

MEETING
STATE OF CALIFORNIA
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
PROPOSITION 65
DEVELOPMENTAL AND REPRODUCTIVE TOXICANT
IDENTIFICATION COMMITTEE

JOE SERNA JR./CALEPA HEADQUARTERS BUILDING
1001 I STREET
SIERRA HEARING ROOM
SACRAMENTO, CALIFORNIA

THURSDAY, NOVEMBER 20, 2008

10:03 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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PETERS SHORTHAND REPORTING CORPORATION (916) 362-2345

APPEARANCES

COMMITTEE MEMBERS

Dr. Dorothy T. Burk, Chairperson

Dr. Ellen B. Gold

Dr. Calvin Hobel

Dr. Kenneth L. Jones

Dr. Carl Keen

Dr. Hillary Klonoff-Cohen

Dr. Linda G. Roberts

Dr. La Donna White

STAFF

Dr. Joan E. Denton, Director

Mr. Allan Hirsch, Chief Deputy Director

Dr. George Alexeeff, Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

Dr. Marlissa Campbell, Staff Toxicologist, Reproductive Toxicology and Epidemiology Section

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

Ms. Amy Dunn, Research Scientists III, Safer Alternatives Assessment and Biomonitoring Section

Dr. Poorni Iyer, Staff Toxicologist, Reproductive Toxicology and Epidemiology Section

Ms. Fran Kammerer, Staff Counsel

Dr. Farla Kaufman, Staff Toxicologist, Reproductive Toxicology and Epidemiology Section

APPEARANCES CONTINUED

STAFF

Dr. Francisco Moran Messen, Staff Toxicologist,
Reproductive Toxicology and Epidemiology Section

Ms. Cynthia Oshita, Proposition 65 Implementation

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

ALSO PRESENT

Dr. Carol Burns, Dow Chemical Company

Dr. Daland R. Juberg, Dow AgroSciences

Dr. Jay Murray, Chlorine Chemistry Division, American
Chemistry Council

Dr. Gina Solomon, Natural Resources Defense Council

Dr. Rebecca Sutton, Environmental Working Group

Dr. Robert Tardiff, Chlorine Chemistry Division, American
Chemistry Council

Mr. Christian Volz, McKenna Long & Aldridge

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INDEX

	PAGE
I. Welcome and Opening Remarks by Director Denton	1
II. Consideration of Chemicals as Known to the State to Cause Reproductive Toxicity	
A. Hexavalent Chromium	
- Staff Presentation by Dr. Campbell and Ms. Dunn	3
- Committee Discussion	21
- Public Comments	23
- Committee Discussion and Decision	23
B. Chlorpyrifos	
- Staff Presentation by Dr. Iyer and Dr. Kaufman	27
- Committee Discussion	68
- Public Comments	71
- Committee Discussion and Decision	112
III. Prioritization of Chemicals for Developmental and Reproductive Toxicant Identification Committee Review	
A. Trihalomethanes	
- Staff Presentation by Dr. Donald, Chief Counsel Monahan-Cummings & Dr. Moran	136
- Committee Discussion	145
- Public Comments	145
- Committee Discussion and Advice and Consultation Regarding Possible Development of Hazard Identification Materials	189
B. Particulate Matter	
- Staff Presentation by Dr. Donald & Dr. Moran	194
- Committee Discussion	197
- Public Comments	197
- Committee Discussion and Advice and Consultation Regarding Possible Development of Hazard Identification Materials	197

INDEX CONTINUED

	PAGE
IV. Update of the Section 27000 List of Chemicals Which Have Not Been Adequately Tested As Required	
- Staff Presentation by Staff Counsel Kammerer	211
- Committee Discussion	213
- Public Comments	213
- Committee Discussion and Decision	213
V. Staff Updates	
- Chemical Listings Via the Administrative Listing Mechanisms and Safe Harbor Level Development by Ms. Oshita	217
- Proposition 65 Litigation by Chief Counsel Monahan-Cummings	219
VI. Summary of Committee Actions and Closing Remarks by Director Denton	220
Adjournment	224
Reporter's Certificate	225

PROCEEDINGS

1
2 DIRECTOR DENTON: Good morning. I'd like to ask
3 everyone to take their seats and we'll get started. This
4 is going to be a very interesting and maybe long meeting
5 today. So it's a probably good idea to start very close
6 to the starting time. My name is Joan Denton and I'm the
7 Director of the Office of Environmental Health Hazard
8 Assessment. And this is a meeting -- this is our
9 pre-holiday annual meeting of the Dart ID Committee for
10 Proposition 65. And I want to just take a minute to
11 introduce the Committee Members whose name plates are in
12 front.

13 But to my left is Dr. Dorothy Burk and she is our
14 Chair. I'll be turning the meeting over to her
15 momentarily. Next to her Dr. Hillary Klonoff-Cohen. Dr.
16 Calvin Hobel is next to Dr. Klonoff-Cohen. And then
17 finally Dr. Linda Roberts on the far left.

18 On my right Dr. Carl Keen, then Dr. Kenneth Jones
19 followed by Dr. LaDonna White and then Dr. Ellen Gold at
20 my very far right.

21 So I just want to -- I just have a couple of
22 opening remarks and then the staff tables, I think that
23 people will be introducing individuals as they begin to
24 speak, so I'll leave that for George to do.

25 I just wanted to remind everyone that at our last

1 DART meeting, which was last December, December 10th, the
2 Committee recommended that OEHHA evaluate or prepare
3 hazard identification materials on eight, what we call,
4 candidate chemicals. This was the result of looking at
5 the epidemiology screen. And those chemicals were or are
6 hexavalent chromium, chlorpyrifos, DDE, methylisocyanate,
7 bromodichloromethane, sulfur dioxide, caffeine, and
8 bisphenol A.

9 Now, all eight of these chemicals have undergone
10 a data call-in in preparation for the hazard
11 identification materials. So 2 of the 8 chemicals will be
12 discussed today, those being hexavalent chromium, which is
13 the first item on the agenda, and then chlorpyrifos which
14 is the second item on the agenda. And the remaining six
15 chemicals will be brought to the Committee at a future
16 date or dates.

17 So with that, I think everyone has a copy of the
18 agenda, and so I don't really need to go through that. I
19 will turn it over to Dr. Burk.

20 CHAIRPERSON BURK: Good morning, everyone. Thank
21 you all for coming today. Particularly, thank the
22 Committee Members. It's great to see everyone here,
23 again, at this, almost, holiday time of year. It won't
24 start for me till after we get past this.

25 I also want to, before I even start, thank the

1 OEHHA staff so much for the huge amount of effort that
2 went into preparing the documents that we're looking at
3 today and for, I think, the presentations that will come.
4 Most appreciative.

5 So the first chemical on the agenda for
6 consideration for listing is hexavalent chromium. The
7 staff presentation will be given by Drs. Marlissa
8 Campbell -- oh, and Ms. Amy Dunn.

9 (Thereupon an overhead presentation was
10 Presented as follows.)

11 DR. CAMPBELL: Good morning.

12 There, how's that?

13 DIRECTOR DENTON: Marlissa, our monitors are not
14 working.

15 Do you --

16 DR. CAMPBELL: Oh, I don't -- Cindy is coming.

17 Do you want me to wait?

18 DIRECTOR DENTON: Why don't you just wait
19 momentarily.

20 I think we're good to go.

21 DR. CAMPBELL: You've got it.

22 Hexavalent chromium compounds contain the
23 metallic element chromium in its plus 6 valence state.
24 Chromium has six oxidation states with the hexavalent
25 state being one of the most stable forms in the

1 environment.

2 Chromium is used in the manufacture of stainless
3 steel and other alloys, as well as in making pigments and
4 in leather tanning and welding. The general public can be
5 exposed to Cr(VI) in ambient area through manufacturing
6 emissions and from cigarette smoke or orally through
7 contaminated drinking water.

8 Chromium and chromium compounds are absorbed
9 after oral, dermal or inhalation exposure. Most studies
10 of absorption of Cr(III) or Cr(VI), after oral
11 administration to rodents, found that only one or two
12 percent of the administered dose is bioavailable.
13 Whereas, similar studies with humans report somewhat
14 higher numbers, particularly for Cr(VI).

15 Human and animal studies show that chromium is
16 widely distributed in the body after oral intra-tracheal,
17 I.V. or I.P. administration of Cr(VI). When given by the
18 oral route, chromium levels were particularly elevated in
19 the liver, kidney and spleen, but were only modestly
20 elevated in red blood cells. In pregnant experimental
21 animals, Cr(VI) given in drinking water has been shown to
22 cross the placenta and reach fetal tissues.

23 --o0o--

24 DR. CAMPBELL: Oral exposure of humans to Cr(VI)
25 have occurred through contamination of well water or other

1 There were some reductions in gestational
2 maternal weight again observed in the rat study, as well
3 as in the mouse studies at concentrations of 500 ppm and
4 above. In all cases, this appeared to be explainable on
5 the basis of decreased litter weights. No maternal deaths
6 or clinical or behavioral signs were reported in any of
7 these studies.

8 In addition to gestational studies, relevant
9 adverse developmental effects may result from exposure of
10 either parent prior to conception. In the pre-gestational
11 exposure studies that are described on this slide, the
12 treatment period for the females ranged from 20 days to
13 three months prior to mating. The treatment ended prior
14 to mating, such that the males were never exposed. In one
15 of these studies, the dams', mothers, were actually the
16 exposed group. And they were exposed to Cr(VI) during
17 gestation and lactation. And then at post-natal day 60,
18 the female offspring were mated with unexposed males. All
19 of these studies used potassium dichromate in drinking
20 water.

21 Observed fetal effects were similar to those
22 found with gestation exposures, including decreased
23 viability, effects on growth and increased frequencies of
24 external and skeletal anomalies. Effective Cr(VI)
25 concentrations range from 250 to 5,000 ppm with most

1 complications during pregnancy and child birth at much
2 higher rates than unexposed women. Due to limited
3 reporting, no conclusions can be drawn as to the role of
4 chromium in causing these effects.

5 --o0o--

6 MS. DUNN: A number of publications are available
7 that consider the potential for male reproductive effects
8 from chromium exposure. Sixteen studies were identified,
9 all of which focus on men occupationally exposed to
10 chromium, primarily due to the welding of stainless steel.
11 Nine studies examined semen quality and seven others
12 looked at fecundability, infertility or male-mediated
13 spontaneous abortion.

14 --o0o--

15 MS. DUNN: In steel welding fumes, much of the
16 chromium occurs as water soluble hexavalent chromium with
17 exposures varying by the method of welding and the
18 material being welded. Chromium levels are higher in the
19 breathing zone for those welding stainless steel as
20 compared to mild steel. Measurement of chromium in
21 workplace ambient area or in urine or blood of workers
22 provide a basis for evaluating an assumption that
23 differences in chromium exposure exist between the groups
24 being compared. Some, but not all, of the studies I'll
25 describe were able to establish such differences.

1 Kumar et al. observed a significant positive
2 correlation between abnormal sperm morphology and blood
3 chromium levels. These studies all had high exposure
4 levels as well as substantial limitations in terms of
5 their design or reporting, with the Danadevi et al. study
6 having the most robust design of these three.

7 --o0o--

8 MS. DUNN: The seven studies that address
9 chromium exposure in relation to fecundability,
10 infertility and male-mediated spontaneous abortion were
11 all conducted in Denmark by Bonde and Hjollund and other
12 collaborators working with them.

13 Three of these studies examined effects in a
14 population of males identified through the Danish Pension
15 Fund, who had been employed for at least one year in
16 companies manufacturing steel. The comparison was of
17 at-risk years with years not at risk in the same
18 individuals.

19 In the first study, the investigators found that
20 the probability of a man's spouse having a child was
21 decreased when the man was welding. This was
22 significantly decreased for any welding, but when limited
23 to those who ever welded stainless steel, the value did
24 not reach statistical significance.

25 The authors of the 1992 study examined

1 than one hour per day.

2 --o0o--

3 MS. DUNN: Finally, results of two studies of
4 couples followed in a prospective cohort design provide
5 fairly compelling evidence of male reproductive effects of
6 stainless steel welding. Couples were recruited by mail
7 sent via metal workers unions and other trade unions.
8 These couples included only those without previous
9 reproductive experiences who intended to attempt to become
10 pregnant. Couples were followed for up to six menstrual
11 cycles or until a pregnancy was clinically recognized.

12 Subclinical spontaneous abortions were detected
13 in an analysis of urine samples via measurements of human
14 chorionic gonadotropin or HCG. The 1998 report provided
15 information on fecundability in these couples, that is the
16 probability of conceiving in a given menstrual cycle. An
17 adverse effect on this measure is seen when the
18 probability of conceiving is decreased. For those
19 currently working as welders of stainless steel, the
20 probability was decreased, an odds ratio of .82.
21 Although, the decrease was not statistically significant.

22 However, when the length of time the man had
23 worked in stainless steel welding was considered,
24 probability of becoming pregnant was significantly
25 decreased, an odds ratio of .39 with a confidence interval

1 that excludes 1.0 for those with six or more years of
2 exposure.

3 --o0o--

4 MS. DUNN: The 2000 report describes the findings
5 for male-mediated spontaneous abortion. The risk for
6 spontaneous abortion with paternal stainless steel welding
7 exposure was significantly increased, a relative risk of
8 2.6. These results include adjustment for potential
9 confounding factors, such as female age, and body mass
10 index, menstrual cycle length, male and female smoking,
11 caffeine and alcohol consumption as well as other factors.

12 Risk of pregnancy loss increased as years of
13 stainless steel welding increased. All of the spontaneous
14 abortions in spouses of stainless steel welding took place
15 before the 10th gestational week. The authors of this
16 study, having conducted studies for more than 15 years on
17 male reproductive effects of welding exposure, stated that
18 their findings indicate quote, "An increased risk of early
19 spontaneous abortion for women whose partners are engaged
20 in stainless steel welding."

21 This concludes my presentation.

22 --o0o--

23 DR. CAMPBELL: And just to do a quick summary of
24 both the human and animal data. The evidence on
25 developmental toxicity of hexavalent chromium includes few

1 and limited human epidemiological studies, which have not
2 provided evidence for significant effects. The animal
3 evidence for developmental toxicity consists of multiple
4 studies demonstrating decreased embryo-fetal viability,
5 impaired growth and increased frequencies of external and
6 skeletal anomalies. Effects were similar whether Cr(VI)
7 exposure occurred during gestation or if exposure of
8 females ended before the mating period.

9 Evidence on the female reproductive toxicity of
10 hexavalent chromium includes some evidence from human
11 studies of occupational exposures for increased
12 complications during pregnancy and child birth. Effects
13 observed in animal studies included length in estrous
14 cycles, decreased mating infertility indices, decreased
15 numbers of corpora lutea, implantation sites and live
16 fetuses per litter and increased frequencies of pre- and
17 post-implantation loss. Also, ovarian changes at the
18 ultra-structural level.

19 Evidence on the male reproductive toxicity of
20 hexavalent chromium includes studies of occupationally
21 exposed men, primarily welders, which provided evidence
22 for an association between Cr(VI) and decreased sperm
23 counts and motility, decreased probability of a spouse
24 becoming pregnant and increased risks of male-mediated
25 spontaneous abortion.

1 Studies in multiple animal species, which
2 identified adverse effects, including testicular
3 histopathology, altered sperm parameters, altered
4 testicular biochemistry, altered sexual and aggressive
5 behavior, altered weights of testes and accessory male
6 reproductive organs, decreases in testicular protein, DNA
7 and RNA contents, and decreased serum and/or testicular
8 testosterone levels.

9 And that concludes our presentation.

10 CHAIRPERSON BURK: Thank you.

11 And are there any questions from the Committee of
12 Dr. Campbell or Ms. Dunn?

13 COMMITTEE MEMBER JONES: Yeah, I just have one
14 question. I didn't read these two uninterpretable studies
15 in Russian, I will admit. But is it those studies that
16 you base the fact that there are possible effects with
17 high exposure in the human -- in female reproductive
18 toxicity?

19 MS. DUNN: Yes. Those are the only studies that
20 are available on human female reproduction.

21 COMMITTEE MEMBER JONES: Yeah. I'm surprised
22 that you say possible effects with high exposure as far as
23 female reproductive toxicity is concerned, based upon
24 those 2 uninterpretable studies. That's the only point I
25 would make.

1 MS. DUNN: Yeah. I think the intention was just
2 to mention that there were some effects seen and we don't
3 really have good information about the study.

4 COMMITTEE MEMBER JONES: Okay.

5 CHAIRPERSON BURK: Please.

6 COMMITTEE MEMBER HOBEL: There appears to be a
7 gender difference in effect in terms of reproductive
8 toxicity in humans. And in the animal model, did there
9 seem to be a gender difference with a greater effect on
10 the male reproductive system?

11 MS. DUNN: Sir, I think, in fact, there aren't
12 really good studies of exposed females that the -- all the
13 studies that really provide good data are on males who are
14 welders. So we don't really have anything comparable to
15 be able to exclude the possibility that women would be
16 similarly or somehow adversely affected.

17 COMMITTEE MEMBER HOBEL: So it's the exposure
18 effects then?

19 MS. DUNN: I'm sorry, I didn't hear you.

20 COMMITTEE MEMBER HOBEL: Well, it's just -- there
21 are no -- I guess, women don't do welding, so I guess only
22 men do welding, so it's exposure difference.

23 MS. DUNN: There could be -- you know, there
24 could be some women, but we haven't seen them in studies.

25 DR. CAMPBELL: You know, with respect to the

1 animal data, I mean, there's plenty of positive evidence
2 for both sexes. I mean, the specifics are different,
3 because the endpoints are different.

4 COMMITTEE MEMBER KEEN: Perhaps it's worth
5 noting, at least when I tried to look at the
6 concentrations, both male and female in the experimental
7 animal model seemed to show similar types threshold
8 levels.

9 DR. CAMPBELL: Similar -- oh, yeah yeah. Those
10 ranges are similar.

11 COMMITTEE MEMBER KEEN: In terms of where you see
12 effects are really quite similar. And I have to concur, I
13 went through the human literature very carefully. And the
14 lack of any evidence in the female population because the
15 females haven't been studied who are welders shouldn't be
16 taken as lack of sensitivity. There are a lot of female
17 welders. It clearly is a question that could be answered
18 if one chose to.

19 CHAIRPERSON BURK: I don't see that we have any
20 public comments, is that correct?

21 All right. Then I guess we'll just begin our
22 discussion. I think we already have. But I have asked
23 Dr. Carl Keen and Dr. Ken Jones to take the lead on the
24 discussion of hexavalent chromium. So I'll turn it over
25 to them.

1 COMMITTEE MEMBER KEEN: Well, I'd be happy to say
2 any contrarian suggestions, but as I read the experimental
3 animal literature, it's relatively straightforward. And
4 refreshingly for a change, it's uncomplicated, in the
5 sense that signs of maternal toxicity do not seem to be a
6 principal driver of some of the reproductive toxicity,
7 which is often times the case when some of these agents
8 are looked at such high concentrations.

9 So I paid particular attention when I went
10 through the literature as to what one observes with, say,
11 50 to 100 parts per million exposure. And there is a
12 remarkable consistency across the literature that there is
13 not effects to speak of on maternal food intake or weight
14 gain independent the obvious lower weights sometimes that
15 are observed if you have lower concepti burden.

16 So unless other members of the Committee read the
17 data differently, it seemed to be relatively
18 straightforward, both on males and females.

19 COMMITTEE MEMBER JONES: I totally agree with
20 Carl, as far as his concern. And furthermore, I was
21 struck by the consistency in the effects from one species
22 to the next, as far as all these different studies were
23 concerned. So I don't think there's much question either.

24 CHAIRPERSON BURK: Are there any other comments
25 from any other Committee members on any of the endpoints?

1 Okay. We will be taking a vote on each of the
2 endpoints. And I will read it exactly as it is written.
3 Although -- no, I won't read it exactly as it is written,
4 because I'll tell you, it's written for cancer.

5 (Laughter.)

6 CHAIRPERSON BURK: But I'll read it the way I
7 think it's supposed to be written.

8 Did I get the wrong one? I don't think they
9 were -- actually, I believe it's actually already on the
10 Prop 65 list as a carcinogen.

11 So, has hexavalent chromium been clearly shown,
12 through scientifically valid testing, according to
13 generally accepted principles, to cause developmental
14 toxicity? All those voting yes, please raise your hand?

15 CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, if we
16 could just be really clear on the designation, it should
17 be chromium in paren, hexavalent compounds.

18 CHAIRPERSON BURK: Say that again, I'll write it
19 down.

20 CHIEF COUNSEL MONAHAN-CUMMINGS: Chromium and
21 then a paren hexavalent compounds closed paren.

22 CHAIRPERSON BURK: Okay. I'll read it again.
23 Has chromium (hexavalent compounds) been clearly shown,
24 through scientifically valid testing, according to
25 generally accepted principles, to cause developmental

1 toxicity?

2 All those voting yes, please raise your hand.

3 (Hands raised.)

4 CHAIRPERSON BURK: Seven. And Linda is recusing
5 herself; is that correct?

6 COMMITTEE MEMBER ROBERTS: (Committee Member
7 Roberts nods her head.)

8 CHAIRPERSON BURK: Okay. So I have 7 yes, and 1
9 recusal for developmental.

10 Again, has chromium (hexavalent compounds) been
11 clearly shown, through scientifically valid testing,
12 according to generally accepted principles, to cause
13 female reproductive toxicity?

14 All those voting yes please raise your hand?

15 (Hands raised.)

16 CHAIRPERSON BURK: Okay. I see 6.

17 All those voting no?

18 (Hand raised.)

19 CHAIRPERSON BURK: One. And again one not
20 voting.

21 And finally, has chromium (hexavalent compounds)
22 been clearly shown, through scientifically valid testing,
23 according to generally accepted principles, to cause male
24 reproductive toxicity?

25 All those voting yes, please raise your hand?

1 (Hands raised.)

2 CHAIRPERSON BURK: Okay, 7, and 1 recusal.

3 Okay. The result then -- it takes 5 yes votes
4 are required to add a chemical to the Prop 65 list. So
5 therefore, chromium (hexavalent compounds) will be added
6 to the list.

7 Moving right along then. Next on the agenda will
8 be a discussion and a consideration for listing of
9 chlorpyrifos. And the staff presentation will be by Drs.
10 Poorni Iyer and Farla Kaufman.

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

13 DR. ALEXEEFF: Dr. Burk, I have a comment. This
14 is George Alexeeff of OEHHA. This presentation will be a
15 little bit long. And we apologize for the length, but it
16 is kind of a complicated analysis for both the animal and
17 the human data. So the staff felt it was important and we
18 felt it was important to give you enough groundwork. And
19 we know that in the public comments will also be talking
20 about very specific details. So we felt this was going to
21 be kind of a full discussion of this issue.

22 CHAIRPERSON BURK: I totally support that. And I
23 hope I'm speaking on behalf of the Committee that take as
24 much time as you need.

25 (Laughter.)

1 DR. IYER: Okay. On that note, my name is Poorni
2 Iyer and I'm going to be presenting the -- we are going to
3 be presenting the evidence for developmental and
4 reproductive toxicity. And initially, we're going to be
5 presenting the background and the animal data. And then
6 my colleague, Dr. Farla Kaufman, will be presenting the
7 human data.

8 --o0o--

9 DR. IYER: Chlorpyrifos is an effective broad
10 spectrum organophosphate insecticide. And it is used as
11 an insecticide on grain, cotton, field, fruit nut and
12 vegetable crops, as well as on lawns and ornamental
13 plants.

14 The general population can be exposed to
15 chlorpyrifos via the oral route in food and water, that is
16 from runoff or leaching, as well as from exposure via the
17 inhalation and/or dermal routes, through volatilization
18 and spray drift for those people living in close proximity
19 to fields treated with chlorpyrifos. Workers who apply or
20 handle chlorpyrifos could also be exposed via the
21 inhalation and dermal routes.

