early  
22 2000s. We were looking at the effects of nickel on the  
23 highest exposed occupational cohort we could find anywhere  
24 in the world. This was a cohort that existed in Russia  
25 using technology that existed from -- previous to World

1 War II. It was in the Kola peninsula.

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

6 --o0o--

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

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

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

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

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

18                           --o0o--

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

1 at in animals is 100 times higher than the REL.

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

7 Thank you.

8 CHAIRPERSON GOLD: Thank you.

9 Any questions for Dr. Bates?

10 Okay. Thank you very much.

11 DR. BATES: Thank you.

12 CHAIRPERSON GOLD: Julie Goodman.

13 (Thereupon an overhead presentation was  
14 presented as follows.)

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

21 --o0o--

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

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

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

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

18 --o0o--

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

25 So what we did was came up with a system based

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

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

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

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

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

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

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

8 --o0o--

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

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

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

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

6 --o0o--

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

10 Thanks very much.

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

13 Dr. Woodruff.

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

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

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

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

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

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

25           And so these are things that do impact how you

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

13 Thanks.

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

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

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

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

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

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

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

14 COMMITTEE MEMBER AUYEUNG-KIM: Okay.

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

17 CHAIRPERSON GOLD: Dr. Sandy.

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

1 COMMITTEE MEMBER AUYEUNG-KIM: Okay.

2 CHAIRPERSON GOLD: Do you have anything else to  
3 add?

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

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

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

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

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

18 DR. DONALD: Essentially, yes.

19 CHAIRPERSON GOLD: Okay. Dr. Carmichael.

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

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

7 CHAIRPERSON GOLD: Dr. Plopper.

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

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

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

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

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

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

6 Dr. Woodruff.

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

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

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

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

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

6 We're not taking a formal vote.

7 (Laughter.)

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

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

16 CHAIRPERSON GOLD: That's good. Thank you.

17 Dr. Kim, you're sticking with that?

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

22 CHAIRPERSON GOLD: Than you.

23 Dr. Plopper.

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

1 elemental nickel, yes, it's medium priority.

2 CHAIRPERSON GOLD: Okay. Dr. Luderer.

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

7 CHAIRPERSON GOLD: Dr. Pessah.

8 COMMITTEE MEMBER PESSAH: Medium to low priority.

9 CHAIRPERSON GOLD: Okay. Dr. Carmichael.

10 COMMITTEE MEMBER CARMICHAEL: Medium priority.

11 CHAIRPERSON GOLD: Dr. Woodruff.

12 COMMITTEE MEMBER WOODRUFF: Medium.

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

15 DR. DONALD: Yes, certainly.

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

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

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

23 DR. DONALD: All right. Thank you.

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

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

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

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

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

11 (Thereupon an overhead presentation was  
12 presented as follows.)

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

16 --o0o--

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

23 --o0o--

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

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

4 --o0o--

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

20 --o0o--

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

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

7 --o0o--

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

13 --o0o--

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

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

18 Dr. Pessah.

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

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

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

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

6 So I don't have any public comments?

7 No public comments.

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

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

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

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

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

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

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

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

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

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

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

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

12           (Laughter.)

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

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

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

1 CHAIRPERSON GOLD: Thank you.

2 Any comments or questions by the Committee?

3 Dr. Pessah.

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

7 CHAIRPERSON GOLD: Anybody know the answer to  
8 this question?

9 Dr. Kaufman.

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

14 CHAIRPERSON GOLD: Dr. Luderer.

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

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

20 CHAIRPERSON GOLD: Other questions or comments  
21 from the Committee?

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

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

1 Is that good for the staff?

2 Okay. Thank you.

3 I wonder if we can fit one more in before lunch?

4 Is everybody up for that?

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

7 (Thereupon an overhead presentation was  
8 presented as follows.)