22 In 2000, nearly all the residential uses were
23 voluntarily cancelled by Dow AgroSciences, but the
24 agricultural use remains.

25 --o0o--

1 DR. IYER: Reviewing the pharmacokinetics for
2 this chemical.

3 Absorption of chlorpyrifos varies with species -
4 in humans about 70 percent is absorbed after oral
5 exposure. From data in the rat, it is rapidly absorbed
6 and transported to the brain with oral dosing.
7 Chlorpyrifos is rapidly metabolized and highest tissue
8 concentrations were found in the liver and kidney, but the
9 chemical does not bioconcentrate.

10 Fetal brain metabolite concentration was found to
11 be twice as high as maternal brain concentration. And the
12 mean half-life of chlorpyrifos in humans was about 27
13 hours.

14 Excretion was in the urine and no parent compound
15 was detected. Metabolites were detected in urine. And
16 we'll be moving onto the metabolism in the next slide.

17 --o0o--

18 DR. IYER: Chlorpyrifos is bioactivated to the
19 chlorpyrifos oxon via cytochrome P450 mediated
20 desulfuration. Chlorpyrifos oxon is subsequently
21 hydrolyzed by A-esterase to diethyl phosphate and
22 3,5,6-trichloro-2-pyridinol (TCP) also referred to
23 sometimes in the literature as TCPY, which is also the
24 major biological metabolite and environmental breakdown
25 product of chlorpyrifos.

1 centers followed by coma and death.

2 In animals, significant inhibition of plasma an
3 RBC cholinesterase occur at doses below that which cause
4 the inhibition of brain cholinesterase.

5 Next slide.

6 --o0o--

7 DR. IYER: In a recent review, results of
8 numerous mutagenicity short-term assays and genotoxicity
9 were looked at. And chlorpyrifos was found to be not
10 mutagenic in bacteria or mammalian cells, but did cause
11 slight genetic alterations in yeast and DNA damage to
12 bacteria.

13 Also, chlorpyrifos did not induce chromosomal
14 aberrations in vitro, was not clastogenic in the mouse
15 micronucleus test in vivo, and failed to induce
16 unscheduled DNA synthesis in isolated rats hepatocytes.

17 DNA damage in lymphocytes of mice exposed to
18 chlorpyrifos was demonstrated using the comet assay.
19 Given that the comet assay is a sensitive assay for DNA
20 damage, typically additional positive responses in in vivo
21 systems are required to be predictive for carcinogenicity
22 in mammalian systems.

23 Next slide.

24 --o0o--

25 DR. IYER: Examining what has thought to be its

1 primary mode of action, this inhibition of
2 acetylcholinesterase results in accumulation of endogenous
3 acetylcholine in nervous tissue and effector organs,
4 muscarinic, nicotinic and CNS receptors are stimulated,
5 with characteristic signs and symptoms occurring
6 throughout the peripheral and central nervous systems as
7 have been described earlier.

8 The sensitivity varies across species with the
9 dog being most sensitive, followed by the rat and then the
10 mouse.

11 In most humans and dogs, plasma cholinesterase is
12 predominantly the butyrylcholinesterase, which is more
13 sensitive to inhibition than acetylcholinesterase. While
14 in rats, plasma cholinesterase consists of approximately a
15 60 to 40 ratio of acetylcholinesterase to
16 butyrylcholinesterase. So it is likely that the human
17 sensitivity for cholinesterase inhibition, relative to
18 rats, is due to species differences between rats and
19 humans in the constituents of plasma cholinesterase.

20 Given this predominant mode of action of
21 organophosphates, as you will see later on, studies
22 examining the effects of chlorpyrifos on
23 acetylcholinesterase have been used in determining the
24 relationship between cholinesterase inhibition and
25 developmental toxicity.

1 Next slide.

2 --o0o--

3 DR. IYER: Moving onto the relevant metabolic
4 changes during pregnancy. We note that female rats,
5 particularly pregnant rats, appear to be more sensitive
6 than adult male rats to cholinesterase inhibition. There
7 is a consistent pattern for several key detoxification
8 enzymes that metabolic activity may decrease during
9 pregnancy. While the reductions are not large in
10 magnitude and the importance of these decreases is unknown
11 at environmental exposures, studies suggest the potential
12 for a reduced capacity to detoxify during pregnancy.

13 Toxicity studies in rats add further support that
14 reduced ability to detoxify chlorpyrifos and/or the oxon
15 effects sensitivity during pregnancy. As mentioned
16 earlier, pregnant female rats had lower plasma, brain and
17 liver carboxylesterase activity than non-pregnant animals.

18 Another key detoxification enzyme discussed
19 previously is PON1. And PON1 activity is reduced during
20 late gestation to about 76 percent in women.

21 Next slide.

22 --o0o--

23 DR. IYER: With this background, we move onto the
24 animal data.

25 Several studies evaluating the effects of

1 development or neonatal growth, survival or
2 histopathology. But the viability index was decreased at
3 the high dose level of 1 mg/kg/day, though it was not
4 statistically significant.

5 --o0o--

6 DR. IYER: Now, actually looking at the results
7 from these two studies in the next slide.

8 For the developmental toxicity study, reduced
9 cholinesterase levels at 3 mg/kg, that is the mid dose,
10 and cholinergic signs, such as excessive salivation and
11 tremors were noted. Decreased cholinesterase levels and
12 decreased body weight gain was noted at the high dose of
13 15 mg/kg/day. And no maternal effects were apparent at .1
14 mg/kg/day, which is the low dose. And for the standard
15 parameters, such as offspring viability and malformations,
16 chlorpyrifos appears not to have an effect at these dose
17 levels.

18 For the two-generation reproduction study, there
19 was significant inhibition of brain cholinesterase of dams
20 at 5 milligrams per kilogram per day. And pup body
21 weight, there was a decrease in pup body weight and
22 increased pup mortality observed only in the F1 litters.

23 The neonatal effects observed in F1 generation
24 was not noted in the F2 generation. And no effects on
25 histopathology of reproductive tissues were noted at any

1 dose level.

2 Next slide.

3 --o0o--

4 DR. IYER: The effects of gestational exposure on
5 neurodevelopment and behavior was undertaken in this
6 developmental neurotoxicity study submitted as Hoberman
7 1998 to regulatory agencies and then it was subsequently
8 published as Maurrissen et al. 2000.

9 In this study, chlorpyrifos in corn oil was
10 administered orally via gavage to Sprague-Dawley, presumed
11 pregnant, rats on gestation day six through postnatal day
12 11 at 0, 0.3, 1, and 5 milligrams per kilogram per day.
13 The protocol is described in detail in the hazard
14 identification materials. An exposure during postnatal
15 day one through 10 in the rat pup would be equivalent to a
16 continuous in utero last trimester exposure in humans.

17 Now, here pups from the high-dose group showed
18 increased mortality soon after birth, gained weight more
19 slowly than controls and had several indications of
20 slightly delayed maturation. No overt effects were noted
21 by the authors in either dams or pups at 1 or .3
22 mg/kg/day. In spite of the apparent delay in physical
23 development, learning and memory as tested on the T-maze
24 spatial alternation tasks, motor activity and auditory
25 startle were not affected in the high-dose animals in the

1 as can be observed in the findings on the next slide.

2 --o0o--

3 DR. IYER: The decrements at postnatal day 66 was
4 slightly higher at 5 mg/kg/day than at 1 milligram per
5 kilogram per day. And the changes were consistent with
6 the postnatal day 12 sacrifice results. And accordingly,
7 a careful review by U.S. EPA concluded that, "Adverse
8 findings in the adult postnatal day 66 offspring, that is
9 the alterations in motor activity, auditory startle
10 response and brain structure, that is the decreased
11 measurements of the parietal cortex and hippocampal gyrus
12 in the absence of significant brain weight deficits,
13 observed at postnatal day 66, in the offspring, long after
14 exposure via the dam can be interpreted to represent
15 long-term sequelae of developmental exposure."

16 --o0o--

17 DR. IYER: For the developmental neurotoxicity
18 study therefore, across all studies, the lowest dose
19 tested was .3 mg/kg/day. No behavioral effects were
20 observed in the offspring at this dose level. Brain
21 morphometric changes were seen at one milligram per
22 kilogram per day, but they were not available for
23 examination at the .3 mg/kg/day.

24 Next slide.

25 --o0o--

1 DR. IYER: From these and other subsequent
2 studies, that is after 2002, in the literature, at the
3 Slotkin/Levin and Calamandrei laboratories that have been
4 described in detail in the hazard identification
5 materials, it appears that adults have persistent
6 behavioral effects following gestational and/or early
7 postnatal exposure in both rats and mice. Some of these
8 studies focused on exposure to chlorpyrifos during
9 specific periods of gestation, targeting specific windows
10 of development and late developmental effects, such as
11 gliogenesis, axonogenesis and synaptogenesis.

12 Findings from these studies suggest a wide window
13 of vulnerability of the cholinergic systems to
14 chlorpyrifos, that the effects of chlorpyrifos on fetal
15 brain development are fundamentally different for exposure
16 in early, compared with late gestation, and prenatal
17 chlorpyrifos exposure elicits marked alterations that
18 emerge in the postnatal period, specifically behavioral
19 abnormalities were observed when pups were tested in
20 adolescence and adulthood.

21 These studies used slightly different protocols,
22 such as the route of exposure and a vehicle, leading us to
23 consider other relevant issues.

24 Next slide.

25 --o0o--

1 DR. IYER: And these issues will be presented in
2 the following slides. And they include use of DMSO as a
3 vehicle for chlorpyrifos administration in animal studies;
4 the differences between developing animals and adults;
5 distribution and metabolism in pregnant females and
6 conceptuses and other possible mechanisms of developmental
7 toxicity.

8 Next slide.

9 --o0o--

10 DR. IYER: Concern for the use of DMSO as a
11 vehicle in studies has been raised due to the possibility
12 of either DMSO's effects on development or its role in
13 interaction with other chemicals. However, there was
14 concordance observed between studies that used DMSO at a
15 vehicle and those that did not for the parameter of
16 cholinesterase inhibition. And also from the recent work
17 of Marty et al. Cmax, area under the curve, and the
18 half-life values for subcutaneous administration in DMSO
19 was similar to bolus oral exposure in a milk vehicle. So
20 this underscores the effects of chlorpyrifos in pups
21 subsequent to maternal exposure.

22 Next slide.

23 --o0o--

24 DR. IYER: As with many organophosphate
25 pesticides, developing animals appear more susceptible to

1 reduced compared to the dams exposure. From the
2 developmental neurotoxicity study of Hoberman earlier on
3 and other modeling, it can be concluded -- it has been
4 concluded that at the high dose, a nursing pup's exposure
5 would be about .1 to .5 mg/kg/day of chlorpyrifos.

6 What was noted was that in spite of exposure via
7 milk, the cholinesterase levels of all tissues of the
8 high-dosage pups rapidly returned to near control levels
9 by postnatal day 5.

10 Since immature animals actually recover more
11 rapidly from cholinesterase inhibition than do adults,
12 measurements of cholinesterase activity alone may not be
13 sufficient for the assessment of adverse effects.
14 Besides, the precise time of measurement of cholinesterase
15 would also be critical and one would also have to take
16 into consideration the time for distribution of the
17 chemical into the milk and other pharmacokinetic
18 considerations.

19 Hence, chlorpyrifos-induced neurochemical and
20 neurobehavioral changes may or may not be related to the
21 cholinesterase inhibition as has been measured in the
22 studies to date. And so the vulnerable period for adverse
23 effects of chlorpyrifos is likely to extend into childhood
24 or adolescence.

25 Next slide.

1 --o0o--

2 DR. IYER: While inhibition of cholinesterase by
3 its active metabolite chlorpyrifos oxon was once
4 considered the lone mechanism for chlorpyrifos
5 neurotoxicity, recent studies have presented additional
6 possibilities. There is evidence that chlorpyrifos
7 directly targets events that are specific to the
8 developing brain and that are not necessarily related to
9 the inhibition of cholinesterase.

10 And these include:

11 Effects on the developing brain, such as cell
12 division; interference with RNA synthesis during
13 differentiation; interruption of cell signaling;
14 interference with important nuclear transcription factors
15 involved in cell differentiation; impairment of
16 cholinergic synaptic function during development; effects
17 on the catecholamine system in the developing brain;
18 oxidative stress in the developing brain; interference
19 with gliogenesis and axonogenesis. And all those could
20 happen in the absence of clinical signs and brain
21 cholinesterase inhibition.

22 Also, neither the magnitude nor the timing of the
23 changes observed in these studies was predictive of the
24 cholinergic defects, rather it appears that the cellular
25 effects may actually result from defective synaptic

1 transmission.

2 Next slide.

3 --o0o--

4 DR. IYER: According to the authors, taking a
5 number of studies, the findings show that the hippocampus
6 appears to be adversely affected by chlorpyrifos,
7 regardless of whether the exposure occurs in early or late
8 brain development, and defects emerged in adolescence or
9 adulthood even in situations where normative values were
10 initially restored in the immediate post-exposure period.
11 This is probably because the alterations may be late
12 emerging and not a result of an initial deficit that
13 continues into later life.

14 Also, based on the disparate mechanisms by which
15 chlorpyrifos perturbs neuronal and glial cell development,
16 there is extraordinarily broad critical period for adverse
17 effects on brain development with a shifting target set of
18 consequences dependent upon the period of exposure.

19 Next slide.

20 --o0o--

21 DR. IYER: Since the behavioral effects noted in
22 the studies were seen long after immediate cholinergic
23 responses, even transient cholinesterase inhibition may
24 alter the complicated progression of development in the
25 nervous system, which could result in long-term changes,

1 even after the inhibition has recovered.

2 Accordingly, prenatal chlorpyrifos appears to
3 elicit delayed onset alterations, disrupting the program
4 for emergence of cholinergic activity. The functional
5 significance on the later-occurring neurochemical
6 anomalies is also corroborated by behavioral deficits in
7 cholinergic contributions to working and reference memory
8 that emerge in adolescence and adulthood after fetal
9 chlorpyrifos exposure, and the same pattern is elicited by
10 prenatal exposure to nicotine. Researchers therefore
11 speculate that these long-term alterations reflect
12 disruption consequent to elevated cholinergic activity
13 during a critical period in fetal development.

14 What is really unknown is whether protection
15 against cholinesterase inhibition, even transiently at any
16 time during development, is adequate to protect the
17 developing organism. And thus relying on cholinesterase
18 inhibition may not be the appropriate upstream marker or
19 event for protecting the fetus or developing individual.

20 In other words, cholinesterase inhibition may not
21 be the upstream marker of choice for regulating exposure
22 of a developing individual to chlorpyrifos.

23 And in the subsequent material that was presented
24 to the Committee, at the Scientific Advisory Panel meeting
25 in September this year, at the U.S. EPA -- the scientists

1 at the U.S. EPA have accordingly stated that, "Although
2 these studies raise many questions, and each took a
3 different approach with regard to dosing and behavioral
4 assessments with different behavioral techniques, when
5 taken together, they provide a basis for concern for
6 susceptibility of persistent effects of chlorpyrifos on
7 neurodevelopment."

8 Moving onto the next endpoint here.

9 --o0o--

10 DR. IYER: According to generally accepted
11 principles, changes in offspring growth or milk quantity
12 and quality may constitute a female-specific endpoint or
13 reproductive toxicity. Hence, the presence of
14 chlorpyrifos in the milk may be considered as affecting
15 lactation, an essential component of female reproduction.

16 On the whole, the animal data both from studies
17 conducted for regulatory purposes per FIFRA guidelines, as
18 well as those from peer-reviewed literature, demonstrate
19 lactational exposure and the effects observed from the
20 presence of chlorpyrifos in the milk.

21 Reproductive effects included reduced pup weights
22 and increased pup mortality in rats, but only at dose
23 levels that induced parental toxicity as evidenced by
24 inhibition of plasma, RBC and brain cholinesterase
25 activities.

1 Next slide.

2 --o0o--

3 DR. IYER: Taking a look at the effects on the
4 male reproductive system. No effects on the
5 histopathology of reproductive tissues were observed at
6 dose levels below the levels that resulted in significant
7 cholinesterase inhibition. And severe testicular damage
8 resulting in reduction in sperm count and fertility were
9 noted in another study, but they were at much higher dose
10 levels, and they seem appropriate for the dose levels
11 exposed.

12 Typically, studies in laboratory animals focus on
13 fertility or sperm abnormalities and do not examine DNA
14 damage per se. The findings of DNA damage noted in few of
15 the studies conducted for evaluating genotoxicity may
16 support the findings in the human studies; however,
17 similar endpoints were not examined in the animal studies.

18 And now I'm going to turn it over to Farla
19 Kaufman who's going to present the human data.

20 --o0o--

21 DR. KAUFMAN: Most of the human developmental
22 studies come from three large prospective cohorts, the
23 Columbia Center For Children's Environmental Health, the
24 Mount Sinai Children's Environmental Health Study, both of
25 which were conducted in New York City, and the CHAMACOS

1 Study, which is an acronym for the Center for the Health
2 Assessment of Mother And Children Of Salinas set in the
3 agricultural area of the Salinas Valley here in
4 California.

5 In addition, there is a cohort study conducted in
6 Sri Lanka, a case control study of neural tube defects,
7 case reports, as well as a related study of brain tumors.

8 --o0o--

9 DR. KAUFMAN: The Columbia prospective cohort
10 included African American and Dominican women residing in
11 specific areas of New York City, definitely considered
12 inner city. Pregnant women were enrolled by the 20th week
13 of gestation. There was a total of 314 mother newborn
14 pairs.

15 Measures of exposure included maternal and
16 umbilical cord blood, chlorpyrifos, as well as maternal
17 personal air levels monitored during the third trimester.
18 Multiple birth outcomes were examined, as well as
19 neurodevelopmental outcomes.

20 And a unique feature of this cohort was that it
21 spans a time over which chlorpyrifos was cancelled for
22 residential use and analyses were conducted which examined
23 pre- and post-differences.

24 --o0o--

25 DR. KAUFMAN: So in this cohort, we see -- I'm

1 DR. KAUFMAN: Results from Whyatt et al. from
2 this cohort showed significant decreases in birth weight
3 and length associated with chlorpyrifos levels. In
4 infants born before the cancellation, birth weight among
5 those with the highest chlorpyrifos exposures averaged 215
6 grams less than those with the lowest combined cord plasma
7 chlorpyrifos and diazinon exposures. This is a
8 statistically significant finding with the confidence
9 intervals not encompassing 1 and a P value of .01.

10 When examining chlorpyrifos alone, that is for
11 each log unit increase in chlorpyrifos -- over here -- in
12 infants born before January 1st, 2001, that's before the
13 cancellation, there was a 67 gram decrease in birth weight
14 or an average deficit of 210 grams, which was highly
15 statistically significant.

16 In infants born after the date of the
17 cancellation, January of '01, there was no significant
18 association between chlorpyrifos and birth weight. Only
19 one infant fell into the highest exposure group here.

20 Similar findings were seen for birth length,
21 where there's a statistically significant decrease before
22 January of '01, but no significant association after
23 January of '01.

24 --o0o--

25 DR. KAUFMAN: These are updated analyses prepared

1 by Whyatt at the request of the U.S. EPA. There is a
2 large sample size in the group born after the
3 cancellation, so we can see the updated analysis. The
4 before ban is pretty similar, but the end in this group is
5 now 193 versus 77 from the previous analyses or the
6 previous slide. The findings are similar to the previous
7 slide, where there was a significant decrease in birth
8 weight in the infants born before the cancellation, but no
9 effect in infants born after.

10 All these analyses controlled for a number of
11 covariates including active and passive smoking,
12 ethnicity, parity, maternal pre-pregnancy weight and net
13 weight gain during pregnancy, gender and gestational age
14 of the newborn as well as season of delivery.

15 --o0o--

16 DR. KAUFMAN: Additional analyses were also
17 prepared where imputed cord blood values were omitted and
18 additional potential confounders were evaluated. Imputed
19 cord blood was originally used where there were missing
20 cord blood levels and values were imputed for maternal
21 blood samples since the two had been so highly correlated.
22 When the imputed cord blood levels were omitted, the
23 values for chlorpyrifos on birth weight and length
24 remained statistically significant with a slightly smaller
25 beta coefficient of 64.5 compared with the 67.3 that we

1 were more highly exposed to chlorpyrifos basically had a
2 two and a half times greater odds of being born small for
3 gestational age. Again, these analyses were adjusted, in
4 this case, for maternal short stature, maternal low body
5 mass index, net weight gain in pregnancy, race/ethnicity
6 and exposure to secondhand smoke.

7 --o0o--

8 DR. KAUFMAN: Rauh et al. in their publication
9 examined neurodevelopmental outcomes in this cohort. And
10 they used the following standardized tests:

11 The Bayley Scales of Infant Development II, to
12 assess mental or cognitive and psychomotor development at
13 12, 24 and 36 months of age;

14 The Childhood Behavioral Checklist measured
15 behavior problems;

16 And the Home Observation for Measurement of the
17 Environment tool to measure the quality of the caretaking
18 environment.

19 --o0o--

20 DR. KAUFMAN: This table presents the odds ratios
21 of the effect of high exposure to chlorpyrifos on
22 neurodevelopmental outcomes. High chlorpyrifos exposure
23 was defined as a blood concentration of greater than 6.17
24 picograms per gram based on the findings of Whyatt et al.,
25 which reported, at this level, a decrease in birth weight.

1 DR. KAUFMAN: Young et al., in a related study,
2 observed a positive association between higher diethyl
3 phosphate levels and the number of abnormal reflexes.
4 Similar associations were also seen with the total dialkyl
5 phosphates and dimethyl phosphate levels. These findings
6 are similar to those reported by Engel et al. in the Mount
7 Sinai Cohort between the diethyl phosphate levels and
8 abnormal reflexes.

9 --o0o--

10 DR. KAUFMAN: We move onto another cohort study
11 by Samarawickrema et al. conducted in Sri Lanka. Pregnant
12 women were exposed to pesticides during the spray season
13 in this study, as compared to women who were pregnant in
14 between spray seasons. Chlorpyrifos was detected in only
15 one maternal cord blood sample. However, this may not be
16 surprising as the limit of detection in the assays used
17 were very high.

18 Lower mean cord blood butyrylcholinesterase
19 activity was seen during the spray season compared with
20 the between spray season. And there was also evidence of
21 increased oxidative stress and DNA fragmentation in the
22 cord blood obtained during the spray season.

23 --o0o--

24 DR. KAUFMAN: This slide compares the three
25 prospective cohorts that we saw before. The studies that

1 use dialkyl phosphates, the nonspecific metabolites of
2 chlorpyrifos as the exposure measure are not included
3 here. The three cohorts differ in population, setting and
4 exposure measures.

5 As we can see, the ethnic differences between the
6 studies are on the left. Since there's a large
7 variability in polymorphisms of the PON1 enzyme by
8 ethnicity, there indeed may be large differences in the
9 susceptibility of exposure to chlorpyrifos in these
10 populations. PON1 status has been shown to vary up to
11 165-fold within a population of Mexican American women and
12 newborns.

13 The environmental settings also varied between
14 these studies. In the two inner-city environments,
15 pesticides were sprayed inside the home in New York City.
16 While in the agricultural setting of CHAMACOS very little
17 exposure came from home use of chlorpyrifos. Chlorpyrifos
18 may persist much longer indoors due to environmental
19 conditions, such as diminished filtered sunlight, reduced
20 moisture, reduced air movement and surface areas are also
21 variables, as well as the lack of soil microorganisms.

22 Therefore, the ratio of the concentration of
23 parent pesticide to the less biologically active
24 environmental degradants -- in this case such as TCPY --
25 is likely to be higher in the indoor settings than in the

1 outdoor settings. The results of Wyatt et al. in the
2 Columbia study showed that pesticides were persistent in
3 the home with very little variability in the air
4 concentrations over a two-month period.

5 The exposure measures used as seen in the center
6 of the column, here, include TCPY, which is easier to
7 measure as there is greater concentration of TCPY in urine
8 than there is chlorpyrifos in blood. However, the urine
9 levels of this metabolite do not differentiate between
10 exposure to chlorpyrifos, exposure to TCPY in the
11 environment or exposure to chlorpyrifos-methyl.

12 Thus, the exposure to TCPY directly from the
13 environment would result in exposure misclassification and
14 would decrease the ability to detect a true effect of
15 exposure if chlorpyrifos -- if one were present in
16 exposure to chlorpyrifos.

17 As you can see, the median TCPY levels were
18 higher in the Mount Sinai cohort than in the CHAMACOS
19 cohort. In actuality, since the limit of detection was
20 about five times higher in the Mount Sinai cohort, the
21 difference between the actual exposure may be even greater
22 between these two studies.

23 These exposure levels cannot be compared with the
24 Columbia cohort since Columbia measured the parent
25 compound chlorpyrifos in blood.

1 Blood chlorpyrifos is considered the best
2 biomarker of exposure with cord blood being in direct
3 conduct with the fetus. Since the levels of chlorpyrifos
4 in blood depends somewhat on the equilibrium between its
5 concentration in adipose tissue and blood, the blood
6 concentrations are best evaluated both with a
7 concentration basis and a lipid basis. The exposure
8 levels from the Columbia study included levels for only
9 the concentration basis.

10 The only study reporting PON1 data in relation to
11 birth outcomes was the Mount Sinai study, which found
12 decreases in head circumference. Only the Columbia study
13 examined the differences between pre- and
14 post-cancellation of chlorpyrifos use in residential
15 settings, which showed decreases in birth weight and
16 length and increases in small for gestational age, as well
17 as delays in mental and psychomotor development and
18 behavioral disorders, including attention deficit and
19 AD/HD and the pervasive developmental disorder.

20 No effects were seen in the CHAMACOS study in
21 relation to exposure to TCPY. As noted earlier in all
22 these studies, there was exposure to multiple pesticides,
23 some of them being other organophosphate pesticides
24 including diazinon, which diazinon, in fact, in the
25 Columbia study was actually controlled for in the

1 analysis. It's also noted, though, that there could be
2 early childhood exposure to lead, which may also be a
3 confounder that was not controlled for.

4 --o0o--

5 DR. KAUFMAN: So moving on out of developmental
6 and into female reproductive studies. These two female
7 reproductive studies in humans were identified on the
8 basis of examining the presence of chlorpyrifos in breast
9 milk. As mentioned earlier by Poorni, according to the
10 U.S. EPA, changes in offspring growth or milk quantity and
11 quality may constitute a female-specific endpoint or
12 reproductive toxicity.

13 So what we see in Wagner et al. in Germany, they
14 examined various samples and detected chlorpyrifos in 1
15 out of 11 human blood samples and 3 out of 11 cervical
16 fluid samples. Chlorpyrifos was not detected in
17 follicular fluid. In a study by Sanghi et al. Bhopal,
18 India, chlorpyrifos was detected in all of the 12 breast
19 milk samples. Estimated intake, as calculated from these
20 measured levels, was more than four times greater than
21 recommended intakes by the World Health Organization.

22 Other pesticides detected included endosulfan
23 malathion and methyl-parathion.

24 --o0o--

25 DR. KAUFMAN: On to male reproductive studies of

1 chlorpyrifos in humans.

2 We see six male reproductive studies, one
3 case-control and five cross-sectional studies by the same
4 group of researchers, Meeker et al., as well as two
5 related studies, one in vitro and one of an agricultural
6 study of multiple pesticide exposure.

7 --o0o--

8 DR. KAUFMAN: So when we look at the case control
9 study by Swan et al., subjects were chosen from men who
10 participated in a multi-centered study of semen quality in
11 fertile men. The men were chosen from Missouri and
12 Minnesota reflecting urban and rural areas. And cases
13 were defined as men having poor semen quality. Numerous
14 pesticides were examined. For TCPY, the odds ratio for
15 low semen quality in men from Missouri was 6.4
16 versus -- sorry -- versus 0.5 for men from Minnesota, but
17 neither were significant, as you can see with the
18 confidence interval encompassing 1.

19 --o0o--

20 DR. KAUFMAN: The five cross-sectional studies by
21 Meeker et al, included males from sub-fertile couples
22 attending an andrology clinic. The exposure measure was
23 TCPY in the urine. The study included 360, mostly
24 Caucasian men, with a mean age of 36 years. And men with
25 urine samples whose specific gravity values were outside a

1 range were excluded from the analysis.

2 --o0o--

3 DR. KAUFMAN: The results from these five studies
4 include the following:

5 Most of these associations are examining an
6 increase in interquartile range in TCPY. Using the comet
7 assay, there was statistically significant associations
8 between higher TCPY and two measures of DNA integrity,
9 thus suggesting DNA damage in human sperm. There were
10 suggestive associations with higher TCPY levels and
11 decreased sperm concentration, sperm motility and
12 straight-line velocity. No association was seen with
13 follicle-stimulating hormone, leuteinizing hormone,
14 inhibin B, or sex hormone binding globulin.

15 And there is a mistake on this slide. There was
16 an association with higher TCPY levels and lower free
17 androgen index. Higher TCPY levels were also associated
18 with lower T4 levels and higher thyroid stimulating
19 hormone, but no association was seen with T3. Estradiol
20 levels were also lower in men with higher TCPY levels.
21 And no change in prolactin was seen.

22 --o0o--

23 DR. KAUFMAN: There are two related studies. The
24 first one looked at the effects in vitro exposure to sperm
25 samples from healthy males with normal semen quality

1 this presentation, the animal data reported no
2 malformations or effects on viability or birth weight.
3 For neurodevelopment findings from studies with oral
4 exposures were indicative of effects on behavior and brain
5 morphometry. In the subcutaneous exposure, there were
6 cholinergic and cellular effects on the hippocampus and
7 cerebral cortex, as well as biochemical changes affecting
8 synaptic nerve terminals and synaptic activity.

9 From the human side of things, there were
10 decreases in birth weight and length, as well as decreased
11 head circumference in association with PON1 activity. In
12 the neurodevelopmental, delays were reported in the mental
13 and psychomotor indices, as well as increases in
14 behavioral disorders, including attention deficit disorder
15 and pervasive developmental disorder.

16 --o0o--

17 DR. KAUFMAN: From the female reproductive data,
18 we saw animal studies demonstrating the presence of
19 chlorpyrifos in milk. Also, reduced pup weight and an
20 increase in pup mortality was noted in the F1 rats at the
21 high dose in a two-generation study. And chlorpyrifos was
22 also detected in the breast milk in humans.

23 --o0o--

24 DR. KAUFMAN: And finally, the effects on male
25 reproductive system show that DNA damage was noted in

1 genotoxicity studies in the animal data. There were no
2 effects of the histopathology of reproductive tissue at
3 doses -- or at dose levels below the levels that resulted
4 in significant cholinesterase inhibition.

5 In the human studies, there were inverse
6 associations with a number of sperm parameters, as well as
7 the male reproductive hormones including testosterone and
8 free androgen index. Significant associations were also
9 seen with lower T4 levels and higher thyroid stimulating
10 hormone, but not with the total T3. Estradiol levels were
11 lower, but prolactin levels were not.

12 And that concludes our presentation.

13 CHAIRPERSON BURK: Thank you. Are there any
14 questions from the Committee for the presenters?

15 We are speechless at the moment.

16 But are there any public comments? I haven't
17 gotten -- let's take a look and we'll see how the timing
18 looks here. This is the order. So we have three. And
19 the first one is requesting 30 minutes. Oh, it's 30
20 minutes for all of them. I think we should go for it.

21 How are you doing?

22 THE REPORTER: I'm fine.

23 CHAIRPERSON BURK: So I think what we'll do is
24 we'll go with this and then we'll take a break after that.

25 So very good.

1 COMMITTEE MEMBER JONES: Dotty, can I ask one
2 question?

3 CHAIRPERSON BURK: Oh, absolutely.

4 COMMITTEE MEMBER JONES: In the studies in which
5 there was an inverse relationship between PON1 and the
6 exposure, was the exposure documented to be just
7 chlorpyrifos or was it all of the organophosphates?

8 In other words, was that a, so-called, related
9 study, the PON1 study or was --

10 DR. KAUFMAN: No, it wasn't --

11 COMMITTEE MEMBER JONES: -- it a specific study
12 related to --

13 DR. KAUFMAN: It was a specific study with TCPY.

14 COMMITTEE MEMBER JONES: It was?

15 DR. KAUFMAN: Um-hmm.

16 COMMITTEE MEMBER JONES: Okay.

17 COMMITTEE MEMBER KEEN: As we're getting some
18 things clarified, I just want to make it clear in my own
19 mind. As I look at the milk data, often times I've
20 interpreted the original EPA as if you see a change in
21 production -- and I see no data that the production is
22 affected -- or the composition, and often times that's
23 been interpreted as it's something other than the compound
24 you're studying, because otherwise virtually anything that
25 shows up in the milk, you'd say okay well, that's an

1 effect. So was there any compositional changes in the
2 milk by the exposed animals, exclusive with the compound
3 being studied?

4 DR. IYER: No. I think it's just the question
5 that they did detect it in the milk, because this was part
6 of the companion developmental neurotoxin.

7 COMMITTEE MEMBER KEEN: Yeah, I appreciate that.
8 But there's a distinct difference between saying the
9 composition of quality of the milk has changed versus
10 merely the compound being detected.

11 DR. DONALD: Right. If I could add to that, Dr.
12 Keen. It's perfectly correct in the way that that's
13 normally been interpreted. But also, we have to bear in
14 mind the specific constraints of Proposition 65 that --
15 the guidance that Dr. Keen is referring to encompasses
16 postnatal exposures to chemicals as contributing to
17 developmental toxicity. And there's really no reason to
18 distinguish whether an effect that results from the
19 presence of a chemical in milk as a developmental effect
20 or a female reproductive effect.

21 Since Proposition 65 is interpreted to exclude
22 postnatal exposures, in this case, we're at least putting
23 forward for the Committee's consideration that the
24 presence of chemical -- that interpreting the presence of
25 the chemical in the milk is not inconsistent with the

1 generally accepted guidance that changes in the
2 composition of the milk can be considered a female
3 reproductive effect.

4 COMMITTEE MEMBER KEEN: Yeah. I think, Dr.
5 Donald, you raise a good point there, but is there any
6 data that you're aware of, just for kind of tidying it up,
7 that cross-fostering studies would suggest that exposure
8 to the compound of the milk is associated with any
9 problems?

10 I looked for it and couldn't find any, but
11 perhaps you have.

12 DR. DONALD: In the case of this chemical, no.
13 No such data exists as far as we know.

14 COMMITTEE MEMBER KEEN: Thank you.

15 CHAIRPERSON BURK: Are there any other questions?

16 I'm sure we may have some later, but let's
17 continue. The first speaker is Christian Volz, McKenna,
18 Long and Aldridge. Maybe you should introduce yourself
19 and make sure.

20 MR. VOLZ: Before I start speaking on behalf of
21 Dow, we would offer to let other speakers who have just
22 recently submitted their intention to speak go ahead of
23 us, that would help us to know how much time we have. We
24 have a rather lengthy collective presentation to make.

25 CHAIRPERSON BURK: The only other request to

1 speak is requesting two minutes.

2 MR. VOLZ: Should we let her go first?

3 CHAIRPERSON BURK: No, I think you can go right
4 ahead since you're there.

5 (Thereupon an overhead presentation was
6 Presented as follows.)

7 MR. VOLZ: Do I have a clicker or do I say, "Next
8 Slide"?

9 MS. OSHITA: Next slide.

10 MR. VOLZ: Okay.

11 Well, good morning, Dr. Denton, Chairperson Burk,
12 fellow members of the Committee.

13 CHAIRPERSON BURK: Could you pull the mic closer?

14 MR. VOLZ: Is that better?

15 DIRECTOR DENTON: Why don't you try putting it up
16 on the podium and see if it's better.

17 MR. VOLZ: How's that?

18 DIRECTOR DENTON: Better.

19 MR. VOLZ: On behalf of Dow AgroSciences, thank
20 you for this opportunity to address the Committee on the
21 subject of the scientific evidence about the potential
22 developmental and reproductive toxic effects of
23 chlorpyrifos and for the opportunity to present our case
24 that the weight of evidence does not support listing.

25 --o0o--

1 you know, the standard isn't that the chemical might cause
2 reproductive toxicity or that there's some evidence. It
3 certainly isn't that there are uncertainties. Some of the
4 phrases that we heard earlier just without pretending to
5 be comprehensive or get them all, we heard a hint of
6 positive outcome. We heard speculation about possible
7 mechanisms, and about novel modes of action. We heard
8 that some studies may or may not show an effect. We heard
9 that other studies raise concerns or raise questions. And
10 finally, we heard that some create suggestive
11 associations.

12 Well, those are all perhaps legitimate
13 observations, but none of them individually or
14 collectively add up to a clearly shown standard. So we
15 ask you to please keep that in mind.

16 --o0o--

17 MR. VOLZ: The regulations under the statute
18 follow the statutory definition, precisely word for word.
19 And so the Committee's job today, as you know, is to
20 render an opinion about whether, on the basis of all of
21 the evidence, chlorpyrifos has been clearly shown to be a
22 developmental or reproductive toxin.

23 --o0o--

24 MR. VOLZ: As you know, the statutory criteria,
25 and while stringent, is not specific, and so the DART

1 Committee has its own guidance criteria for listing, which
2 are considerably more specific.

3 --o0o--

4 MR. VOLZ: You know your criteria well. And I
5 wouldn't presume to lecture you on them. What we've done
6 instead is to selectively highlight certain provisions of
7 the criteria that we think are particularly relevant to
8 chlorpyrifos and to the scientific data that you will be
9 weighing and that our scientists will be discussing.
10 These particular criteria in your guidance document will
11 be referred to specifically by Drs. Burns and Juberg when
12 they come up to the podium.

13 In terms of general principles, as indicated on
14 this slide, the two principle -- the two most important
15 principles are, first of all, that a weight of evidence
16 approach should be taken evaluating all the science. And
17 second, in the case of quite a few studies, it's important
18 to focus on biological plausibility. And like I said,
19 Drs. Burns and Juberg will elucidate the particular
20 studies where those issues are important.

21 --o0o--

22 MR. VOLZ: The guidance criteria specify that in
23 order to be listed, the chemical has to be shown as
24 reproductively toxic or developmentally toxic by either
25 sufficient evidence in humans or sufficient animal

1 just a one-time urinary measurement and may not be
2 reflective of the three months prior to that.
3 Furthermore, I think it's important to notice that the
4 levels, even though they talk about high and low, were all
5 within the range of normal in the CDC NHANES data. And
6 that may be reflective of its just an exposure to TCP
7 itself and not to the chlorpyrifos parent.

8 --o0o--

9 DR. BURNS: So quickly, I'll move onto the other
10 developmental studies, the clinical -- the case reports,
11 the four cases by Sherman. Reviews in the literature have
12 indicated there's no syndrome in those four cases and not
13 a consistent pattern to the anomalies.

14 And then the attempted suicide, clearly very high
15 exposure. And perhaps suicidal behavior beyond just the
16 ingestion of chlorpyrifos.

17 --o0o--

18 DR. BURNS: So in preparing my presentation
19 today, I looked at the standard for listing to look at the
20 weight of evidence criteria and try to match my
21 interpretation of the data with that standard for listing.

22 And that includes that the effect should be seen
23 in more than one human study. And if there is some super
24 study, that you would use that unless there were not
25 equally well-conducted studies.

1 In addition to just Epi, it was also trying to
2 evaluate exposures, learning how to reduce exposures in
3 using pesticides effectively. So it has a multiple
4 component to it besides just the epidemiology.

5 --o0o--

6 DR. BURNS: And just quickly, I want to talk
7 about some strengths of this study. Again, it focused on
8 pesticides. And I don't think that's a weakness.
9 Epidemiology is designed to evaluate the environment that
10 we have exposure, whether it's pesticides and lots of
11 different pesticides or if it's the inner-city
12 environment. But this one is very specific to the issue
13 today.

14 The study conducted was very robust. And I just
15 give you a couple of examples of what they did to try and
16 make the study conduct really good. They didn't just use
17 bilingual people, it was bicultural interviewers. They
18 interviewed the moms twice during pregnancy and they
19 collected urines at both times. And when it came time to
20 evaluating the children, they didn't just use a graduate
21 student and say this is how to do it. They used
22 psychometricians.

23 --o0o--

24 DR. BURNS: And then I think it's important to
25 talk about their use of the urine metabolite TCP. Now

1 we've heard discussed that this could be exposure to the
2 metabolite and there may be some weaknesses to that. On
3 the other hand, the blood method used in the Columbia
4 study has been viewed as a strength. And I don't disagree
5 because you're evaluating the parent. However, we, at
6 Dow, we're in conversations with Dana Barr at CDC to try
7 and do some other studies, getting the methods so we could
8 look at our workers and maybe, you know, some other
9 populations, so we could look at the blood lipid factor.

10 Well, she let us know the method has changed
11 already. And so the ability to replicate and test this
12 method is unavailable.

13 The nice thing about the urinary metabolite in
14 the CHAMACOS study is that then we can compare it to other
15 studies. You know, what are these moms exposed to to
16 compare to other populations, both occupational and
17 residential.

18 --o0o--

19 DR. BURNS: Every Epi study has limitations and
20 that's what we like to do is point them out. And I think
21 realistically, it's important to notice that this study
22 probably isn't representative of all Californians. The
23 high percentage that are Mexican born and about a quarter
24 were field workers.

25 On the other hand, if you're going to study

1 However, for the Wyatt paper, and you see the
2 negative indication, birth weight decreases with
3 increasing cord blood, so that would be a bad thing.

4 And the yes indicates statistically significant,
5 and we only see that for cord blood in the Wyatt paper.

6 --o0o--

7 DR. BURNS: The same format looking at birth
8 length. Again, birth length increases with increasing
9 exposure in the Eskenazi and Berkowitz papers. It
10 decreases in the Wyatt publication. And here we see two
11 yeses. We see a positively significant association for
12 the nonspecific metabolite in the CHAMACOS study. And a
13 positive -- a statistically significant in the negative
14 direction for the CHAMACOS -- the Columbia study. I'm
15 going to get mixed up here. I better slow down.

16 --o0o--

17 DR. BURNS: All right. Then head circumference.
18 And this is a little less clear. Head circumference
19 increases for the CHAMACOS study. And I think it's worth
20 pointing out that when you don't talk about PON1 in the
21 Berkowitz paper, the means are equal by TCPY level. And
22 with respect to PON1, if it's greater than the limit of
23 detection, it was statistically significant. But I think
24 it's relevant to point out that when you look at the means
25 for less than the limit of detection, they're very, very

1 similar. The pattern is the same.

2 So it would suggest that the PON1 results are
3 correlated with head circumference irrespective of
4 exposure to TCPY.

5 And then lastly, head circumference decreases
6 with increasing cord blood, but is not statistically
7 significant for the Whyatt paper.

8 --o0o--

9 DR. BURNS: So quickly we'll put everything
10 together. And if we just look at the yeses, that's the
11 statistically significant associations, for the CHAMACOS
12 study, for the nonspecific metabolite birth length and
13 head circumference increase with increasing levels.

14 And for Whyatt et al. in New York City, they
15 decreased significantly for birth weight and birth length.

16 --o0o--

17 DR. BURNS: Now, let's talk about what happens
18 when the babies get a little older. Both studies of
19 CHAMACOS by Eskenazi, and Columbia by Rauh et al. reported
20 on the Bayley scores for mental developmental index. And
21 you can see here by the nose, that none of them was
22 statistically significant at 12, 24 or 36 months. And so
23 far we have not seen results for the kids at three years
24 of age in the CHAMACOS cohort.

25 Now, quickly I'm just going to introduce the

1 born in '99 were higher than kids born in 2002.

2 Now, a lot of discussion has been made about if
3 you stratify this down the middle, that those 200 plus
4 children born prior to 2001, the results are statistically
5 significant, and the ones born after are not.

6 The question is, and in none of the 60 papers or
7 the additional reports by the investigators, does it say
8 are the babies bigger. We know statistically significant
9 and we know modeling. But we wouldn't expect it to be
10 statistically significant, because there's no exposure.

11 The question is, do the babies get bigger,
12 longer, better?

13 And there's no evidence in any of the papers that
14 tell me that. What they do show, however, is in their
15 2006 paper, they do show mean scores over a three-year
16 period that correlate with the change in exposure.

17 And if you read the written comments, this looks
18 a little different, the lines are bars and the bars are
19 lines, but essentially it's the same. For example, for
20 the kids born in 2000, that bar up around three and a half
21 picograms per gram, they were three years old in 2003. So
22 that's their mean level. The red bar is the mental
23 development score and the blue bar is the physical
24 development.

25 So you see, their exposure was less and they are

1 The data that was taken from the paper, Rauh et
2 al. 2006, in this context is ecologic data. So that means
3 that there's no individual data, so the scores that you're
4 seeing are not related, in any way, to that individual's
5 blood level. So that's one point on this graph.

6 Also, none of these are adjusted for any of the
7 confounders or potential confounders or covariates that
8 we've mentioned that could be so important. So this is
9 unadjusted data.

10 In addition, Dr. Rauh felt that it was kind of
11 not really logical to expect to see the kind of change
12 that we saw in birth weight over time, because this is a
13 neurodevelopmental outcome. And as Dr. Burns noted, the
14 variability in neurodevelopmental outcomes that could be
15 related to chlorpyrifos is a very small percentage of the
16 variation. So one would not expect to see large changes
17 in these outcomes. And it's certainly not unless one was
18 adjusting for all the potential covariates that we know
19 influence neurodevelopment.

20 So I think this slide is a bit misleading.

21 DR. BURNS: May I comment?

22 Certainly not my intent to mislead. And these
23 numbers are taken verbatim from the 2006 paper from their
24 discussion.

25 I only present the two together just to

1 demonstrate the dramatic decrease in chlorpyrifos over
2 time. That certainly if, as public health decision
3 makers, that removing exposure to chlorpyrifos will solve
4 any problem or if this is highly correlated with the
5 effect, ecologically, you may or may not see effect. But
6 I'm just presenting the results from their paper, that
7 they did not show that the scores were -- you know,
8 improved over time.

9 DR. KAUFMAN: I thank you for clarifying that.

10 I just also want to clarify that Dr. Rauh added
11 the comment that she did conduct the analysis between
12 exposures to chlorpyrifos in the blood levels and the
13 neurodevelopmental outcomes and that's what she presented.
14 These values were included in the paper, but not intended
15 for this use. As she said, it would be completely
16 under-powered to be able to, if you looked at it by year,
17 because of the numbers and the covariates that had to be
18 included. So they haven't looked at the analysis by year.
19 They've looked at the effect by chlorpyrifos levels. They
20 feel that it just wouldn't be possible.

21 I mean, if you do the calculations, it's not
22 possible to analyze it properly by year, as what you've
23 presented here.

24 DR. BURNS: Okay.

25 --o0o--

1 DR. JUBERG: Okay. How do I get to the first
2 slide?

3 Is this on and can you all hear me or should I
4 not -- it is?

5 Okay.

6 I was all prepared to say good morning, but I'm
7 going to have to say good afternoon --

8 (Laughter.)

9 DR. JUBERG: -- to you all. My name is Daland
10 Juberg. I'm the toxicologist responsible for chlorpyrifos
11 for Dow AgroSciences. I want to begin my presentation by
12 thanking Dr. Iyer and the OEHHA for giving us the
13 opportunity -- me the opportunity to speak to you today on
14 our scientific views on the animal data. I also want to
15 express my appreciation to the DART Identification
16 Committee for considering these views.