9 DR. KAUFMAN: I am. Thank you.

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

13 So this is the evidence for prioritization of  
14 tetrachloroethylene. Tetrachloroethylene, also known as  
15 perchloroethylene, or perc, is a volatile synthetic  
16 chlorinated solvent. It is used in textile processing and  
17 dry cleaning. However, the use of perc in dry cleaning in  
18 California is being phased out and will be completed by  
19 2023.

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

23 --o0o--

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

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

5 --o0o--

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

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

16 --o0o--

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

22 --o0o--

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

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

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

9 --o0o--

10 DR. KAUFMAN: That concludes this presentation.

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

14 Dr. Carmichael.

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

17 DR. KAUFMAN: Yes, exactly.

18 CHAIRPERSON GOLD: Dr. Woodruff.

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

21 CHAIRPERSON GOLD: Yes, it is.

22 COMMITTEE MEMBER WOODRUFF: Okay. Thanks.

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

25 I have no public comments, is that correct?

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

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

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

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

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

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

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

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

1 exposures is also PCP.

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

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

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

25           CHAIRPERSON GOLD: Very good. Thank you.

1 Questions for Dr. Luderer from the Committee?

2 Comments, questions?

3 None. I'm hearing none.

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

6 Any disagreements?

7 Dr. Nazmi.

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

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

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

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

4 CHAIRPERSON GOLD: Okay. Any other comments?

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

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

10 Should we reconvene -- what?

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

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

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

16 CHAIRPERSON GOLD: Fine.

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

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

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

20 CHAIRPERSON GOLD: 1:15.

21 CHIEF COUNSEL MONAHAN-CUMMINGS: Please.

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

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

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

3 Thank you.

4 CHAIRPERSON GOLD: We'll stand adjourned until  
5 1:15

6 (Off record: 12:23 PM)

7 (Thereupon a recess was taken.)

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

2                   (On record: 1:30 PM)

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

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

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

19                  CHAIRPERSON GOLD: Very good. Thank you.

20                  Anything else?

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

25                  (Thereupon an overhead presentation was

1           presented as follows.)

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

7           CHAIRPERSON GOLD: Okay. Thank you.

8           Dr. Kim.

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

13   --o0o--

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

20   --o0o--

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

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

5                           --o0o--

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

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

18                           --o0o--

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

25                           --o0o--

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

8 --o0o--

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

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

18 --o0o--

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

24 --o0o--

25 CHAIRPERSON GOLD: Thank you. Does the Committee

1 have any questions for Dr. Kim?

2 Dr. Auyeung-Kim.

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

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

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

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

16 So Geary Olsen.

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

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

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

1 20 some odd pages quick review of some of the issues that  
2 are -- you have to deal with PFOA and ultimately with the  
3 compound that will follow this compound. These are  
4 chemicals that are basically attached to proteins. And so  
5 with that in mind, you have to think about where they  
6 traverse from the body standpoint.

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

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

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

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

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

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

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

22           COMMITTEE MEMBER WOODRUFF: (Shakes head.)

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

25           But the issue becomes is some of the associations

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

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

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

16           So that would conclude my comments for PFOA.

17           CHAIRPERSON GOLD: Thank you.

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

20           Very good. Thank you.

21           DR. OLSEN: Thank you.

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

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

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

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

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

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

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

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

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

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

20 Dr. Nazmi.

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

23 CHAIRPERSON GOLD: Dr. Woodruff.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 CHAIRPERSON GOLD: Okay. Thank you. Questions?  
5 Dr. Pessah.

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

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

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

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

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

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

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

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

19           CHAIRPERSON GOLD: Okay. Thank you.

20           Any other questions or discussion by the  
21 Committee members?

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

25           Everybody sort of in agreement this is a high

1 priority for prioritization?

2 Thank you.

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

6 (Thereupon an overhead presentation was  
7 presented as follows.)

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

11 --o0o--

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

18 --o0o--

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

25 The most recent data from Biomonitoring

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

5 --o0o--

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

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

19 --o0o--

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

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

1 were also 56 related human studies.