17 --o0o--

18 DR. JUBERG: Briefly, my background today --
19 outline is going to be a brief one slide on chlorpyrifos
20 and its mode of action. I will then move into some
21 discussion of the developmental toxicity studies focusing
22 in on the guideline studies that we've conducted and other
23 registrants have for FIFRA purposes. I will talk briefly
24 about some of the studies included in C.2.2 of the HID,
25 some of these other studies that Dr. Iyer has discussed.

1 I would then like to share a view or two on the
2 developmental neurotoxicity study that Dow conducted on
3 this molecule back around the year 2000. I will then talk
4 about reproductive toxicity and the studies we have
5 available for review and finally some conclusions.

6 --o0o--

7 DR. JUBERG: First of all, this is a molecule
8 that has an extensive toxicological database. We have
9 conducted over 3,600 studies not all on toxicology. But,
10 in fact, many of those hundreds have been toxicology
11 studies. And we know a bit about its developmental and
12 reproductive toxicity potential. As with other
13 organophosphates, it's toxicological mode of action is
14 through cholinesterase inhibition. And I point this out
15 because this has been, over the 40-year history of its
16 use, the most sensitive effect that's been determined
17 through a number of different studies.

18 And just so I give you some context to that,
19 before we inhibit plasma cholinesterase, there's a tiered
20 layer of protection that goes on beginning with portal of
21 entry metabolism continuing on with protein binding. We
22 then have a hepatic metabolism. All these A and B
23 esterases. So before we even begin to get to plasma and
24 RBC inhibition, we have these layer protections. And I
25 know a lot's been made of PON1. We certainly acknowledge

1 there's a genetic polymorphism.

2 But PON1 doesn't come into play. It's a
3 high-dose modest detoxification mechanism that really
4 doesn't play a role in environmental exposures. This has
5 been supported in a mouse model, Kohl et al. It's also
6 been supported by the PBPK model that's available by Chuck
7 Timchalk out of Battelle Northwest.

8 So it's something to keep in mind, before we even
9 get to those layered -- or before we get to brain
10 cholinesterase inhibition is where you really begin to see
11 toxicity, cholinergic effects. We've got a tiered system
12 of protective devices.

13 --o0o--

14 DR. JUBERG: Moving onto the developmental tox
15 studies. There is a rich database for chlorpyrifos
16 relative to the design and the conduct of studies that we
17 have for FIFRA purposes. We have the fortune of having
18 four studies in three different animal species. These
19 have all been conducted according to U.S. EPA guidelines.
20 These are comprehensive studies, meaning that if we are
21 going to look for some developmental effects, we are
22 likely to see these through these studies. These are
23 designed over multi years through a multi-stakeholder
24 process. And they're designed to determine and detect
25 effects. These are what I would consider scientifically

1 severe maternal toxicity, including death, did we begin to
2 see evidence of developmental toxicity in the offspring.

3 --o0o--

4 DR. JUBERG: Moving onto some of the other
5 studies. And I've taken a look at the studies that were
6 included in the HID C.2.2., and there are a number of
7 studies. There are 18 others that OEHHA has evaluated and
8 I applaud them for their accurate description of some of
9 these. They've pointed out some of the limitations.

10 But before I get to those, some of the DART
11 criteria that are used for developing a sufficient
12 evidence in experimental animals is based on adequacy of
13 the following: Experimental design, route of
14 administration needs to be relevant to expected human
15 exposures; we have to have a number of dose levels that
16 are evaluated; and, in fact, 11 of the 18 studies that I
17 looked at had fewer than -- two or fewer dose levels, such
18 that a dose response could not -- relationship could not
19 be evaluated; and finally, consideration of maternal
20 toxicity.

21 --o0o--

22 DR. JUBERG: Now, looking at some of these
23 studies, they provide value, in terms of investigation
24 into unique and interesting aspects of chlorpyrifos, under
25 perhaps different routes of exposure and so forth. When

1 you look at the sum total of these, some of the
2 deficiencies I see as a toxicologist are the following:

3 In fact, 13 of 18 used either a subcutaneous
4 intraperitoneal route of exposure. Some involve postnatal
5 day PND exposure only. Those were 4 of 18. I've
6 mentioned the inadequate dose groups. And OEHHA did a
7 good job of pointing out where there are limitations with
8 each of these studies.

9 I want to pause on the next, because I think it's
10 been under appreciated the significant role that dimethyl
11 sulfoxide has and is known to affect on neurotoxicity
12 effects of its own. There's some very recent evidence.
13 But going back, there's a growing literature on the
14 effects of this particular solvent. It affects a number
15 of different things.

16 And let me just read a couple of these things
17 that DMSO on its own will affect: Structural changes in
18 peripheral nerves, reduction in nerve conduction velocity,
19 spontaneous changes in exploratory behavior, altered sleep
20 behavior. The point is not only can DMSO do these, but
21 the CAR and Kneel recently has shown that the volume of
22 the vehicle can cause dramatic effects, not only on birth
23 weight, but also on brain cholinesterase inhibition.

24 The DNT study guideline from OECD specifically
25 calls out and says the vehicle should not be -- should not

1 toxicologists to incorporate a particular design to
2 measure memory in learning.

3 I will acknowledge this did encompass both
4 prenatal and postnatal exposure. And I understand the
5 significance of excluding postnatal exposure. But what I
6 want to offer is the following: In this study, there was
7 no evidence of developmental toxicity in the absence of
8 maternal toxicity. There were no effects on birth weight,
9 except at maternally toxic -- the top dose of 5 milligrams
10 per kilogram. There were no effects on learning and
11 memory even at the top dose. There was no evidence -- and
12 these are the author's conclusions of selective
13 developmental neurotoxicity following exposure to
14 chlorpyrifos.

15 The one piece of information that's very critical
16 to review that's probably not been included in the OEHHA
17 HID nor in a number of other things, is what's called
18 Supplement 3, which when after this thinning of the
19 parietal cortex. This is what Dr. Iyer referred to
20 earlier. The situation was at the time when this study
21 was conducted, there were no historical control data.
22 What Argus Laboratories did was review after they
23 conducted another four studies, they submitted, what they
24 called, Supplement 3. And this is available. It's been
25 submitted in our written comments. And I can show you a

1 then went back to our oncogenicity chronic studies,
2 because it's important to look both in the long-term rat
3 and mouse studies, gee, were we seeing any evidence of
4 histopathology, organ weight changes in reproductive
5 structures? The answer is no.

6 And then I alluded to there are three other
7 multi-gen studies, albeit these were at lower dose levels,
8 but they essentially confirm the absence of reproductive
9 effects.

10 --o0o--

11 DR. JUBERG: In conclusion then, as the
12 toxicologist for Dow AgroSciences who works with this
13 molecule familiar with the database, it's my perspective
14 that studies representing scientifically valid testing,
15 according to generally accepted principles, do not
16 indicate developmental toxicity across a number of species
17 in the absence of maternal toxicity.

18 And I think we're seeing consistent evidence
19 across studies, which demonstrates fetuses to be less
20 sensitive than dams. There was a companion study that was
21 attached to the DNT study that specifically looked at
22 differential sensitivity and this did not show any.

23 Point 3, the weight of the scientific evidence
24 does not demonstrate that chlorpyrifos produces male or
25 female reproductive toxicity in animal studies. And

1 collectively and conclusively then, I would submit that
2 the scientific data indicate that chlorpyrifos has not
3 been clearly shown to cause developmental or reproductive
4 toxicity.

5 --o0o--

6 DR. JUBERG: On behalf of my colleague Dr. Carol
7 Burns and Dow AgroSciences, I would summarize then that
8 chlorpyrifos has not been clearly shown, through
9 scientifically valid testing, according to generally
10 accepted principles to cause either developmental, female
11 reproductive or male reproductive effects, and this
12 predicated on a lack of evidence in both humans and
13 experimental animals.

14 That's all I have today. And I'd be happy to
15 answer questions if I could, if you have those. Or if you
16 want me to show you the one bar graph, I'd be happy to
17 show you the control data for that study. But Supplement
18 3 is a very critical part of the assessment of the DNT
19 study.

20 CHAIRPERSON BURK: Yes. I thank you for bringing
21 that up, because I was a little confused on it here in our
22 materials. I don't need to see the details necessarily,
23 but I just wanted to verify that with the data that we
24 had, we had a study called Hoberman and that's where they
25 found the morphometric differences. And then you're

1 saying that the published study that came later was after
2 this Supplement 3?

3 DR. JUBERG: The published -- actually, Dr. Burk,
4 it did not have that conclusion. And so even the
5 published study didn't have the benefit of that.
6 Subsequent to that though --

7 CHAIRPERSON BURK: Because that wasn't mentioned
8 in the published study, was it?

9 DR. JUBERG: It was not. It was not. These were
10 submitted four months after the EPA actually reviewed the
11 data back in 2000. And so it's one of those things as a
12 toxicologist, I just like to keep bringing up, because
13 it's pretty insightful to the overall DNT study, and at
14 least should be thrown into the mix of the discussion I
15 believe. Historical control data can be invaluable in
16 cases like these. And, in fact, it shows this five
17 percent thinning to be right in the middle of where you
18 would normally expect control animals to be.

19 COMMITTEE MEMBER JONES: I'd like to see your
20 data.

21 DR. JUBERG: Okay. Do we have that?

22 It's slide 53.

23 And will you all work it from there or will I
24 operate it?

25 MS. OSHITA: We will get it up and you can do it.

1 DR. JUBERG: Okay.

2 Again, this was a finding of about five percent
3 seen in the mid- and high-dose animals, females only. And
4 when Alan Hoberman at Argus did then was to bring in the
5 data from four other DNT studies in conjunction with our
6 study, the 5th. It's the 10th -- middle on the -- yeah,
7 there you go.

8 I don't know if we can highlight that. What
9 we're demonstrating here is parietal cortex thickness,
10 again, measured at two months out, day 66. And you can
11 see either by the bar graphs or the tabulated data there,
12 you can benchmark it against the percent historic mean,
13 where we basically are running from a high of 105 down to
14 95. But if you look at the 1 and 5 milligram per kilogram
15 per day -- these are the mid- and high-dose levels --
16 those numbers fall right at the historic low is 92.4.

17 But looking at the bar graph, they're just right
18 in line with where these effects -- or where parietal
19 cortex thicknesses will be.

20 Dr. Hoberman and others went on to bring a number
21 of facets of this thing -- a number of findings before
22 saying, you know, given a 5X difference in dose, if the
23 effect were treatment related, we certainly should have
24 seen it in the males as well. So it was not reported in
25 the males at all.

1 DR. IYER: I'd like to add that I did talk with
2 the U.S. EPA reviewers about this. And, A, they were --
3 you know, they thought that you have -- concurrent
4 controls have more value than historic controls. And
5 given that, you know, it's a matter of semantics, these
6 may not have been historic, because these were actually
7 done afterwards, so there's some question about that. But
8 they did take that into account and they still felt pretty
9 strongly that for the concurrent controls, there was an
10 effect. It may be just a hint of that this is maybe
11 happening. They actually looked at it though and found
12 it, even in the mid-dose. I think that's what really kind
13 of convinced them. Seeing it at the high dose would have
14 been one thing.

15 And then they didn't have the benefit of looking
16 at the low dose, because that wasn't done, so they
17 couldn't tell what was happening. So that was their view
18 on looking at this closer examination, because at first
19 glance, it doesn't look like there's an effect. But when
20 you look at it again, you see that there is actually an
21 affect by their estimation.

22 DR. JUBERG: I would note, there were no
23 histopathological effects associated at any dose level.
24 So while they had this thinning effect, its histopathology
25 wouldn't support that there was any finding. But Dr. Iyer

1 makes a good point.

2 Thank you.

3 Any other questions?

4 Thank you all very much.

5 CHAIRPERSON BURK: Thank you.

6 And next we have Dr. Gina Solomon, NRDC, two
7 minutes.

8 DR. SOLOMON: Sure. I don't have a PowerPoint
9 prepared. Thank you for your patience and for going into
10 your lunch time. I'm Gina Solomon. I'm a senior
11 scientist with NRDC, the Natural Resources Defense
12 Council. I'm also an Associate Clinical Professor of
13 Medicine at UCSF, where I'm an Associate Director of the
14 Pediatric Environmental Health Specialty Unit there.

15 And so I was just listening to this and it's sort
16 of striking to me how -- well, first of all, I also wanted
17 to thank the staff, because I thought that the
18 presentation were really very strong, very well done and
19 reflected a lot of work.

20 And this is a chemical that I've been interested
21 in for quite a number of years. And it, I think, is a
22 testament to a new improved priority-setting process that
23 you're now getting really meaty interesting chemicals with
24 quite a lot of data to chew on. And it was sort of
25 interesting to me to see how a chemical with such a strong

1 data set, that is really so consistent when you look at
2 the developmental neurotoxicity data in animals. And, of
3 course, cortical thinning is not a super-sensitive
4 endpoint. It's pretty gross histology. But if you look
5 at both the animal toxicity and the human data, you really
6 see very much the same kinds of effects. You see really
7 very nice dose-response relationships in many, many
8 studies.

9 And, of course, folks can point out issues with
10 individual studies and sort of make the whole thing seem
11 more confusing than I actually think it is.

12 But I, of course, am not a toxicologist. So my
13 expertise is more in the epidemiologic area. And I have
14 spent a fair amount of time looking at the CHAMACOS study,
15 the Mount Sinai study and the Columbia study and really
16 feel that they're not inconsistent with each other when
17 you take into consideration some of the dose metrics used.

18 In other words, whether they're looking directly
19 at chlorpyrifos, directly at cord blood versus a
20 metabolite in urine; when you look at the dose differences
21 that were found in those studies, so that you have higher
22 doses. Certainly, I think in both of the New York studies
23 that's a little hard, as Farla mentioned, to compare the
24 two.

25 But there's no reason to think that populations

1 would be that different between Mount Sinai and Columbia
2 in terms of, you know, the exposure pathway, because it
3 was all indoor extermination.

4 So we see much lower exposure levels in CHAMACOS
5 in a much less dramatic effect. But still something that
6 is completely consistent with what we see in terms of
7 neurodevelopmental toxicity.

8 And just going back to the R squared question. I
9 don't think that any of us are saying that chlorpyrifos is
10 as potent a developmental toxicant as cocaine. I think
11 we're saying that it is -- you know, we're seeing really
12 pretty dramatic data showing developmental neurotoxicity,
13 not something that will swamp everything else like, you
14 know, cocaine or lead, but certainly something that is an
15 important developmental neurotoxicant that is very much
16 within the purview of this Committee to designate as such.

17 And so I'm just asking you to look at the big
18 picture, look at the consistency and to designate
19 chlorpyrifos as known to the State to cause birth defects
20 or reproductive harm or whatever the big picture is. I'm
21 actually not going to speak to the male reproductive
22 endpoint, because it's not something I've looked at at
23 all.

24 So thank you very much.

25 CHAIRPERSON BURK: Thank you.

1 And I think this is a time to take a break.

2 How long do you recommend?

3 What time should we reconvene?

4 Oh, absolutely. We do have a full agenda left.

5 We have to discuss this and we have other things. So

6 1:30?

7 No later than 1:30. We absolutely will start

8 right at 1:30.

9 CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, I just
10 wanted to remind --

11 CHAIRPERSON BURK: Yes, Carol.

12 CHIEF COUNSEL MONAHAN-CUMMINGS: -- the Committee
13 Members not to discuss this issue or any of the others
14 that are on the agenda while they're at lunch. So we need
15 to keep it in the public forum.

16 Thank you.

17 (Thereupon a lunch break was taken.)

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1 well, we also have case control studies and
2 cross-sectional studies. But I think in terms of
3 establishing a causal relationship, the prospective study
4 certainly does that.

5 The next point is that it requires accurate
6 exposure. Now, in terms of accurate exposure, I think
7 that these studies, all three of them, were designed very
8 well, to be honest. They might actually measure different
9 metabolites or use different mediums, whether it be blood
10 or urine. But in terms of the accurate exposure, I think
11 that they certainly do that.

12 As far as the confounding factors, for all three
13 studies -- I've been on this Committee a long time. I've
14 not seen such a long list of confounders for particular
15 studies. And I'll just read a few of them just to give
16 people the idea.

17 But for the CHAMACOS study, some of the potential
18 confounders are maternal education, marital status,
19 parity, county of birth, poverty, smoked during pregnancy,
20 caffeine use. So you can see that they certainly have
21 adjusted for a great deal of confounders.

22 As well for the Columbia study, the same thing
23 and even more I might add. So they have a lot of
24 demographics in terms of maternal age, race/ethnicity, et
25 cetera, et cetera, maternal IQ, environmental tobacco

1 smoke, season of delivery, home environment, marital
2 status. So once again -- and I'm just reading a partial
3 list. So I think they've also done an excellent job of
4 the confounders that they considered.

5 And last of all for Mount Sinai, they also had
6 looked at in maternal age, race/ethnicity, infant sex,
7 gestational age, et cetera.

8 So in order to address the criteria in terms of
9 the studies, I think the studies are rigorous studies, and
10 I think that they are designed very well.

11 Now, having said that, there are certainly
12 differences within the studies. And the beauty of doing
13 research is that we tend to look at studies and improve
14 upon them and do different things. So the fact that the
15 CHAMACOS and Columbia and Mount Sinai aren't absolutely
16 measuring the same things to me is not necessarily a flaw.

17 I want to start with the ethnicity or the racial
18 breakdown in terms of these three studies. And I wanted
19 to say that CHAMACOS was looking at the low-income Latino
20 pregnant women. Whereas, Columbia was looking at a
21 African American and Dominican women and Mount Sinai was
22 looking at African American, White Mexican and Puerto
23 Rican.

24 And I have to say that having sat on this
25 Committee for a long time, a lot of the studies have been

1 primarily Caucasian. So this also, I think, is a plus.

2 If you look at the demographics for CHAMACOS,
3 you'll see that 82 percent of the women are married and 81
4 percent had less than a high school education. But what
5 was nicely balanced and yet different in the other studies
6 were that only 25 to 29 percent of the women were actually
7 married. And that 35 percent -- 32 to 35 percent had less
8 than a high school education.

9 So differences sometimes are good, because when
10 you look and compare and contrast studies, it helps to
11 explain things. So as well, it's been brought up that the
12 New York studies were, of course, measured indoor in terms
13 of the exposure assessment. Whereas, the CHAMACOS study
14 was outdoors. Certainly, there are a whole myriad of
15 other pesticides that were taken into account, but I think
16 that the studies acknowledge those limitations.

17 So to me, at the end of the day, you really have
18 to somehow combine these studies and be able, after
19 thinking and acknowledging the limitations of each and
20 every study, what does it all mean, and whether or not
21 there is, in fact, an effect.

22 And so what I've done, which is fairly similar in
23 terms of the wonderful presentation we had, was to
24 basically separate the study designs by prospective
25 case-control cross-sectional and just basically tabulate

1 what the different outcomes were just for my own personal
2 understanding, because there is a lot of literature and
3 it's hard to actually, at the end of the day know what it
4 all says.

5 So I will start with the prospective studies, and
6 looking at the effects, in terms of the neonatal
7 characteristics. So Berkowitz was the one who found a
8 decrease in head circumference. So there was one study on
9 decreased head circumference. There were two studies on
10 decreased birth weight, and those were from Whyatt, who
11 was from Columbia and Wolf from CHAMACOS. There was two
12 studies for decreased birth length, one from Whyatt, one
13 from Wolf. And then there was an increase SGA from
14 Whyatt. So those are basically the summaries of all of
15 the neonatal characteristics.

16 Now, when we go onto the developmental
17 characteristics, we have one study by Rauh, who found a
18 decrease in psychomotor development index, and as well a
19 decrease in the MPI. There were two studies by Whyatt and
20 Eskenazi that had an increase in pervasive developmental
21 disorders. And as well, Whyatt found an increase in
22 Attention Deficit -- ADHD. And there were three studies
23 that found abnormal reflexes and those were Young,
24 Eskenazi and Engel. So that sort of covers those
25 characteristics.

1 Now, when we go onto the sperm DNA, those are all
2 cross-sectional studies. And for people that are in
3 epidemiology, they know that cross-sectional studies don't
4 necessarily establish the temporal situation as well as
5 prospective studies.

6 Certainly, in terms of the Meeker studies, there
7 were five studies and they were all on the same study
8 sample. Having said that, he found a percentage tail,
9 where there's a percentage of the DNA in the comet tail,
10 there was an increase. He found an increase in DNA damage
11 and Perez found a decrease in motility and viability and
12 integrity.

13 So I could sit there and sort of tease out in
14 terms of who used what, whether they used maternal blood
15 or they used urine or if they used DAP or DEP or CPF. But
16 at the end of the day, you have to say to yourself what
17 are the characteristics that they found and whether or not
18 it is important.

19 And so I think if you take together with the
20 animal studies, of course, with the caveat that there are
21 certainly variations in the outcomes that all of these
22 studies looked at, because they chose the outcomes they
23 wanted to choose to look at. And certainly how they
24 measured their exposures and what confounders they used
25 were their own choices. But as I said, taken together

1 with the animal studies, there is concern for this.

2 So that's what I have to say.

3 CHAIRPERSON BURK: Is there any discussion, I
4 hope?

5 Questions?

6 Shall I go ahead and talk about the animal
7 studies and give you more time to think?

8 (Laughter.)

9 CHAIRPERSON BURK: All right.

10 DR. BURNS: Can I ask a question?

11 CHAIRPERSON BURK: I guess so sure. Come on up.

12 DR. BURNS: Carol Burns again. Thank you for
13 that interesting summary.

14 I have a question about accurate exposure
15 assessment when the nonspecific metabolites are used. I
16 mean, I need to know where we are on that? Could you
17 explain that?

18 COMMITTEE MEMBER KLONOFF-COHEN: In terms of for
19 each of the studies in terms of --

20 DR. BURNS: Well, if you, for example, the -- I'm
21 getting them mixed up in my head, but --

22 COMMITTEE MEMBER KLONOFF-COHEN: When you're
23 talking in terms of for instance like DAP and DEP in the
24 urine versus if you're using the blood of the cord blood
25 versus --

1 DR. BURNS: When one publication of the Mount
2 Sinai study, the Berkowitz paper, did evaluate the
3 specific metabolite. And then I think it's Wolf for Mount
4 Sinai that was nonspecific. So --

5 CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me. I
6 just wanted to point out that this is the time for the
7 Committee to do their deliberation and their discussion.

8 CHAIRPERSON BURK: Okay. Carol, so in other
9 words, this is our discussion time now.

10 CHIEF COUNSEL MONAHAN-CUMMINGS: We already had
11 the public comment period. And so if it's not a
12 clarification of something that was said during public
13 comment and it's just a question about what you just said,
14 I'm not sure that that's an appropriate thing to do at
15 this point. This is the time when the Committee is
16 deliberating and discussing among themselves.

17 CHAIRPERSON BURK: All right. We will do that.

18 When it comes to the animal studies, there were
19 many. A lot to read. A lot to wade through. After
20 getting through them all, kind of put them into three
21 categories, which, I think, are consistent with the way it
22 was discussed earlier, we have the standard developmental
23 tox type of studies, that are mostly done for registration
24 purposes. And in those cases, they were pretty much all
25 negative or finding effects only at maternally toxic

1 doses, if -- as that's defined as inhibition of
2 cholinesterase activity. So I don't think the evidence is
3 very strong for a listing just based on standard
4 developmental tox.

5 The next sort of group of studies or the ones
6 that look at neuro and behavioral toxicology, and these
7 are much more interesting. And it's nice to actually have
8 some. It's not something we've talked about that much on
9 the Committee yet, so it's a little bit of a new thing for
10 us. And I'm certainly not an expert on this, but, you
11 know, I looked at what we were given, the Hoberman study
12 first, which was using the standard EPA procedure at the
13 time at least. And although they considered that their
14 results were spurious, there were a number of findings,
15 morphometric changes and behavioral changes.