2 --o0o--

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

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

14 CHAIRPERSON GOLD: Thank you, Dr. Kim.

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

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

20 That's it.

21 MS. ROBINSON: That's it.

22 CHAIRPERSON GOLD: Dr. Olsen.

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

1 statement. And I'll do this comment first.

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

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

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

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

1 -- make you aware of other literature.

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

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

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

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

4 So those are my comments. Thank you.

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

7 DR. OLSEN: Thank you.

8 CHAIRPERSON GOLD: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Any further discussion?

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

5 I'm not hearing any. High prioritization.

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

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

13 (Thereupon an overhead presentation was  
14 presented as follows.)

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

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

1 Carol will discuss this shortly.

2 --o0o--

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

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

12 --o0o--

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

17 Now, I'll turn things over to Carol.

18 Thank you.

19 CHIEF COUNSEL MONAHAN-CUMMINGS: Thanks,  
20 Michelle.

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

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

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

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

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

1 depending on the outcome of the base case.

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

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

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

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

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

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

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

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

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

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

18           So any questions?

19           CHAIRPERSON GOLD: Thank you. Any questions for  
20 counsel?

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

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

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

6 Dr. Woodruff.

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

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

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

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

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

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

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

23 DR. DONALD: I think it was 2008.

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

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

4 COMMITTEE MEMBER WOODRUFF: Oh, you mean like  
5 BPA.

6 DR. DONALD: Among others.

7 CHAIRPERSON GOLD: Are you suggesting  
8 perchlorate?

9 COMMITTEE MEMBER WOODRUFF: Perchlorate and then  
10 chlorpyrifos.

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

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

20 COMMITTEE MEMBER WOODRUFF: Oh, what year?

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

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

1 DR. SANDY: So --

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

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

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

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

12 COMMITTEE MEMBER WOODRUFF: I see. Okay.

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

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

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

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

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

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

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

16           Dr. Woodruff.

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

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

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

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

25           CHAIRPERSON GOLD: Would the staff like to

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

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

8 CHAIRPERSON GOLD: Okay. Thank you.  
9 Anything else?

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

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

23 Dr. Luderer.

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

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

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

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

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

1 the other, was I understanding that correctly?

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

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

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

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

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

23 ACTING DIRECTOR ZEISE: Okay. So the Committee  
24 deliberated on two chemicals, methyl-n-butyl ketone and  
25 2,5-hexanedione. And the Committee decided on whether

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

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

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

17           For 2,5-hexanedione for the male endpoint, there  
18 was a unanimous vote that it had been clearly shown  
19 through scientifically valid testing, according to  
20 generally accepted principles to cause male reproductive  
21 toxicity. So for that endpoint, it will be added to the  
22 Proposition 65 list. For the female endpoint, there were  
23 4 yeses, 4 noes, and no abstentions, so it will not be  
24 added for that endpoint.

25           For developmental toxicity, there were 4 yeses, 3

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

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

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

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

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

13 DR. KAUFMAN: Oh, I'm sorry.

14 CHAIRPERSON GOLD: Four, 3, and 1.

15 ACTING DIRECTOR ZEISE: Four, 3, and 1.

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

21 CHAIRPERSON GOLD: Thank you for that  
22 clarification.

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

25 Okay. So again, the Committee asked us to

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

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

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

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

20           Carol.

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

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

1 and that was PBDEs, perchlorate, and chlorpyrifos.

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

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

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

18           So thank you all and safe travels.

19           Ellen.

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

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

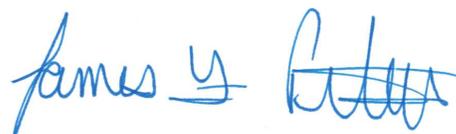
## 1 C E R T I F I C A T E O F R E P O R T E R

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

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

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

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

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22 JAMES F. PETERS, CSR  
23 Certified Shorthand Reporter  
24 License No. 10063  
25