16 Again, the follow-up to that, I guess, the
17 published study appeared to be negative, and we heard
18 about this other thing about the historical controls
19 versus the concurrent controls. But nevertheless, I mean,
20 I think in light of the human findings, I wouldn't totally
21 dismiss these findings. Again, by themselves, I'm not
22 sure it would be, you know, strong enough, but certainly
23 it's an adequate study and to be considered.

24 Then there are a whole bunch of studies that I
25 found the most fascinating, because I'm interested in

1 mechanisms, and, you know, what's actually going on. And
2 so I spent perhaps too much time reading those, but those
3 were the ones from the Slotkin lab. And many of them --
4 and I had to go in the back to try to figure out who all
5 works in that lab. It must be quite an enterprise.

6 But the criticisms there, of course, are the
7 route of exposure and the use of DMSO and all that.
8 Again, I would not, on the basis of those alone, find
9 support, but I do think that their findings lend support
10 to the human data. So particularly looking at the windows
11 of vulnerability, you know, different times of exposures,
12 the behavioral alterations emerging later times during
13 adolescence and adulthood, certainly suggesting there may
14 be another mechanism other than cholinesterase inhibition.

15 Again, I don't think these studies alone would be
16 adequate to support a listing, but I'm kind of looking
17 holistically at the weight of the evidence here. And I do
18 see support for the human findings, particularly the
19 Columbia study. There are other issues to be considered
20 that, you know, were mentioned before, all of which I
21 guess are designed to have us think well, this study
22 doesn't count, this doesn't count, this doesn't count, but
23 I still try to look at this more globally.

24 So I cannot give you, you know, a checklist of
25 positive studies that make this very clear. I can only

1 say that there's a vast amount of information, all perhaps
2 with limitations, but that in kind of the big picture on
3 the weight of the evidence, I think we should discuss it
4 seriously.

5 So I will ask for comments now on the whole
6 picture.

7 COMMITTEE MEMBER KEEN: Just a -- I guess it's
8 not even the whole picture. I can't help but wonder if
9 we'd flipped it around and we'd done the experimental
10 animals first, because what I'm impressed by is there are
11 clearly, in my opinion, are some effects. Where the
12 confusion comes in is over to what extent are they driven
13 by maternal toxicity.

14 And when I went through the papers, and then went
15 through the papers that were cited in those papers, I
16 became very much impressed with the fact that maternal
17 toxicity seemed to be an overarching problem in the vast
18 majority of cases.

19 And if we then used the strict, sort of,
20 guidelines that we've largely used in the past, we'd say
21 well then we have to be very cautious here.

22 So if one starts from that, I would agree the
23 animal data do not disagree, assuming one takes the
24 interpretation of the human literature that there is in
25 effect, that they don't argue against it, but the only way

1 that could happen if you saw absolutely no effect with the
2 animal data.

3 Given the maternal toxicity there, I would almost
4 tend to view it as maybe being a draw. We're missing the
5 critical set of data, and that is something which is below
6 evidence of maternal toxicity, then do we see effects?

7 If so, I would argue that would buttress my view
8 of the human data is it's not overwhelmingly strong. And,
9 in fact, I think that was pretty well what I heard in
10 your -- you have to take it in totality and you can say
11 well it seems like the suspects are all there. But I do
12 wonder if we -- unless we can point to some data on the
13 animal side where maternal toxicity isn't a major factor,
14 is the right conclusion to say, we're just not going to
15 get anything useful here. And we shouldn't arbitrarily
16 say we'll use it to support that human data. Either the
17 human data should be strong enough on their own or they
18 shouldn't be. That's kind of -- I'd love to hear other's
19 opinions on that.

20 CHAIRPERSON BURK: I would like to hear from
21 those that -- just relative to the human data, is it
22 strong enough on its own?

23 Dr. Hobel

24 COMMITTEE MEMBER HOBEL: Yeah. I think that the
25 human data is great for characterizing the fact that there

1 is concern about hazard to this chemical. And that puts
2 us in a frame of mind that this is something that we need
3 to seriously consider. But then when I go to the animal
4 studies, it seems to be somewhat overpowered by a much
5 higher focus on toxic levels, which do seem to affect
6 various things in biology.

7 So I'm finding it hard to compare both to
8 convince me that this is a serious problem at this time.
9 My greatest concern is that with all the new techniques
10 available to look at the epigenetics of the effect of an
11 environmental substance, there are a lot of new tools that
12 can be used today to focus more on really what is
13 happening by looking at certain biomarkers.

14 So I don't think we're really at the stage yet
15 where we can really make a major decision about listing
16 this drug or this chemical compound.

17 COMMITTEE MEMBER WHITE: I'm just going to
18 mention, I do agree. I'm not quite convinced that we're
19 there yet. I see the hazard as well, but I can't
20 personally look at the data and say, well, yes, this is a
21 hazard and we need to -- I mean, not a hazard, but this is
22 definitely something that could truly affect reproduction
23 and maternal fetal health. I'm just quite not there yet.
24 I don't see it.

25 And it's still a little bit confusing for me too,

1 because of the animal data. So I would agree, I just
2 don't think we're there yet to be able to list it.

3 COMMITTEE MEMBER JONES: Can we ask Hillary to
4 say whether she thinks the human data, from an
5 epidemiologic standpoint, stands on its own.

6 COMMITTEE MEMBER KLONOFF-COHEN: Does it stand on
7 its own?

8 I guess I was interested in hearing the summary
9 of the animal data, because from the presentation, it
10 seemed very striking that the animal data was supportive.
11 But hearing what -- but it sounded very supportive. I
12 don't get that strong a sense now hearing what's been
13 discussed at this point with the animal data. And on it's
14 own, the human data without the animal data...that's a...

15 CHAIRPERSON BURK: I think this is one of these
16 difficult ones, where we think there's something there,
17 but we don't perhaps quite have what actually would make
18 it crystal clear.

19 I do think the animal data supports it, but I
20 think what supports it is actually the studies that look
21 at a different mechanism than cholinesterase inhibition,
22 and that would be at a much lower level. But they're not
23 done in the standard way and all that, so therefore we
24 have these kind of limitations that we're looking for the
25 standard type of studies done in the accepted way, and you

1 know all that.

2 But I think finding out more about mechanisms
3 other than cholinesterase inhibition, which you would
4 consider maternal toxicity is, would be really important.

5 So, Ellen.

6 COMMITTEE MEMBER GOLD: I just want to ask a
7 question again about the human data. Because there's this
8 concern in the animal data about the effects of it being
9 mediated through maternal toxicity, what about the male
10 effects that were observed in the human data?

11 COMMITTEE MEMBER KLONOFF-COHEN: I think that
12 it's a good question. I think the hesitation I have about
13 the male data, I think the results are very interesting
14 and very exciting.

15 The difficulty is that it's the same data sets,
16 so it's multiple publications by the same gentleman. And
17 so that's why it sort of tempers my -- if somebody else
18 had come and done a similar study with a different study
19 sample, I would feel more excited.

20 It's basically five studies by the same
21 gentleman.

22 CHAIRPERSON BURK: There was one positive animal
23 study for male repro effects. Although, there were quite
24 a number -- well, at least three that were not. And in
25 that one, that's the Joshi 2007. There were reduced

1 testes weights, reduced testicular sperm counts,
2 degenerative changes in the seminiferous tubules, and 85
3 percent negative results for fertility in the high-dose
4 group. But, again, it's at the high dose, so that makes
5 it less than crystal clear unfortunately.

6 Other comments? We didn't talk about the female
7 repro. I think, earlier when you asked about the
8 lactation, Carl, you were probably saying you didn't think
9 that was going to fly. But the one thing I wanted to
10 point out, and again it's a constraint that we have, is
11 that a number of the neuro and behavioral studies need to
12 go from gestational times into the early part of postnatal
13 development. And that's the way they're set up, because
14 that actually corresponds to a third, say, trimester in
15 the human, which I think is a valid model and shouldn't be
16 discounted either. But we do have that issue.

17 If it comes via breast milk in the -- or directly
18 to the pups on the early days after birth, is that female
19 reprotox? You know, is it or -- you know, you could sort
20 of stretch it, I think, and would say that --

21 COMMITTEE MEMBER KEEN: Yeah. I would have no
22 trouble moving out of the harbor and saying yes, it is, if
23 I saw data cross-fostering. The dilemma here is we're not
24 seeing that information. I mean, so, you know, I see an
25 awful lot of suggestive evidence. But if we use the

1 strict interpretation that we're charged with -- you know,
2 is it really conclusive -- that's what I -- in my mind, it
3 seems to be a little short.

4 COMMITTEE MEMBER HOBEL: A quick comment. I
5 think that we're all dealing with this issue of timing. I
6 look at things in a life-course perspective. The
7 information that was mentioned about the effect on testes
8 and sperm, this happens very early in the continuum.
9 There's a lot of interest now in looking at genetic
10 changes, methylation changes that occur in sperm early in
11 the reproductive cycle. And these can now be monitored
12 and measured.

13 But then later on, I'm really thinking about the
14 mechanism that we're dealing with here. And I don't think
15 it's necessarily affecting an enzyme system that affects
16 nerve transmission. It's -- I think there's something
17 going on here that might need to be carefully looked at.
18 And you have to look at it very early in reproductive
19 life. You have to look at it during pregnancy, and then
20 also during the infancy. So with a constant focus on
21 really what is the mechanism.

22 CHAIRPERSON BURK: Any other comments?

23 Any other comments?

24 Does anyone -- I feel like -- we want to make
25 sure we've discussed this thoroughly because it's a

1 serious issue.

2 Does anybody think that the human data can stand
3 on its own?

4 You're not willing to go out on a limb there.
5 Because I really do think that the Columbia data set is
6 impressive to me, but I know it's only one study
7 and -- all right, so are we ready to vote, one last
8 chance.

9 Speak up.

10 COMMITTEE MEMBER GOLD: Well, I'm just going to
11 be thinking out loud here. But if we want to take the
12 totality view rather than saying it -- putting our weight
13 on one study, can we look at the totality and get a sort
14 of gestalt of leading us in a certain direction, both
15 human and animal. Rather than saying we'll, I'm really
16 convinced by one study. So I would raise that question to
17 the two primary reviewers.

18 CHAIRPERSON BURK: Yes. Well, I mean, I think
19 there's two things you're asking. One, are we permitted
20 to do that? And I know earlier we were shown something
21 that said you had to have sufficient human or sufficient
22 animal or sufficient both. I think the sufficient both
23 could be a -- I don't know how -- a totality type
24 of -- yes. Well, Carol, why don't you comment legally on
25 what that means.

1 CHIEF COUNSEL MONAHAN-CUMMINGS: Right. One
2 thing I would point out to you is that when you're talking
3 about all these criteria, those are your criteria that the
4 Committee developed. They're not a mandatory -- you know,
5 they're not part of the statute or the regulations. Those
6 are certainly important, but they -- what we're -- what
7 you need to rely on is your own expertise. That's why
8 you're put on the Committee and what you're feeling is on
9 all of the evidence. And certainly under your own
10 criteria, you can look at both the animal and human
11 evidence together. You don't have to have separate -- you
12 know, it's only based on animal or only based on human.
13 In fact, one of the items on your criteria says that you
14 can list based on limited evidence or suggestive evidence
15 in humans supported by sufficient experimental animal
16 mammalian data. Okay. So, you know, you can kind of look
17 at it in terms of all of it together. And it is a weight
18 of the evidence argument. It's not beyond a reasonable
19 doubt.

20 CHAIRPERSON BURK: Does that make it any clearer?

21 COMMITTEE MEMBER KLONOFF-COHEN: Ellen, I just
22 want to say that when I presented it, I tried to give a
23 total presentation to be honest. So when I was listening
24 and it wasn't based on one parameter or one outcome, I
25 tried to sort of present all of the outcomes that were

1 described in all of the studies to try to get a sense if
2 there were findings where more than one study had found
3 those, but to also give a sense of what all the neonatal
4 characteristics, all of the neuropsychological.

5 Okay, so --

6 COMMITTEE MEMBER GOLD: I do have one other
7 thing. So if we divide this up into sort of developmental
8 female and male, maybe that helps us a little bit. And
9 then if the animal and human data, although we don't have
10 a single study that we'd like it to stand on, do they
11 together help us reach a decision in each of those three
12 areas? Personally, I would find that a more helpful
13 approach.

14 And with regard to the one study where it's the
15 same study population for the male data, but they've got
16 multiple publications, if we thought that that was a
17 really excellent study, it wouldn't particularly bother me
18 that it was multiple publications on the same study
19 population. So if you want to comment on what you think
20 the quality of that study is, that would also be helpful.

21 COMMITTEE MEMBER KLONOFF-COHEN: So I'm just
22 looking to see in terms of Meeker's -- let's see. His
23 sample was anywhere between 260 and 322. What he was
24 doing was he was looking at environmental exposure to
25 other things, for instance, like carbaryl and other

1 things.

2 To be honest, I don't have any limitations down
3 for him, so it's not like I didn't like the study. But
4 would I pass it based on his study alone, is that the
5 question?

6 COMMITTEE MEMBER GOLD: No.

7 COMMITTEE MEMBER KLONOFF-COHEN: Okay, good.

8 I have to say honestly to me, since it was
9 brought up, and I was really looking at, in terms of where
10 it says where epidemiology data are suggestive, and I do
11 think that the human data is highly suggestive. I think
12 it's a good word. Do I think it's overwhelming? I don't
13 think it's overwhelming. I think it's suggestive. I
14 think that is definitely what it is.

15 It says, "A listing must be supported by
16 sufficient experimental animal data." So to me, to be
17 honest, that was my approach was I thought the human data
18 was very suggestive. There were a lot of really important
19 endpoints that were established in a multitude of studies.
20 And I was going for the fact that in combination with the
21 animal studies that was how we would consider it.

22 COMMITTEE MEMBER HOBEL: I think that based on
23 all the information available, one could sit down and
24 design a very good study. And just to give you an
25 example, we've been able to demonstrate there is some data

1 on the effect of the chemical on sperm and genetics. And
2 you have to keep in mind, that during pregnancy, the genes
3 don't -- genome of the infant and the placenta is a
4 combination of the mother and father. So that if
5 something happens in the father during pre-gestation and
6 during gestation, then that can influence what happens to
7 the pregnancy.

8 And one can actually begin to look at the
9 genetics of the placenta, which is a combination of the
10 woman and the father. And that's where these changes can
11 begin to be passed onto and affect the pregnancy, early in
12 pregnancy, during pregnancy or then even affect the child.
13 So I think that's really where something like this has to
14 go to be studied. Because all the pieces are there, but
15 you can't connect them, unless you study them.

16 CHAIRPERSON BURK: Other comments?

17 I actually agree that the Meeker studies are very
18 suggestive. The main problem I have there -- it's not a
19 problem, but I'm kind of balancing that against a negative
20 Epi study that we also were given, the Swan study. So
21 obviously they're not measuring the same thing. And I see
22 that DNA damage is serious business. But do you think it
23 was a limitation that they only measured things at one
24 time point, too. I think you said -- right.

25 COMMITTEE MEMBER KLONOFF-COHEN: Yeah,

1 absolutely.

2 CHAIRPERSON BURK: Any other discussions?

3 I don't want to draw it out, but I also don't
4 want to cut anyone off. So I think we're ready to vote.

5 And I will, again, read this for each of the
6 three endpoints. Has chlorpyrifos been clearly shown,
7 through scientifically valid testing, according to
8 generally accepted principles, to cause developmental
9 toxicity? All those voting yes, please raise your hand?

10 (Hand raised.)

11 CHAIRPERSON BURK: And I'm voting yes, but I'm
12 the only one.

13 Okay, all those voting no?

14 (Hands raised.)

15 CHAIRPERSON BURK: Six no. And, again, Linda
16 recusing.

17 Next one. Has chlorpyrifos been clearly shown,
18 through scientifically valid testing, according to
19 generally accepted principles, to cause female
20 reproductive toxicity? All those voting yes, please raise
21 your hand?

22 Zero.

23 All those voting no, please raise your hand?

24 (Hands raised.)

25 CHAIRPERSON BURK: Seven.

1 Has chlorpyrifos been clearly shown, through
2 scientifically valid testing, according to generally
3 accepted principles, to cause male reproductive toxicity?

4 All those voting yes, please raise your hand?

5 (Hand raised.)

6 CHAIRPERSON BURK: Okay, one.

7 All those voting no, please raise your hand?

8 (Hands raised.)

9 CHAIRPERSON BURK: She changed?

10 Okay. So we're making that two.

11 Anyone else?

12 So now we're on the noes?

13 (Hands raised.)

14 CHAIRPERSON BURK: Okay, 2 to 5.

15 And we had one abstaining for each one.

16 Okay. So the result then is chlorpyrifos will
17 not be added to the Proposition 65 list for any of the 3
18 endpoints, because we did not get five yes votes.

19 All right. So moving along in the agenda, the
20 next portion will be two chemicals to discuss relative to
21 prioritization for developmental reproductive toxicant
22 identification -- well, recommending they be moved on for
23 hazard identification material production, I guess you
24 call it.

25 So the first one are trihalomethanes. And the

1 staff presentation will be given by Dr. Francisco Moran.
2 Oh, and Jim Donald.

3 (Thereupon an overhead presentation was
4 Presented as follows.)

5 DR. DONALD: If I could just introduce the item
6 briefly. At the Committee's last meeting in December 10th
7 of last year, eight chemicals had been identified as
8 potential candidates for consideration through OEHHA's
9 current prioritization process were discussed. And while
10 all eight chemicals were recommended by the Committee as
11 candidates for development of hazard identification
12 materials, two of the chemicals also prompted discussion
13 of additional related chemicals.

14 Bromodichloromethane or BDCM was one of the eight
15 chemicals discussed. BDCM is a trichloromethane or THM
16 and the Committee noted that the data for total
17 trihalomethanes in drinking water would likely be stronger
18 than for any individual THM alone.

19 The Committee requested that OEHHA prepare the
20 same prioritization materials for total THMs as had been
21 prepared for other potential candidates.

22 OEHHA has done so and Dr. Francisco Moran will,
23 in a moment, present a brief overview of the materials.

24 All of the abstracts previously included in the
25 prioritization materials for BDCM are also included in the

1 current materials, along with abstracts of studies on
2 other THMs and mixtures of THMs. Two points to note are
3 that although the search terms used OEHHA encompassed all
4 THMs, only data on chlorinated and brominated compounds
5 were identified.

6 The second point is that the epidemiological
7 screen of two analytical studies of sufficient quality was
8 not reapplied to this data set, since it had already been
9 established that the screen was met by BDCM alone and
10 hence would necessarily be met by the larger data set that
11 encompassed BDCM.

12 So in the meantime, OEHHA is proceeding with the
13 development of hazard identification materials for BDCM.
14 And we published a request for relative information for
15 inclusion in the hazard identification materials.

16 Some members of the Committee may also recall
17 that chloroform, another individual THM, was previously
18 considered by the Committee on November 4th of 2004 and
19 not listed. Since that consideration, one additional
20 study of chloroform has been identified and is included in
21 the abstracts provided to the Committee.

22 So, in summary, we're seeking your recommendation
23 as to whether the information we've provided to you on
24 THMs merits the development to full hazard identification
25 materials on THMs as a group or on a subset of THMs, such

1 as the chlorinated and brominated THMs as a group or if
2 you wish to consider some or all of the chemicals
3 individually.

4 If you recommend proceeding with a broader group
5 of THMs, we presume you would want us to merge the hazard
6 identification materials we're preparing on BDCM into the
7 larger package on THMs, so that you could make a listing
8 decision encompassing the broader group. If you recommend
9 that we do not proceed with the broader group, we will
10 still bring BDCM before you as an individual chemical for
11 a listing decision, pursuant to your recommendation at
12 last year's meeting.

13 So to summarize, we're asking your advice
14 concerning whether to, one, prepare HIMs for total
15 trihalomethanes or, two, prepare hazard identification
16 materials for certain trihalomethanes, for example, the
17 chlorinated and brominated trihalomethanes. A third
18 option is to prepare hazard identification materials for
19 each of the four trihalomethanes with available data. Or,
20 finally -- the final option is to not proceed with hazard
21 identification materials for any trihalomethane other than
22 BDCM.

23 And with that, I'll turn it over to Carol.

24 CHIEF COUNSEL MONAHAN-CUMMINGS: Good afternoon.
25 The comments you received concerning prioritization of the

1 trihalomethanes raise some legal and scientific issues
2 about whether it would be proper for this Committee to
3 list chemicals as a group or a class or whether you are
4 required to consider and list each chemical individually.

5 While this is not a new issue, I thought it might
6 be helpful for you to clarify the issue prior to your
7 discussion of the next two items on the agenda, as they
8 both relate to classes or groups of chemicals or mixtures.

9 Proposition 65 applies to "chemicals", quote
10 unquote, known to the State to cause cancer or
11 reproductive toxicity. But the law does not provide a
12 specific definition of the word "chemical".

13 OEHHA and the Attorney General's office have
14 interpreted this language not to be limited to individual
15 elements or compounds, but rather to apply to a range of
16 substances, including groups of related chemicals,
17 mixtures of chemicals and substances made up of a variety
18 of different chemicals, so long as the mixture or group of
19 related chemicals meets the requirements for listing.

20 This is consistent with the practices of other
21 authoritative bodies and agencies that identify chemical
22 hazards, such as IARC, NTP, NIOSH and U.S. EPA among
23 others. Accordingly, existing Prop 65 listings include
24 chemical groups and mixtures, such as PCBs, which were
25 listed by this Committee, anabolic steroids, cadmium and

1 cadmium compounds, conjugated estrogens, estrogen
2 steroidal, coke oven emissions, tobacco smoke, oral
3 contraceptives combined, unleaded gasoline (wholly
4 vaporized) and diesel exhaust, for example. And these are
5 all found in Title 27 of the Code of Regulations 27001.

6 Although you are not being asked today to make a
7 listing decision concerning trihalomethanes or particulate
8 matter, which is the next item, if you were to eventually
9 list a group or class of chemicals, such as all
10 trihalomethanes, the substances in the class must be
11 sufficiently well-defined so that the public has
12 reasonable notice as to what is included in the listing.

13 In addition, this Committee would need to
14 conclude that the scientific evidence, even if it comes
15 only from a subset of the chemicals in the group,
16 persuades the Committee that all chemicals within the
17 group are clearly shown to cause reproductive toxicity.

18 In making this determination, the Committee
19 should consider all of the appropriate evidence before it,
20 including the member's scientific judgment as to the
21 similarity of all chemicals and the extent to which
22 results of a study of one or more of the chemicals would
23 apply to other chemicals within that group or class.

24 Similarly, if this Committee were to decide at a
25 future meeting to list a chemical mixture, such as

1 DR. MORAN: The major source in the environment
2 of trihalomethanes are produced mainly as byproducts of
3 water disinfection with halogenated compounds.

4 The most common THMs are bromodichloromethane,
5 BDCM; dibromochloromethane, DBCM; tribromomethane,
6 bromoform; or trichloromethane, commonly known as
7 chloroform.

8 I will present the data for the whole class and
9 separated for the four members from this group.

10 --o0o--

11 DR. MORAN: The epidemiology data research found
12 that six epidemiologic studies reported increased risk of
13 adverse developmental or reproductive outcomes.

14 Also, five studies reported no increased risk
15 were identified, as well as 11 other related studies or
16 meeting presentations.

17 --o0o--

18 DR. MORAN: In the four member -- more common
19 members for this group we found that for BDCM four studies
20 reported increased risk, as well as four studies reporting
21 no increased risk of adverse developmental or reproductive
22 outcomes. And also four related articles or meeting
23 abstracts on BDCM were identified.

24 For DBCM, one study reported increased risk, as
25 well as one study reported no increased risk of adverse

1 outcomes. And six animal-related meeting abstracts were
2 also identified for total trihalomethanes.

3 --o0o--

4 DR. MORAN: For the animal studies for each of
5 the four members of this group that we found information,
6 five studies for BDCM reported increased risk and five
7 studies reported no increased risk of an adverse
8 developmental or reproductive outcomes, as well as nine
9 related articles or meeting abstracts were identified.

10 For DBCM, we have the three studies where no
11 animal studies -- with no effect were identified.

12 For bromoform, two studies reported increased
13 risk and three reported no increased risk of adverse
14 developmental or reproductive outcomes, as well, three
15 related articles or meeting abstracts were identified.

16 For chloroform, we have the three studies
17 reported increased risk of adverse developmental or
18 reproductive outcomes and one related article or meeting
19 abstract was also identified.

20 --o0o--

21 DR. MORAN: The most common effect in the animal
22 studies for these chemicals, in rats we have this
23 fetotoxic response; there is developmental toxicity -- oh,
24 I didn't press the slide -- thank you. Fetotoxic
25 response; developmental toxicity; pregnancy loss; and also

1 resorption in rats. Testicular histopathology and sperm
2 parameters also were found as a common effect. Decreased
3 serum progesterone and luteinizing hormone (LH) levels in
4 vivo were altered and disruption of the LH secretion and
5 disruption of the corpus luteum ability to respond to LH
6 among the effects of THM.

7 --oOo--

8 DR. MORAN: And the last slide is just a summary
9 table that was created with the intent of clarifying how
10 there was the distribution of the abstracts found. So we
11 have it separated by categories. The human studies and
12 animal studies reporting high increase, no increase or the
13 animal studies in positive or negative. And to your
14 right, we have several columns where THMs and the four
15 members of this group with a number of particular
16 abstracts for each one.

17 So that pretty much will tell you a little bit of
18 the distribution of the abstracts. I hope that will help
19 recognizing the number of the studies involved.

20 That concludes my presentation.

21 CHAIRPERSON BURK: Thank you. Are there any
22 questions about the presentations?

23 No.

24 Are there any public comments?

25 I guess there are.

1 Okay. We have two. The first one is Rebecca
2 Sutton of the Environmental Working Group.

3 DR. SUTTON: Can you guys hear me?

4 All right. So my name is Dr. Rebecca Sutton.
5 And I'm a senior scientist with Environmental Working
6 Group. I'd like to thank you guys for considering
7 trihalomethanes, because we're very concerned about these
8 chemicals, especially because of the epidemiological data
9 related to spontaneous abortion.

10 We think it makes a lot more sense for you guys
11 to consider these chemicals in aggregate, because that's
12 the way we're exposed to them. So we'd like to recommend
13 that you guys move forward in that direction.

14 Thank you.

15 CHAIRPERSON BURK: Thank you.

16 And the next speaker is Dr. Jay Murray and Dr.
17 Robert Tardiff on behalf of the -- well, you can say the
18 Chlorine Chemistry something.

19 DR. MURRAY: Thank you, Dr. Burk and Committee
20 Members, and good afternoon. I'm Jay Murray. I'm
21 speaking on behalf of the Chlorine Chemistry Division of
22 the American Chemistry Council. So I appreciate why you
23 didn't want to tackle that one.

24 What I'm going to cover are the reasons why you
25 should not prioritize any additional THMs, either

1 you heard about just a few minutes ago from Ms.
2 Monahan-Cummings. And what I'm going to do, I'm going to
3 go through this very quickly.

4 --o0o--

5 DR. MURRAY: This is the language of the statute.
6 And I'll let you read it for yourselves and that's where
7 this issue comes from about whether Prop 65 applies to
8 chemicals or groups of chemicals. But what I want to
9 repeat, and I'll encourage Chief Counsel to correct me if
10 I misstate, but what I heard her say was if you list a
11 group of chemicals, all chemicals in the group would have
12 to be clearly shown. And we're in agreement.

13 --o0o--

14 DR. MURRAY: This was a slide that had the duties
15 and responsibilities, render an opinion as to specific
16 chemicals. You actually saw the same quote earlier this
17 morning, so I'm going to breeze over that one as well.

18 --o0o--

19 DR. MURRAY: The category of THMs is not clearly
20 defined. It was clarified by Dr. Donald that what you are
21 being asked to weigh in on is THM -- the four brominated
22 or chlorinated THMs as a group or individually or
23 combinations of individual THMs. And you just want to be
24 sure if you do anything with THMs, be very clear, because
25 there are over 20 THMs. The brominated and chlorinated

1 THMs are the most common. And that's what most people
2 think of when you talk about THMs. But in the world of
3 chemistry, THMs are trihalomethanes and there are five
4 different halogen groups and so it gets you to more than
5 four chemicals real quick.

6 --o0o--

7 DR. MURRAY: Now, neither prioritizing nor
8 listing THMs as a group is scientifically appropriate.
9 And this was the point about if you list a category, THMs,
10 for purposes of Prop 65, it means that you're determining
11 that each and every THM is clearly shown to cause. And
12 from Dr. Moran's last slide, it was the table of animal
13 studies and human studies, it should be obvious that the
14 data are extremely limited for some of the individual
15 THMs.

16 And the one that I've used as the example here is
17 the DBCM. And I'm just telling you what's in that table.
18 There are no animal studies. There's one positive
19 epidemiologic study, one negative epidemiologic study.
20 The one positive Epi study I'm going to read you the
21 author's conclusions.

22 It says, "These findings suggest that THM
23 exposure..." -- not DBCM exposure, THM exposure... --
24 "...may affect ovarian function and should be confirmed in
25 other studies."

1 So that one Epi study is not going to be enough
2 to meet the prioritization criteria and certainly isn't
3 going to come close to meeting the clearly-shown standard.
4 So you want to be careful about tackling this as THMs as a
5 group, because you're going to have some individual THMs
6 that will miss by a long shot.

7 --o0o--

8 DR. MURRAY: I missed one. How did I do that?
9 There we go.

10 Listing THMs would be unworkable. And there's a
11 real practical problem here. And that is, if you were to
12 list THMs as a group, then there is no NOEL for THMs as a
13 group. We just said there are no animal studies of THMs
14 as a group. And the problem with the Epi studies is it
15 just doesn't lend itself for a dose response, where you
16 can say well here's the NOEL from the epidemiologic
17 studies. And if you don't have a NOEL, there's no way to
18 establish a Maximum Allowable Dose Level under the law.

19 And the consequence is that there's no defense
20 available to say that exposure is below the MADL. And the
21 upshot is that all THM exposures, no matter how small,
22 would require or potentially require a
23 known-to-cause-reproductive-toxicity warning. So the
24 bottom line is THMs, as a group, is unworkable.

25 --o0o--

1 DR. MURRAY: This is my last slide before I turn
2 things over to Dr. Tardiff. Our recommendations are to
3 advise OEHHA that you do not wish to consider the
4 potential group listing of THMs. Simply said, choose
5 Option 4. BDCM and chloroform are off the table. You've
6 already decided by a 4 to 3 vote to go forward on BDCM.
7 Chloroform was evaluated by your committee in 2004. You
8 chose not to list chloroform.

9 So it really only leaves two others. The data
10 just are not there with the two others. Neither of them
11 made it through the recent prioritization process with
12 good reason. There's just not sufficient evidence for
13 them to go through.

14 So, look, no one is telling you to limit the
15 relevant evidence when you consider BDCM. You can look at
16 any evidence you think is potentially relevant. So you're
17 not going to miss anything scientifically. If you want to
18 look at other studies as you look at BDCM to make a
19 decision about whether BDCM is clearly shown to cause,
20 there's nothing that precludes that.

21 So the bottom line is, you know, I urge you not
22 to prioritize any additional THMs, either as a group or
23 individually. Stick to BDCM.

24 Thank you.

25 Questions, before I turn it over to the other

1 speaker?

2 Yes, Dr. Roberts.

3 COMMITTEE MEMBER ROBERTS: I get to turn on my
4 microphone now.

5 (Laughter.)

6 COMMITTEE MEMBER ROBERTS: In the comments
7 submitted by Dr. Tardiff and yourself, and I don't expect
8 you to memorize them, but on page 10, there is a sentence
9 that says, "While Waller et al. 1998 reported a
10 statistically significant increase for spontaneous
11 abortion, Savitz et al. 2005, in a much more sensitive and
12 sophisticated study, found no such association and EPA
13 disqualified the Waller et al. study as a positive
14 finding." Can you elaborate on why the Waller study was
15 disqualified?

16 DR. MURRAY: I tell you, I'm actually going to
17 shift the question to Dr. Tardiff, because we each sent,
18 you know, comments in. And I think the one that you're
19 reading from was actually Dr. Tardiff's question. And
20 he's more up to speed on the epidemiology than I am. So
21 we'll go to the A Team.

22 Thank you.

23 CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me,
24 before Dr. Tardiff speaks, can I just clarify a couple of
25 things based on Dr. Murray's comments.

1 The prioritization procedure that he was
2 referring to is for OEHHA. We developed it for our
3 process to bring chemicals to the Committee. While it's,
4 you know, of interest to you and we've discussed it with
5 you, it's certainly not binding on this Committee at all.
6 You can bring up chemicals as you did at the last meeting
7 and they don't have to meet any of the criteria in the
8 prioritization process. You can decide that you want to
9 look at any chemical that you want to look at. Just so
10 you're clear on that.

11 And also, in terms of the question on the MADL,
12 as you probably know MADLs are not required by the
13 statute. They're something that OEHHA develops and puts
14 out to help people comply with the requirements of the
15 act. And, at least, it's my understanding that even
16 though one MADL may not be able to be developed for a
17 group of chemicals, that we can develop them for chemicals
18 within the group. And so it's not -- it wouldn't be
19 impossible to do that. I just wanted to clarify those two
20 things.

21 DR. DONALD: And if I might add to that. If some
22 subset of THMs was identified by this Committee, we also
23 believe that it's quite feasible that we could develop
24 guidance for considering whether or not a warning had to
25 be provided for mixtures or THMs, rather than individual

1 THMs.

2 COMMITTEE MEMBER KEEN: Can I ask a quick
3 question, since you just raised something that was a
4 little unclear to me.

5 If, hypothetically, we said, yes, we want to look
6 at them as a group, now looking sometime in the distant
7 future, would we then vote on them as individual compounds
8 or vote on them as a group, because that makes a large
9 difference, potentially.

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's one
11 of the choices you have. And that's one of the questions
12 that we're asking you, is do you want them presented to
13 you as individual compounds?

14 COMMITTEE MEMBER KEEN: But, if hypothetically,
15 we said we wanted to see it as a group, when it comes down
16 to the time to vote, can we deconstruct that group or do
17 we, by definition, work on the group?

18 CHIEF COUNSEL MONAHAN-CUMMINGS: You could do
19 either one at that point. You would say, you know, I
20 don't think that we should list these as a group. I think
21 there's only enough evidence for three, one whatever. So,
22 at that point, we can talk about what the different
23 choices might be and how you could frame that. What I had
24 mentioned before is we just want to be clear to the public
25 what category or what chemicals you're referring to when

1 you do the listing so they know. But you can do that at
2 the later point once you see all of the evidence.

3 COMMITTEE MEMBER KEEN: Thank you.

4 DR. MURRAY: May I respond to two quick points.
5 On the prioritization procedure, I was pretty sure that
6 all of you are familiar, this is the one that went into
7 place in 2004 and you are all asked to review. And I
8 certainly didn't mean to imply you are stuck with
9 following that and can't deviate and can't do anything
10 other than that. But I thought it was important for you
11 to note that these other compounds presumably went through
12 that prioritization process and didn't spit out at the
13 end.

14 The other thing I want to comment on was what Dr.
15 Donald just said. And I think it's not so simple to come
16 up with a MADL for THMs as a group. And EPA just tackled
17 this recently in the Stage II Disinfection Byproducts
18 Rule. And I'm going to read you part of the quote. It
19 says, "A combined MCLG..." -- MCLG is Maximum Contaminant
20 Level Goal or limit goal -- level goal, thank you. It's a
21 drinking water goal, like a public health goal in
22 California.

23 And it says, "A combined MCLG for THMs..." -- and
24 they're talking about the four brominated and chlorinated
25 THMs -- quote, "...is not appropriate because the THMs

1 have different modes of action and health endpoints." So
2 I don't think it's going to be that easy to come up with a
3 MADL for THMs as a group.

4 But more importantly, I think what you've got to
5 look at is what the Chief Counsel said. Is if you list
6 THMs as a group, you've got to be sure that every THM in
7 that group has been clearly shown to cause. And I don't
8 think the data is there.

9 Thank you.

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Let me -- I'm
11 sorry to keep doing this, but let me just say again, what
12 I said about listing a group. So if you decided to list a
13 group in order to make a determination that that group is
14 known to cause reproductive toxicity, "The Committee would
15 need to consider all the appropriate evidence before it,
16 including the member's scientific judgment as to the
17 similarity of the chemicals and the extent to which
18 results of a study of one or more of the chemicals would
19 apply to the other chemicals within that group or class."
20 That's different than saying that every single chemical
21 within the group has been individually clearly shown. I
22 mean, if that's the case, then you don't need to list the
23 group.

24 So I just wanted to clarify that, that you can
25 list groups and they have been listed that way, because

1 there's evidence on members of the group that can be
2 applied to the others, based on your own scientific
3 expertise.

4 DR. MURRAY: May I ask a question of
5 clarification?

6 If you list a group, all the members of that
7 group would be treated, for purposes of the law, as if
8 they had been clearly shown to cause. Am I right?

9 CHIEF COUNSEL MONAHAN-CUMMINGS: And that's the
10 finding that they would make, is that the group is known
11 to cause. But what I'm saying is that the evidence can be
12 from members of the group.

13 DR. MURRAY: So you would be able to tell from
14 other members of the group that --

15 CHIEF COUNSEL MONAHAN-CUMMINGS: Maybe they have
16 the same mechanism, they have the same makeup, they have
17 whatever. They have to be similar enough and they would
18 need to understand that. But it's not --

19 DR. MURRAY: So the mode of action would be the
20 same and then, you know --

21 CHIEF COUNSEL MONAHAN-CUMMINGS: Or something
22 like that, right. I'm not going to say exactly the
23 scientific criteria you would use, because I'm not a
24 scientist. But what I'm saying is that you wouldn't have
25 to find every single chemical, whether it's 20 or 100, in

1 a particular group is separately, clearly shown in order
2 to list a group.

3 DR. MURRAY: Thank you.

4 CHAIRPERSON BURK: Before you begin, there's one
5 more question.

6 COMMITTEE MEMBER GOLD: I actually have two
7 questions now, because this partially applies to the next
8 thing that's going to come up. So if chemicals tend to
9 occur together, they might have different mechanisms, but
10 you can't separate them out because they occur together.
11 What are our options in that circumstance?

12 And secondly, do we have a copy of what you read
13 to us, because I would find it helpful to have it in front
14 of me.

15 CHIEF COUNSEL MONAHAN-CUMMINGS: I don't have --
16 I didn't make copies for you, but I can give it to your --
17 it will be in the transcript. But what you're talking
18 about, the question is about a mixture, which is different
19 than a chemical class or group. And what I mentioned to
20 you on the mixtures, which is more related to PMs, but
21 could be considered a mixture in terms of the THMs as
22 well, would be that you would have to conclude that the
23 mixture itself is clearly shown to cause reproductive
24 toxicity. And because the mixtures can vary in their
25 exact composition, you know, they may have different

1 levels of different chemicals or components, the Committee
2 would need to conclude that any variation of the mixture,
3 so long as it still falls within the definition of the
4 mixture that you define, is clearly shown to cause
5 reproductive toxicity.

6 And that conclusion could, once again, be based
7 on studies of the mixture as a whole or individual
8 components within the mixture. Okay. It's like ETS or
9 diesel exhaust or any of those where there's a lot of
10 different things in it and we know that the -- that
11 mixture causes harm, but we may not know every piece of
12 the mixture individually would cause that harm.

13 COMMITTEE MEMBER GOLD: Thank you.

14 Could I just say one thing that probably in
15 post-prandial confusion --

16 (Laughter.)

17 COMMITTEE MEMBER GOLD: -- I may ask you to repeat
18 the options again when we get to the next one.

19 CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, actually
20 we gave them to Dotty so she has those.

21 DR. TARDIFF: Ready to proceed?

22 CHAIRPERSON BURK: Yes, go ahead.

23 DR. TARDIFF: Okay. Dr. Denton, Dr. Burk,
24 members of the DART Committee, thank you very much for the
25 opportunity to address you this afternoon about this

1 subject.

2 I'm going to, in deference to Dr. Roberts, just
3 jump ahead to try to answer her question now rather than
4 for fear that I might forget it a little bit later.

5 The Waller study was a very well done study for
6 that particular period of time. They looked at pregnant
7 women during the course of their pregnancy to see what
8 kind of water they were getting from the different water
9 systems using traditional water data. They used three
10 different water systems within northern California.

11 And it was only out of one water system in which,
12 despite the fact that they were the same levels of
13 exposures from one water system to the other, that they
14 found that there was a statistically significant increase
15 in spontaneous abortions.

16 That study, while well done, was actually
17 replicated several years later by Dr. Savitz in his
18 research group, work that was funded by the Environmental
19 Protection Agency. The improvements that were made was to
20 increase significantly -- first of all, they did another
21 three water supplies with the same kind of underlying
22 brominated and chlorinated substances from the
23 chlorination of drinking water.

24 Then they took about twice as many people in the
25 cohorts as there had occurred in the prior study. They

1 looked at far more refined information about exposure. So
2 they were able, because of EPA's input, able to get much
3 more information than the standard rolling three month
4 averages that were normally available for many of the
5 studies that had been looked at over the past 15 and 20
6 years.

7 And they looked at far more confounders and were
8 able to control for them much more tightly. And the
9 bottom line was that this study was negative. There were
10 not statistically significant findings associated with
11 them. And it was believed that that would actually co-opt
12 or supplant, if you will, the results that had been
13 obtained by Dr. Waller and her team.

14 EPA took a look at that with the Science Advisory
15 Board. And the conclusion was pretty, in a sense, kind of
16 startling. They basically said that it disqualified the
17 Waller study, that this was so much better. That the
18 negative finding was the one in which we should place the
19 greater degree of confidence.

20 And Dr. Savitz even went so far as to say that
21 this issue has been so heavily studied now, not only from
22 his experiments but others, that there needn't be any
23 further epidemiologic investigations associated with those
24 particular endpoints. Again, another unusual outcome.

25 So if I could just return to my script for a

1 moment. And I'll entertain more questions as we go along
2 and finish up.

3 --o0o--

4 DR. TARDIFF: My purpose today is to try to
5 provide you with some help in making your decision about
6 whether to prioritize trihalomethanes as a group. And I
7 do believe that there really isn't any evidence that would
8 suggest that you should prioritize it for the
9 consideration, as a group certainly or even for some of
10 the other individual elements within the four-compound
11 class, because you're already pursuing
12 bromodichloromethane anyway. So that one is somewhat off
13 the table.

14 The evidence that I want to summarize from the
15 submission that we submitted to your group earlier on
16 falls into basically three categories. One is we do have
17 U.S. EPA and WHO who have come out and spoken on this
18 particular issue. They've looked globally at the extent
19 to which there is or is not evidence to support causation.
20 And their conclusions I will read to you in a few moments.

21 Secondly, we've taken a close look at those
22 abstracts and the studies behind the abstracts that were
23 submitted to you for your consideration by the OEHHA staff
24 at your request.

25 And third, we have basically been responsible, my

1 team has, for doing two major reviews, one in 2001 and
2 2006. And then we've taken into account the fact that
3 there have been additional studies since that time. And
4 we want to give you a sense of what the overall evidence
5 suggests in this regard.

6 --o0o--

7 DR. TARDIFF: Okay. So let's, first of all, talk
8 about the abstracts that were provided by OEHHA in the
9 background document.

10 There are actually six epidemiology abstracts
11 that are listed. And I've just highlighted the main
12 features of these. We have the Hwang study, which is the
13 most recent in 2008. It was not significant for three
14 endpoints. But it was significant for one thing, the
15 cluster of all birth defects not isolating any one
16 particular birth defect. It occurred only at the low dose
17 and not at the other two higher doses, which is a very
18 peculiar phenomenon. There was an opportunity to see dose
19 response, if, in fact, the effect were biologically
20 plausible, but none was seen.

21 Other studies have examined this particular issue
22 and there are five of them that found, for the same
23 endpoint, no statistically significant findings. So the
24 weight of evidence for that would really suggest that
25 there really isn't any association between trihalomethanes

1 and these particular outcomes.

2 The Toledano study in 2005 was found to be not
3 significant for a variety of endpoints, because the lower
4 confidence interval was well below one, and, in fact, they
5 were not able to accomplish statistical significance.

6 There were significant findings however for low
7 birth weight and very low birth weight. But the
8 difficulty in interpreting those findings is that the
9 association was really with low socioeconomic status of
10 the cohort that they had. And they were unable to adjust
11 for that in their calculations. So you can't tease apart
12 whether it was trihalomethanes in the drinking water or
13 that it was some other factors within the lifestyle and
14 background of the individuals.

15 And the statistical significance was only in one
16 water supply where the other two were actually negative.
17 And when they tried to combine the results from all three
18 supplies to try to enhance the power of the study, they
19 found that there was no statistical significance
20 associated with that.

21 If you take a look at the larger body of
22 evidence, which I tried to submit in my written comments,
23 you find that overall for low birth weight, there are two
24 positives and five negative studies. So basically the
25 data bounced around and the two positive studies are

1 studies that had been reported so far, we've got now two
2 positives, including the King study and two negatives. So
3 there's no consistent finding of positive associations
4 with these.

5 The Waller study I already described a few
6 moments ago. And basically that one, at this point, is
7 not really in play and is supplanted by the Savitz study.

8 --o0o--

9 DR. TARDIFF: Now, some of the considerations
10 that we brought to bear on evaluating these studies,
11 included the chemical structure of THMs. We've had a lot
12 of experience in the work that we've done over the past
13 decade or more, with structure activity relationships with
14 regards to both reproductive outcomes as well as cancer.

15 And we've looked at those particular structures.
16 And, in fact, I've worked on trihalomethanes, by the way,
17 for 35 years, toxicologically and looked at all the
18 different factors associated with modes of action.

19 These particular structures do not permit one to
20 extrapolate from one compound, let's say, BDCM to the
21 other compounds in the class. Nor does it allow us to say
22 that the other compounds in the class are likely to be
23 reproductive toxicants when the neighboring compound is
24 not.

25 Probably, one of the best illustrations that I

1 DR. TARDIFF: I mentioned earlier that we've got
2 some support for these conclusions from the Environmental
3 Protection Agency in 2006, as part of its activities with
4 the development of drinking water standards. This was in
5 the Stage II DBP rule. And they concluded that a causal
6 link between adverse reproductive health effects and
7 exposure to chlorinated drinking water or DBPs has not
8 been established.

9 Now DBPs -- I'm not sure how much of a background
10 you have. And I apologize if I'm getting into too much
11 detail. But the reality is that chlorination byproducts
12 really span over 200 substances at one time. THMs that
13 have been identified by OEHHA are only four of those.
14 Those four, in some cases, happen to be there at higher
15 concentrations than other substances. But some people
16 incorrectly conclude that they are also the ones with the
17 highest toxic potency. That, in fact, we know not to be
18 true. They're haloacetic acids, such as DCA, which are
19 far more toxic, in some cases, in the reproductive system,
20 I might add, which may send them chasing after something.

21 Secondly, we also know that there are now some
22 chlorinated nitro-organic substances that are produced
23 from chlorine that are also considered chlorination
24 byproducts. And those have a very high degree of toxicity
25 and are now in the process of being investigated more

1 different designs. No statistical association with those.

2 We have eight endpoints in which you can't make a
3 distinction between THMs and chlorination byproducts.

4 Why can't you do that?

5 Well, very simply, because people were doing
6 epidemiology studies as a screening tool. They would
7 basically say, give me a chlorinated drinking water supply
8 and an unchlorinated drinking water supply, probably a
9 groundwater supply. And let's see if there's a difference
10 in morbidity rates or perhaps even mortality rates. And
11 if there is, then there's an opportunity to do some
12 further research to explore what might be the cause of it.

13 Well, those studies exist. They certainly need
14 to be considered. And they basically don't tell us that
15 THMs are likely to cause any kind of reproductive or
16 developmental toxicity.

17 We have three endpoints in which the data are
18 inconsistent, and I mentioned some of those earlier. You
19 have one positive study, no dose response, but then you
20 have other studies in which they're completely negative.
21 And then we have finally one in which a very novel outcome
22 was determined, in which there has been no confirmation,
23 despite a number of other studies able to find it, no
24 replication, no dose response. What is it? It happens to
25 be an anatomical defect in the esophagus. Very unusual.

1 Usually, we're finding, if there's going to be effects,
2 there's skeletal effects or other behavioral effects and
3 the like. And this one has yet to be confirmed in any
4 particular way.

5 So it simply doesn't provide any confidence that
6 we can say that THMs, as a group, produce reproductive or
7 developmental toxicity.

8 There are comprehensive factors that we looked
9 at, which doesn't support prioritization. I wanted you to
10 have a good sense of this is we've taken a look at
11 positive and negative studies and brought them all
12 together, at one point. We've looked at all the major
13 study types. We haven't excluded any from our process.
14 All of the studies combined produce over 40 endpoints that
15 have been looked at, which means that the investigators
16 have been out there beating bushes pretty hard to try to
17 find something that's associated with THMs. We've looked
18 at the quality of the studies. They varied considerably
19 not surprisingly. Some have looked at confounders with a
20 great deal of precision and accuracy, others less so.

21 We've looked for dose response as a measure of
22 internal consistency. And it's been extremely rare that
23 any of that has ever come to the table. We've looked at
24 the way they've statistically analyzed the data. And
25 we've looked also at what kind of criteria we would use

1 So now the question is what do you do about the other two
2 for which there is little or no data.

3 I'd be happy to take your questions.

4 Yes, sir.

5 COMMITTEE MEMBER HOBEL: Sir, you mentioned the
6 U.S. EPA study in 2006, or recommendations, and the WHO in
7 2000?

8 DR. TARDIFF: Indeed, yes.

9 COMMITTEE MEMBER HOBEL: And you failed to
10 mention the Canadian study in 2006. Why didn't you
11 mention that study?

12 DR. TARDIFF: The Canadian -- well, there's a
13 Canadian -- the latest Canadian activity is in 2008. And
14 it's reported, I believe, in my written report to you.
15 That one dealt exclusively with bromodichloromethane. And
16 I'm not sure if that's the same one you're alluding to.

17 COMMITTEE MEMBER HOBEL: Yeah, that's why I'm
18 asking you the question, because they made it very clear
19 they sort of set drinking water guidelines for total THMs
20 to 1,000 micrograms per liter. Yet, when they looked at
21 DBCM, they set it at 16.

22 So why did they take that action? They must have
23 been concerned.

24 DR. TARDIFF: They were then. But the conclusion
25 has been reversed in 2008. I was, in fact, part of the

1 study group a couple of months ago that was up in Ottawa
2 looking at this issue.

3 As I understand it -- I was not part of the 2006
4 review. In 2006, there was, I guess, a matter of urgency
5 that was concerned about the possibility that short-term
6 exposures could lead to reproductive malfunctions, which
7 would include the possibility of developmental toxicity.

8 The evidence -- well, at that time, the
9 precautionary principle, which was originated in Europe,
10 was what probably pushed the conclusion to increase the
11 concern and to set a not-to-exceed limit.

12 In the meeting that we had a couple of months
13 ago, the conclusion was reversed to indicate that there
14 are no associations any longer, and that, in fact, the
15 not-to-exceed concept should no longer be applied to
16 bromodichloromethane.

17 COMMITTEE MEMBER HOBEL: Okay. Thank you.

18 DR. TARDIFF: You may want to revisit
19 bromodichloromethane based on that and other
20 considerations. I don't know.

21 Yes.

22 COMMITTEE MEMBER ROBERTS: The Narotsky paper
23 though from 2006, that used the four trihalomethanes,
24 didn't it?

25 DR. TARDIFF: I'm trying to remember which --

1 that was -- I think that was the in vitro study?

2 COMMITTEE MEMBER ROBERTS: It's on page 48 of our
3 section. It's Effects of Defined Mixtures of
4 Trihalomethanes and Haloacetic Acids on Pregnancy
5 Maintenance and Eye Development Fischer 344 Rats.

6 I believe it's only shown here as an abstract.

7 DR. TARDIFF: Right. I don't think that it was
8 ever published afterwards. And it was a mixture of
9 trihalomethanes and haloacetic acids.

10 COMMITTEE MEMBER ROBERTS: Yes. And I've assumed
11 that his THM --

12 DR. TARDIFF: There was no positive control like
13 -- or no negative control, whichever you want, with THMs,
14 per se, as I recall.

15 The finding suggests that haloacetic acids cause
16 pregnancy loss in the Fischer 344 rats.

17 COMMITTEE MEMBER ROBERTS: Yeah. About half way
18 through -- let me see, they dosed on gestation day 6 to
19 20. It says for the THM-4 mixture, pregnancy loss was
20 seen in 0 of 14, 0 of 25, 11 of 14, and 12 of 13, of the
21 dams at 0, 307, 613 and 925 micromoles per kilogram.

22 I'm sorry. I'll repeat it.

23 It says about part way down through the abstract,
24 for the THM4 mixture, pregnancy loss was seen in 0 of 14,
25 0 of 25, 11 of 14, and 12 of 13 of the dams at 0, 307, 613

1 and 920 micromole per kilogram respectively.

2 DR. TARDIFF: Yeah. What's not apparent in the
3 abstract is the high doses all produce substantial
4 maternal toxicity.

5 The reality is that in all of the animal studies
6 for the individual THMs, invariably people pushed the
7 envelope to try to get some toxicity in the mother. And,
8 of course, they're always examining the fetuses or
9 examining fetal resorption, if they all die.

10 But when you get down to those doses that don't
11 produce maternal toxicity, you don't get any injurious
12 consequence.

13 Yes.

14 COMMITTEE MEMBER HOBEL: Could you explain to us,
15 is there any way to alter the chlorination process so you
16 don't get certain compounds in the mixture? Is that
17 controllable?

18 DR. TARDIFF: No. Well, yes and no. You can do
19 a variety of different kinds of pre-treatments. And if
20 you go to the southeastern part of the United States,
21 where they have a lot of naturally occurring bromine and
22 bromides, you can pre-treat for the reduction -- it's not
23 complete removal -- of the bromides, so that you get fewer
24 brominated and chlorinated species afterwards. That's
25 more than THMs, by the way.

1 The other thing that you can do, when there isn't
2 much of a background of bromine, is reduce the amount of
3 organic material going into the treatment plant prior to
4 chlorination. And, in fact, that's being practiced very
5 actively today. So depending upon what kind of organic
6 materials there are, if it's just humic substances coming
7 out of the river, for example, you can actually use a very
8 strong precipitant and you can actually put an accelerant
9 into that process, so everything precipitates out. You've
10 got, you know, very small amounts of total organic carbon
11 that now can come in contact with the chlorine to produce
12 chlorination byproducts, and so you can reduce them
13 appreciably.

14 Can you change anything like if you wanted to
15 target -- there's a compound called MX, highly potent
16 carcinogen and mutagen, there in small quantities. You
17 want to target getting rid of that, that becomes more
18 difficult. You now have to start playing around with the
19 pH. But when you change the pH, you change a lot of other
20 characteristics that might not be so favorable. If you go
21 too low on the pH side, you start corroding the pipes on
22 the other end. So trying to balance out to get a win-win
23 situation is not easy for the water quality engineers.

24 But EPA has really done a great job, in my view.
25 It's spear-heading ways to engineer out and constantly

1 reduce the level of contamination contaminants that may
2 get into drinking water. And that's what the, you know,
3 the chlorination byproduct rule -- disinfection byproduct
4 rule has been. It's just a steady decline, so that
5 there's less and less of the material and less and less
6 chance that anybody could get injured.

7 Now, at this point, you know, we're down to such
8 low levels in many water supplies, not all. We're
9 probably at the point where the human body has got plenty
10 of detoxification and other defense mechanisms to be able
11 to handle them, even though there are chlorine and bromine
12 species associated with them.

13 COMMITTEE MEMBER HOBEL: Thank you.

14 COMMITTEE MEMBER KEEN: Yeah. Actually, I'm
15 going to make a few observations and then I have a
16 question for Dr. Donald.

17 I'm feeling just -- while I appreciate the
18 presentations we just had, I'm feeling a little
19 uncomfortable, because I get the sense we're being asked
20 to analyze data without seeing the data, so we're getting
21 distillations. An example of that, for example, while the
22 BDC I think clearly we want to look at, you know the idea
23 that we wouldn't want to look at chloroform because in
24 2004 we said we don't think the data is sufficient.

25 I'm reminded that this Committee, at one time,

1 looked at the second-hand smoke data set and said it's
2 insufficient for it to be listed. New data occurred, and
3 then we said, of course it should be listed.

4 Time marches on. So the sheer fact that the
5 Committee previously has said there's insufficient data,
6 in my opinion, should not, in any way, be interpreted as a
7 reason we wouldn't look at it again. The key question is
8 whether or not there has been substantial new data that's
9 emerged, and sometimes that could be a single publication,
10 which was the case with the secondhand smoke.

11 The question to Dr. Donald that I'd like to pose
12 is, what I'm hearing is it could be a significant staff
13 workload associated with trying to assemble the data for
14 these individual compounds. Where clearly we have some
15 reason to suspect there's a level of urgency that we, at
16 least, look at one or two.

17 If, by bundling them together, would that
18 significantly delay the process? I'm not too worried
19 about the bundle after the counsel has informed us that we
20 can deconstruct the list. If when we look at it, you
21 know, whenever at time X and say look, we don't see any
22 real evidence for two or three of these compounds, then
23 frankly many of the arguments I've heard against looking
24 at the class, to me, seem to evaporate.

25 But of much more serious concern is that if by

1 bundling them together, it causes a significant delay
2 because there's simply no resources, which I know OEHHA
3 often times is faced with severe constraints. So to the
4 best you can, if you could give us a little help here,
5 that would be of value, at least to me.

6 DR. DONALD: Well, clearly, there are more
7 studies to be considered if we look at THMs or a subset of
8 THMs than if we look at individual ones. On the other
9 hand, if you asked us to look at all of the individual
10 ones, then the workload would actually probably be higher
11 than it would be to look at them as a group.

12 At this point, we believe we've identified the
13 majority of the studies. We realize there may be other
14 relevant data out there that may come to light, if we
15 prepare hazard identification materials.

16 But I think the short answer to the question is,
17 it probably wouldn't significantly delay the process if
18 you asked us to prepare materials on the group, compared
19 to preparing materials on individual THMs.

20 COMMITTEE MEMBER KEEN: Thank you.

21 CHAIRPERSON BURK: That was a good question. And
22 I kind of observed maybe you two -- I asked Linda and
23 Calvin to take the lead on this, but aren't a lot of
24 studies the same ones and they're just put in these
25 different categories because they looked at more than one

1 of the trihalomethanes. So I'm not looking for work for
2 you, but I'm just saying some of them you might as well do
3 it and it covers several at the same time.

4 Did you have another comment, either of you or
5 any edification here?

6 COMMITTEE MEMBER ROBERTS: I just, in trying to
7 look it over, tried to kind of summarize -- condense it
8 and specifically look at the trihalomethanes data as well
9 as the individuals, and it was a really nice way that this
10 was laid out by OEHHA. And as was shown, there are both
11 positive and negative epidemiology studies and positive
12 and negative animal studies.

13 One of the complications on the human studies, I
14 think, is that the level of exposure is by drinking water
15 and what one person says is high might be 20 micrograms
16 per liter and that might be in another study's low group
17 and their high group might be 75 micrograms per liter.

18 Epidemiology studies tend to have more
19 statistical power if they have larger sample sizes. And
20 so the number of negative studies in there, one of the
21 things I looked at -- and I'm not an epidemiologist -- and
22 the abstracts really didn't go into, you know, confounders
23 and how well those are controlled -- were whether or not
24 the negative studies were the smaller studies and maybe
25 couldn't have picked anything out.

1 That was not particularly the case. The sample
2 sizes went from not being clarified in the abstract to
3 being a couple thousand to, in one case, they said it was
4 in essence 2.6 million birthes in their records. So, some
5 of the negative studies were a large size. They may be
6 completely crummy in terms of their design, but they at
7 least had plenty of material.

8 The biggest group actually had a quote in their
9 abstract that there was little evidence of trihalomethane
10 exposure and birth defects. There were a couple of
11 analyses that came up with birth defects that were
12 statistically significant. One of them was in a
13 meta-analysis for ventricular septal defects in the Hwang
14 study, which is a Taiwanese population.

15 The other one, and I'll mispronounce this, was
16 Nieuwenhuijsen, for VSDs also. And that was in a
17 population of England and Wales. But they said overall
18 when they looked at birth defects, they didn't consider
19 the finding. If where there were positive findings and
20 there are also negatives to these, this positive findings
21 tended to be small birth weight or stillbirth. And those
22 adjusted odds ratios tended to somewhere around 1.1 to
23 1.9. So they're not huge, but they had some. And then
24 they also had the others where the confidence intervals
25 were not different from null.

1 The animal data is kind of interesting. And they
2 did have that one study where the four trihalomethanes
3 were exposed. And they appeared to me, at least from the
4 abstract, to have an appropriate control group. But in
5 that one, they used the Fischer 344 Rat, which is typical
6 for EPA in North Carolina to use, but not too typical for
7 other people to use.

8 But they found with BDCM, the
9 bromodichloromethane, that there is a really strong
10 strain-specific difference in sensitivity. Sprague-Dawley
11 rats don't respond to the full litter resorption for BDCM.
12 Whereas, the Fisher 344's do.

13 They have some mechanistic data that suggests
14 that there's something there in terms of altering
15 progesterone secretion and progesterone seems to rescue
16 it. That's specific to the BDCM, which we're going to see
17 anyway. That hasn't been shown with the trihalomethanes.

18 And I know that one of the slides said that there
19 was testicular histopathology and altered sperm
20 parameters. But the only one I spotted from the abstracts
21 was a change in sperm motility, and that was for the BDCM
22 rather than the trihalomethanes as a group. So it looked
23 to me overall like we could get a lot more data to look at
24 by looking at the trihalomethanes, but not necessarily
25 that we get a clearer picture.

1 (Laughter.)

2 CHAIRPERSON BURK: Yes.

3 COMMITTEE MEMBER JONES: I must admit, I am not
4 for looking at this as a group, but rather looking at it
5 as individuals. And I think there's been plenty of
6 experience, as far as this is concerned, at least in terms
7 of specific categories of medications and their effect on
8 human pregnancy. That it's very appropriate to look at
9 individual drugs within the category, rather than look at
10 the category as a whole in terms of teratogenicity.

11 So I really am against the concept of looking at
12 this as a drug. And, you know, when I reflect back on
13 this prioritization exercise that you and I went through
14 in 2004, and we came up here on three or four occasions
15 and set up this way to prioritize things, we made
16 it -- one of the things that we looked at was you looked
17 at agents that have good human epidemiologic studies
18 first. And we've got some of these agents in here. And
19 it seems to me that by looking at this entire group, we're
20 just going to be spending a lot of time looking at a lot
21 of agents that there is no good data on.

22 So I would say we should be looking at the drug
23 that we -- or the agent that we have already agreed to
24 look at. And I would agree with Carl, we should be
25 looking at chloroform again or at least we should be

1 considering it. And I don't think we should be looking at
2 the other agents in this category.

3 COMMITTEE MEMBER ROBERTS: Yeah, I would agree.
4 Chloroform and the bromodichloromethane, I think, have
5 sufficient data. There wasn't -- we just wouldn't be
6 there with bromoform or DBCM.

7 CHAIRPERSON BURK: Let me review what the choices
8 were here, the four possibilities. Oh, Jay -- well, we're
9 in our discussion phase, but if it's really, really short.

10 DR. MURRAY: Let me tell you what it is and then
11 you decide.

12 I wanted to answer Dr. Keen's question about
13 additional chloroform data and suggest he ask the same
14 question of Dr. Moran who reviewed the data recently. Is
15 that okay? I don't want to be presumptuous.

16 COMMITTEE MEMBER KEEN: Actually, I would almost
17 cut it short. I was saying it's a matter more of
18 principle. If the argument is made the Committee has
19 looked at something in the past and found it's wanting,
20 there's no need to revisit, that is not a correct
21 principle.

22 DR. MURRAY: Right. I agree with you in
23 principle. I'm saying that you don't have the same
24 situation here that you did with ETS.

25 COMMITTEE MEMBER KEEN: We might have a different

1 committee now though, Jay, who might come up with a
2 different decision and keep the same data set.

3 (Laughter.)

4 DR. MURRAY: Well, it is possible. But, you
5 know, if you're trying to set priorities, you want to
6 think about do you really have, you know, enough new
7 information. And my understanding is, in the case of
8 chloroform, you don't, but I was going to suggest you ask
9 Dr. Moran and see if he could answer that question for you
10 as well.

11 Thank you.

12 DR. DONALD: Well, actually to reiterate what I
13 said in my introduction, there is one additional study of
14 chloroform that we've identified that was included in the
15 abstracts that were provided to you.

16 DR. TARDIFF: Can I ask a question. I'm not sure
17 what study you're talking about.

18 DR. MORAN: On page 41 of the abstract summary
19 results, 2004 Lim et al. endocrine.

20 Do you have it?

21 COMMITTEE MEMBER HOBEL: What page is that on?

22 DR. TARDIFF: Page 41.

23 DR. MORAN: Yes, it was the newest abstract that
24 we found. The next one is 1998 and then '83. There were
25 only three.

1 DR. TARDIFF: If I could.

2 That's the one that deals with the whole issue of
3 blood glucose. And they really didn't find any effects.
4 They had postnatal growth problems, but the main
5 hypothesis that they had was, you know, glucose
6 homeostasis was not changed by chloroform treatment at
7 high doses. Yes, it's a chloroform study, but it isn't a
8 positive study.

9 CHIEF COUNSEL MONAHAN-CUMMINGS: This is not the
10 time to have a discussion with Dr. Moran about the study.

11 DR. TARDIFF: Sorry. He reflected it as a
12 positive.

13 COMMITTEE MEMBER WHITE: No, he didn't. He just
14 said it was a new study.

15 CHAIRPERSON BURK: All right. Well, I think we
16 need to make a decision here and I'll review the four
17 possibilities that we will vote on. One would be to
18 prepare hazard identification materials for total
19 trihalomethanes.

20 Number two was to prepare them for certain
21 trihalomethanes, which, as I read it, would be, for
22 example, chlorinated and brominated trihalomethanes, is
23 that what you're saying.

24 Okay, the third one would be for each one of the
25 four trihalomethanes.

1 And the fourth one was not proceed with hazard
2 identification materials other than BDCM.

3 So the fifth one is -- well, that would be
4 certain ones, but two certain ones, right.

5 So, I would -- yeah, I guess that would be a
6 fifth. All right, so we'll make a number five, which
7 would be to proceed with chloroform and, of course,
8 continue with DBCM.

9 All right. So I need to go through each one of
10 these. Is everyone clear on what they are?

11 COMMITTEE MEMBER KEEN: What's unclear to me
12 though is how we vote, because hypothetically I can see
13 my -- I know what my number one choice is, but if I don't
14 get that, I might go for number two.

15 (Laughter.)

16 CHAIRPERSON BURK: Well, you know, that's a good
17 point, because --

18 COMMITTEE MEMBER KEEN: Are we allowed to make --

19 CHAIRPERSON BURK: -- we have five choices. If
20 we each pick one of them, we might not get much of a
21 consensus.

22 COMMITTEE MEMBER KEEN: Would we be allowed to
23 make a motion here or a suggestion?

24 DIRECTOR DENTON: Well, you know, this is not a
25 listing decision where we have to be very prescriptive on

1 the language and exactly what the chemical is. I think
2 the Committee, in whatever form and however you want to
3 take a vote, can give us your advice on what you think
4 would be the best thing to do. And if you want to ignore
5 the outline that we've provided, that would be fine. We
6 just need your clear advice on what the Committee thinks
7 that is the appropriate approach.

8 COMMITTEE MEMBER KEEN: That's great, because
9 that allows me then to make a suggestion. And I would
10 like to propose that we do BDCM and chloroform, those two.
11 Because, as I look at it, the totality of the evidence is
12 most informative in those two cases.

13 CHIEF COUNSEL MONAHAN-CUMMINGS: Excuse me, just
14 to clarify what you're saying. Are you saying separately,
15 but you'd probably want to consider them at the same
16 meeting?

17 COMMITTEE MEMBER KEEN: That's correct, yes.
18 That's just a suggestion for the Committee to ponder.

19 CHIEF COUNSEL MONAHAN-CUMMINGS: No, that's fine.

20 COMMITTEE MEMBER ROBERTS: Would it be possible
21 to vote yes or no on each of those individually? So, in
22 other words, following with what Carl suggested, someone
23 could vote on BDCM yes and chloroform no, if they wished
24 or vice versa.

25 CHAIRPERSON BURK: Yeah. Well, BDCM we don't

1 have to vote on that because it's already there. So what
2 we're really just saying is do you want to add chloroform
3 or do you want to add the whole group or any other
4 individual one?

5 COMMITTEE MEMBER WHITE: I guess my question
6 would be so have we decided not to look at them as a total
7 group? We haven't discussed that part of it. So my
8 recommendation would be that we make that decision and
9 then go from there. I think that would be a more
10 organized way in my brain to consider it.

11 CHAIRPERSON BURK: I'm willing. Is that okay
12 with you?

13 So that's voting on the number one here, so
14 that's the only thing up for consideration right now.

15 So the question is do you advise OEHHA to begin
16 preparation of the hazard identification materials for
17 total trihalomethanes? All those advising yes, please
18 raise your hand.

19 (No hands raised.)

20 CHAIRPERSON BURK: Zero.

21 All those advising no, please raise your hand?

22 (Hands raised.)

23 CHAIRPERSON BURK: So I'm assuming that's going
24 to be the full eight.

25 Now, you feel like -- okay, we've got that one

1 out of the way. And now can we proceed to Carl's motion.
2 And that one would be, do you advise OEHHA to proceed with
3 BDCM, and, in addition, chloroform? All those advising
4 yes, please raise your hand?

5 (Hands raised.)

6 CHAIRPERSON BURK: So I see six.

7 And no?

8 (Hands raised.)

9 CHAIRPERSON BURK: Two, okay.

10 Is there any other thing you two would want us to
11 vote on? This is not a certain number carries. It's just
12 a recommendation. But, at this point, I see it 6 to 2 to
13 continue with BDCM plus revisit chloroform.

14 All right.

15 Are you okay?

16 THE COURT REPORTER: I could use a break.

17 CHAIRPERSON BURK: How long do you want?

18 THE COURT REPORTER: Ten minutes.

19 CHAIRPERSON BURK: Ten-minute break. Okay, ten
20 minutes.

21 (Thereupon a recess was taken.)

22 CHAIRPERSON BURK: Well, in the interests of some
23 people that have flights back to southern California,
24 let's reconvene.

25 And the next chemical to consider, is the

1 prioritization of Particulate Matter. And, again, we have
2 Dr. Francisco Moran, and, again, I assume we have Dr. Jim
3 Donald to start off.

4 (Thereupon an overhead presentation was
5 Presented as follows.)

6 DR. DONALD: Yes, again, brief introductory
7 remarks.

8 During the Committee's discussion of sulfur
9 dioxide at the last meeting, it was noted that sulfur
10 dioxide commonly co-occurs with particulate matter as
11 components of air pollution. The Committee requested that
12 we prepare prioritization materials on particulate matter
13 and Dr. Moran will, in a moment, present a brief overview
14 on these materials.

15 Once again, since there is substantial overlap
16 between the data sets for sulfur dioxide and particulate
17 matter, and since the epidemiological screen was met for
18 sulfur dioxide, the screen has not been reapplied to this
19 data set.

20 Also, OEHHA is currently proceeding with the
21 development of hazard identification materials for sulfur
22 dioxide and has published a request for relevant
23 information for inclusion in the hazard identification
24 materials.

25 But specifically we're seeking your

1 increased risk of adverse developmental or reproductive
2 outcomes; four meeting abstracts reporting increased risk
3 of adverse developmental or reproductive outcomes were
4 also identified; four epidemiologic studies reporting no
5 increased risk of developmental or reproductive outcomes
6 were identified; and 12 related studies were also found.

7 --o0o--

8 DR. MORAN: Particulate matter epidemiologic
9 effects summarized as low birth weight in both pre- and
10 term-born infants; intrauterine growth retardation; and
11 pre-term birth.

12 --o0o--

13 DR. MORAN: In the animal data search we found
14 that 11 animal studies reporting reproductive or
15 developmental toxicity were identified. Also, two studies
16 reporting no reproductive or developmental toxicity, as
17 well as three related articles were identified.

18 --o0o--

19 DR. MORAN: Among the particulate matter animal
20 effects, we have found that in rats it suppresses
21 testicular function, especially spermatogenesis and sperm
22 motility. In mice it can influence the glutathione
23 oxidation deoxidation system, GSH, and cause DNA damage in
24 male reproductive system and may also affect development
25 of the oocyte.

1 which -- spatial distribution of PM2.5 and PM10 are often
2 similar, because PM2.5 is such a large fraction of PM10.

3 And PM2.5 particles can penetrate in the
4 inner-most portions of the lung. And a fraction of them
5 can cross the lung epithelially and reach the blood
6 circulation.

7 So fine particles are of concern when they occur
8 in combination with other chemicals, such as nonorganic
9 compounds, like sulfur dioxide, nitrous dioxide and
10 certain metals, elemental carbon, carbon monoxide and
11 organic species, including polycyclic aromatic
12 hydrocarbons. And several biologic mechanisms have been
13 suggested as to how they might lead to intrauterine growth
14 retardation, such as hypoxia, reduced maternal placental
15 blood flow, inflammatory process, genetic and endocrine
16 disruption and so forth.

17 So, as described, there were 30 epidemiologic
18 studies showing a positive relation with particulate
19 matter to adverse developmental and reproductive outcomes,
20 along with four meeting abstracts. Four additional
21 epidemiologic studies showed no increased risk, two of
22 which were median abstracts and 11 animal studies showing
23 relation of PM to reproductive and developmental toxicity
24 were identified, in addition to the two showing no
25 effects.

1 Most of the studies examined PM10, but several
2 examined smaller particles, PM2.5. Most of the studies
3 examined and found an adverse effect on birth weight as a
4 continuous variable, low birth weight, although the
5 definitions varied, and pre-term birth.

6 A few studies examined intrauterine growth
7 retardation, small for gestational age, birth defects,
8 stillbirths, head circumference and intrauterine
9 mortality.

10 Most of the positive epidemiologic studies
11 reported relatively modest relative risks, but a few
12 showed fairly large effects. Some of the studies assessed
13 personal exposures, but most assess ambient county- or
14 area-level exposures on routine monitoring. Most of the
15 studies adjusted for some confounding factors and were
16 factors that were considered different from study to
17 study.

18 Some of the studies observed dose-response
19 effect. Although most of the studies did not record it in
20 their abstracts, at least they identified that they didn't
21 analyze the data in this way. And some of the studies
22 found adverse reproductive and developmental effects of
23 PM10 independent of other pollutants.

24 So I think based on this, I'd love to hear
25 further discussions from the Committee, but I would be

1 supportive of giving it priority for further
2 investigation.

3 COMMITTEE MEMBER WHITE: I agree. In looking at
4 the -- there was at least three 2004 studies in
5 Pennsylvania and Michigan. And the PM10 and sulfur
6 dioxide were really the pollutants that sort of ferreted
7 out from the others, with respect to low birth weight and
8 pre-term delivery, really taking a look at those. And so
9 we're really looking at this as a mixture of pollutants, I
10 mean.

11 But in examining the studies and reading these
12 abstracts, those two, particularly PM10 and sulfur
13 dioxide, were the two that seemed to have the most, for
14 me, not so much compelling, but to something else to just
15 look at, to look at those two.

16 And then looking at the studies with respect to
17 southern California, because, you know, the Los Angeles
18 area, et cetera, there's a lot of pollutants -- it holds a
19 lot of pollutants. If you've ever lived down there and
20 seen a pair of lungs, you can honestly say that they look
21 like smoker's lungs. But if you can imagine fetuses being
22 exposed to those kinds of pollutants, it would have an
23 impact.

24 And I feel as though, yes, this needs further --
25 we need to take a further look at this, particularly those

1 two, PM10 and sulfur dioxide.

2 CHAIRPERSON BURK: I have just one question,
3 would you want to distinguish between PM10 and PM2.5?
4 Would that be possible or is that --

5 COMMITTEE MEMBER GOLD: I think the literature
6 suggests that they co-occur so much that you probably -- I
7 mean, you could try, but I don't think it's worth focusing
8 on.

9 CHAIRPERSON BURK: Right. So we're talking
10 particulate matter including both of those. And sulfur
11 dioxide is already in the hopper.

12 So is there any other discussion on this?

13 COMMITTEE MEMBER KEEN: If I could just get a
14 clarification. I fully endorse it as well. 2.5, I agree,
15 looks like PM10, but the new actor on the block,
16 nanoparticles, and with the construction of tires, which
17 just this change occurred recently along traffic
18 corridors. The predictions of nanoparticle concentrations
19 are both quite high. Is it the idea that this potential
20 review would include that, because that could be an entire
21 field in itself. And you'd hate to draw either a false
22 positive or false negative. So maybe, just for clarity,
23 if it said it is or is not supposed to include that, that
24 would completely change the scope, I think, of some of the
25 work.

1 COMMITTEE MEMBER GOLD: I would say the materials
2 we received didn't really deal with that so --

3 COMMITTEE MEMBER KEEN: Yeah, I understand that,
4 but that's what I -- before we walk away from it. It is
5 that particulate matter is one that's going to be more and
6 more in the public eye.

7 COMMITTEE MEMBER WHITE: There is a whole
8 literature on that.

9 COMMITTEE MEMBER KEEN: And there's a big
10 literature on experimental animals. So I think that's
11 important just to be aware of that. My sense is that it
12 should be -- that that would be beyond the scope. But
13 before one just kind of blithely makes that assumption as
14 such, just asking for clarification.

15 CHIEF COUNSEL MONAHAN-CUMMINGS: It depends on
16 how you want to define it. I mean, if you think that's
17 important, we can do -- we can include that or we can look
18 at it separately as an additional item for you to
19 consider. But you can define what the group is that you
20 want us to look at in the mixture and look at the data
21 that's available.

22 COMMITTEE MEMBER KEEN: Well, just to give one
23 person's opinion and others can state their opinions. I
24 think it's going to be a very important topic. I think it
25 may be a little premature to address it. And the reason

1 that I brought this up is that I didn't want OEHHA to be
2 suddenly caught in the process saying it's moving so
3 quickly that we need yet two or three more studies,
4 because, I mean, literally when -- typically, under tire
5 construction, they almost had ignored this, and then
6 suddenly it's there.

7 And so it could be a floating target over a
8 period of the next three or four years. And I think it
9 should -- it would stand on its own, but I just like -- I
10 thought it was very important to get it identified one way
11 or the other.

12 So my sense would be, yes, it has to be looked
13 at, but probably the database isn't large enough yet. You
14 can easily draw a false negative based on that.

15 CHIEF COUNSEL MONAHAN-CUMMINGS: Would you want
16 to define this as PM not including the --

17 COMMITTEE MEMBER KEEN: Yeah, there's others who
18 are better versed in this than I am, but that would be my
19 instinct.

20 COMMITTEE MEMBER WHITE: That would be my
21 recommendation as well.

22 CHIEF COUNSEL MONAHAN-CUMMINGS: I don't know
23 whether or not, from a scientific standpoint, you can
24 separate those out, but that's not --

25 DR. ALEXEEFF: Yeah, I think the simplest thing

1 would be for us to bring in the data regarding PM and
2 PM2.5. And you can make a decision on how you want to
3 list it. But I think what you're suggesting is that we
4 not go to the animal literature, that there might exist on
5 nanoparticles and try to figure that out. I think that's
6 what you are saying.

7 COMMITTEE MEMBER KEEN: And that's precisely what
8 I'm suggesting.

9 DR. ALEXEEFF: Yeah. So we can focus on the more
10 typical air pollution issue. And then you can decide if
11 it's PM, PM10, PM2.5.

12 CHAIRPERSON BURK: May I ask a question, too, of
13 Carol. The way that -- the two choices that are put down
14 here are, one, do we want to begin preparation of the
15 materials for particulate matter? And the second one is,
16 do we want to prepare materials for particulate matter and
17 sulfur dioxide together as components of air pollution?

18 So I want to make sure, what's the subtlety,
19 because we already have sulfur dioxide in the works,
20 right?

21 CHIEF COUNSEL MONAHAN-CUMMINGS: I think Jim can
22 answer that.

23 CHAIRPERSON BURK: Can you clarify that?

24 DR. DONALD: Sure. As I mentioned, we will be
25 doing HIM, hazard identification materials, on sulfur

1 dioxide as a discrete gas.

2 The question would be, since many of the studies
3 are essentially of air pollution, as opposed to -- even
4 though in some instances they try and parse out the
5 particulate components of air pollution that are
6 associated with effects. The question would be, do you
7 want us to look only at studies that address particulate
8 matter specifically or would you want us to look at
9 studies where particulate matter and sulfur dioxide were
10 co-components of air pollution.

11 COMMITTEE MEMBER GOLD: I think the problem is
12 that you're not always going to be able to separate them.
13 And so I think we're going to have to ask to broaden that.

14 COMMITTEE MEMBER WHITE: I agree.

15 CHAIRPERSON BURK: All right, Dr. Hobel.

16 COMMITTEE MEMBER HOBEL: A quick question. You
17 know, there's also the issue of ozone as part of air
18 pollution. And a paper was just published that's not
19 listed here from Australia, where they did a very careful
20 surveillance of pregnancies. And they actually monitored
21 fetal growth throughout pregnancy and they identified
22 different timing points where particulate matter played a
23 role later in pregnancy, in terms of its effect on fetal
24 growth. Whereas, ozone had an effect earlier in
25 pregnancy.

1 And it's a reference by -- the first author is
2 Hansen, C.A. Hansen. And I can give you the reference,
3 because it is something that you should add to the list.
4 It was published in Environmental Health Perspectives,
5 Volume 116, number 3, March of 2008.

6 So I think looking at a combination of substances
7 that contribute to pollution would be important.

8 CHAIRPERSON BURK: And how would you phrase that?
9 So you want to broaden this to everything to do with air
10 pollution? I mean, we've already considered carbon
11 monoxide a long time ago and I know there are many other
12 components.

13 COMMITTEE MEMBER HOBEL: Well, the four that I
14 think people are looking at is ozone, particulate matter,
15 sulfur dioxide and carbon monoxide. So those four things.

16 CHAIRPERSON BURK: So what would your --

17 COMMITTEE MEMBER JONES: But these still look
18 like solvents -- the whole solvent story. The more you
19 start adding to this -- so, I mean, if it's possible to
20 separate these things, I would suggest separating them,
21 rather than lump them all into one.

22 CHAIRPERSON BURK: I tend to agree, because I
23 know when we get this, it's just such a massive amount of
24 work to look at everything. And not only -- you know,
25 basically, the sulfur dioxide came out in the screen. And

1 then we just said oh, it's got particulate matter with it
2 a lot and then we added that. But I personally think
3 maybe we should call it quits right there for the moment.
4 Even though ozone would certainly, I'm sure, have plenty
5 of data.

6 So I'm not trying to steer this one way or the
7 other. Should I add that as a thing to vote on?

8 COMMITTEE MEMBER HOBEL: Well, I just mention it
9 because it was an important part of differentiating the
10 timing of the effect on fetal growth. I think this is
11 sort of where oxidative stress -- and it occurs at
12 different points in time during pregnancy, and it can be
13 caused by different components.

14 And if you're going to have oxidative stress
15 occurring at different points in time, you need to be
16 aware of that, because the timing of these events is very,
17 very important.

18 CHAIRPERSON BURK: I think so. I think maybe
19 we'll take a vote on particulate matter. And then if you
20 want to bring up something else, I think we can do that.

21 COMMITTEE MEMBER GOLD: I wonder if I might
22 suggest that the net be set at particulate matter and
23 ozone -- that the net be set at particulate matter and if
24 ozone happens to fall into the net, because it co-occurs,
25 that will enhance our information. But I think if we go

1 off in the direction of looking specifically for ozone, it
2 is going to get huge.

3 CHAIRPERSON BURK: I think so too. So as I
4 understand it, we're going to vote on whether OEHHA should
5 begin preparing hazard identification materials for
6 particulate matter and sulfur dioxide together as
7 components of air pollution. Is that reasonable?

8 So all those advising yes, please raise your
9 hand?

10 (Hands raised.)

11 CHAIRPERSON BURK: Okay. And Linda is
12 abstaining, so that's seven.

13 COMMITTEE MEMBER ROBERTS: Recusing.

14 CHAIRPERSON BURK: Recusing, sorry. One recusal.

15 All right. So did you want to bring up

16 officially the ozone for some future --

17 COMMITTEE MEMBER HOBEL: No, I don't have
18 any -- I just mention it, because I was aware of the
19 literature and it's listed and it plays an important role
20 as I mentioned. So I just want people to be aware of
21 that. And as long as we review the paper and include it,
22 it needs to be in our sight.

23 CHAIRPERSON BURK: Okay.

24 DIRECTOR DENTON: Can I ask for a clarification?

25 We've already got SO2 that we're working on. So now is

1 the Committee advising that we also take a look at PM
2 together with SO2 is that what -- or are you asking us to
3 look at PM separately from SO2? I'm still kind of
4 confused about the vote.

5 CHAIRPERSON BURK: Yeah, I am confused, too. And
6 that's my fault, because we have two different things on
7 here.

8 One was just particulate matter, and the other
9 was particulate matter and sulfur dioxide together. So
10 there's a subtle difference here, because one's already --
11 sulfur dioxide is already done. So are we asking for two
12 separate considerations or were we asking them to be
13 lumped together?

14 I thought what we were voting on was lumping them
15 together.

16 Does that make sense to you? I don't know if
17 that's going to interfere with what you've already started
18 working on and you better tell us, if so.

19 CHIEF COUNSEL MONAHAN-CUMMINGS: The caveat was
20 that sulfur dioxide occurs in other ways besides in air
21 pollution, so we'd still be having a document on sulfur
22 dioxide.

23 But the question was whether you want to just
24 look at PM separately or if you want to look PM and sulfur
25 dioxide together.

1 CHAIRPERSON BURK: Okay. So what we voted on was
2 together in air pollution. Does anyone want to change
3 their mind and just look at particulate matter separately?

4 COMMITTEE MEMBER GOLD: Well, if I could just
5 clarify that though. If we have a paper on PM that
6 doesn't mention the sulfur dioxide, it still ought to fall
7 in the net.

8 CHAIRPERSON BURK: Right. So we probably should
9 have asked for particulate matter as the topic. And then
10 if sulfur dioxide happens to be in there, then that's
11 fine, but we wouldn't miss the papers that were just
12 particulate matter. So perhaps we should revote.

13 (Laughter.)

14 CHAIRPERSON BURK: Now that we're a little
15 clearer. So the option now is, do you advise OEHHA to
16 begin preparation of the hazard identification materials
17 for particulate matter? All those advising yes, please
18 raise your hand?

19 (Hands raised.)

20 CHAIRPERSON BURK: Okay, the same vote seven and
21 one recusal. I'll cross out that other one.

22 All right, moving along. Our next agenda item is
23 update of the Section 27000 list of chemicals, which have
24 not been adequately tested as required. And the staff
25 presentation is by Fran Kammerer.

1 (Thereupon an overhead presentation was
2 Presented as follows.)

3 STAFF COUNSEL KAMMERER: Good afternoon. This
4 afternoon you've been -- all day actually -- looking at
5 perhaps this, which is one list you're all familiar with.
6 And some of you are familiar with another list, which is
7 in Section 27000 of the Act. It used to be in Section
8 14000, but it's been changed.

9 The second list determines that the State publish
10 a list of chemicals that are required to be tested under
11 federal or State law, because they have not been
12 adequately tested.

13 You have a copy in your binder of Section 27000.

14 COMMITTEE MEMBER HOBEL: This is Title 27?

15 STAFF COUNSEL KAMMERER: Yes. No Section 27000.
16 Yes, it is Title 27. All of it is under Title 27. It's
17 been moved from Title 22.

18 This list is a compilation of chemicals that
19 already have been required to be tested by regulations
20 such as FIFRA, which is the Federal Insecticide
21 Rodenticide Act. However, this regulation also says that
22 the State's qualified experts, which is you, must
23 determine that they have not been adequately tested. It's
24 a ministerial duty.

25 They've already been required by law to be

1 currently being shown now.

2 Exhibit B -- next slide, please.

3 --o0o--

4 STAFF COUNSEL KAMMERER: -- and the next few
5 slides will be a continuation of this list, because it's a
6 pretty long list. It's a list of chemicals that have been
7 determined by U.S. EPA and the California Department of
8 Pesticide Regulation to have been sufficiently tested.

9 So as I said, this is a ministerial duty that you
10 must find that they have been adequately -- they have not
11 been adequately tested -- through other agencies'
12 determinations that they have not been adequately tested.

13 So, hopefully, I've made myself clear on this.

14 Are there any questions?

15 (Laughter.)

16 STAFF COUNSEL KAMMERER: Okay. Well, then, Dr.
17 Burk, will read you the voting protocol.

18 CHAIRPERSON BURK: I lost it.

19 COMMITTEE MEMBER ROBERTS: I have one question.
20 Do we vote on this together or do we vote on each one of
21 these lists?

22 STAFF COUNSEL KAMMERER: You will vote on each
23 one. She'll read you the protocol and then you vote.

24 CHAIRPERSON BURK: Yes. There are two votes
25 coming up here. So the first one is, based upon the

1 information you have been provided from U.S. EPA, should
2 the ten chemicals noted on Exhibit A be added to the list
3 of chemicals required by State or federal law to be
4 tested, but which have not been adequately tested as
5 required? All those voting yes, please raise your hand?

6 (Hands Raised.)

7 CHAIRPERSON BURK: That's Exhibit A we're voting
8 on.

9 Okay. Good, I think it's pretty easy, because
10 it's a ministerial function.

11 (Laughter.)

12 CHAIRPERSON BURK: Okay. So that's eight and
13 zero.

14 And then the second one is based on the
15 information you have been provided from U.S. EPA and CDPH,
16 should the chemicals noted on Exhibit B be removed from
17 the list of chemicals required by State or federal law to
18 be tested, but which have not been adequately tested as
19 required? All those voting yes, please raise your hand?

20 (Hands raised.)

21 COMMITTEE MEMBER HOBEL: Could you give us a
22 minute to look at them.

23 CHAIRPERSON BURK: Okay.

24 COMMITTEE MEMBER ROBERTS: Dotty, looking at the
25 list, I think I have to recuse myself from voting on

1 Exhibit B.

2 CHAIRPERSON BURK: Okay. That's fine.

3 COMMITTEE MEMBER GOLD: Have we actually been
4 provided evidence about Exhibit B that the testing has
5 been done?

6 CHIEF COUNSEL MONAHAN-CUMMINGS: We provided you
7 the letter from U.S. EPA and from CDPR that says that
8 these are the chemicals they want added or deleted from
9 the list. So it's basically you're relying on their
10 determination that the testing has not yet been done or
11 that it has been done. It doesn't mean that they haven't
12 been tested at all. It means that they have to be tested
13 to a certain standard that is acceptable to the U.S. EPA
14 or DPR.

15 Just for the Committee's knowledge, I just wanted
16 to let you know that we are going to initiate a process of
17 changing this regulation, so you all don't have to do this
18 and you can just delegate the task to us, because there
19 really isn't a reason for you to spend your time doing it.
20 But right now the law and the regulations say you need to.

21 CHAIRPERSON BURK: Okay. He's had enough time.
22 He's comfortable.

23 (Laughter.)

24 CHAIRPERSON BURK: Okay, so this is Exhibit B. I
25 read that part. So all those voting yes, please raise

1 your hand.

2 (Hands raised.)

3 CHAIRPERSON BURK: And I see seven and one
4 recusal.

5 All right, so that's that.

6 STAFF COUNSEL KAMMERER: Thank you.

7 CHAIRPERSON BURK: Next on the agenda, staff
8 updates --

9 COMMITTEE MEMBER HOBEL: I have a question. May
10 I ask a question?

11 CHAIRPERSON BURK: Please.

12 COMMITTEE MEMBER HOBEL: On the 27000 list, some
13 of them have an asterisk on them and what does that mean?

14 CHIEF COUNSEL MONAHAN-CUMMINGS: Hold on. Let me
15 get the regs.

16 COMMITTEE MEMBER HOBEL: Like acid blue, acid
17 yellow. And then methanol is listed, castor oil. Why are
18 they --

19 CHIEF COUNSEL MONAHAN-CUMMINGS: In the actual
20 regulation some of the chemicals who have an asterisk next
21 to them and there's -- it references to -- claims --
22 claiming that review of this data should not be required.

23 So basically it's saying that someone is claiming
24 that they shouldn't have to review the data -- I mean,
25 that they shouldn't have to present the data. So it's not

1 really germane to the question you just decided about
2 whether or not they should remain on the list or not.
3 It's just additional information for someone who might be
4 referencing this.

5 COMMITTEE MEMBER HOBEL: Okay.

6 CHIEF COUNSEL MONAHAN-CUMMINGS: I'm not sure
7 what value this list has, to be honest.

8 CHAIRPERSON BURK: Are we ready for staff
9 updates?

10 This will be Cynthia Oshita.

11 MS. OSHITA: We're almost done here.

12 Okay. Good afternoon. Since the Committee last
13 met in December of 2007, OEHHA has administratively added
14 ten chemicals to the Prop 65 list. Three of the chemicals
15 were listed as known to cause reproductive toxicity. And
16 they include hexafluoroacetone, nitrous oxide and vinyl
17 cyclohexene.

18 And seven chemicals were added as known to the
19 State to cause cancer, which include dibromoacetic acid,
20 benthiavalicarb-isopropyl, mepanipyrim, pirimicarb,
21 resmethrin, gallium arsenide and oryzalin.

22 And a summary sheet of these latest additions to
23 the Prop 65 list are in your -- and their effective
24 meeting dates are in your meeting materials behind the
25 staff updates tab.

1 In addition to these listings, there are a couple
2 of chemicals that are under consideration for
3 administrative listing. And they include methanol, as a
4 chemical known to the State to cause reproductive
5 toxicity. And the other chemical is 4-methylimidazole, as
6 a chemical known to the State to cause cancer.

7 Also, included in your binders, is a summary of
8 the safe harbor levels that have been adopted this past
9 year. That includes a Maximum Allowable Dose Level for
10 di-n-butyl phthalate, which was effective July 23rd, 2008.
11 And a no-significant-risk-level, which was established for
12 nitromethane effective April 28th, 2008. And for C.I.
13 Direct Blue 218, which was effective September 7th, 2008.

14 DIRECTOR DENTON: Cindy, excuse me. In the
15 binders it says it was effective for the di-n-butyl
16 phthalate July 28th.

17 MS. OSHITA: Oh. I believe it's supposed to be
18 the 23rd and it's the nitromethane that's April 28th.

19 There was also a rule-making package adopting the
20 MADL for di-n-hexyl phthalate. And it's been submitted to
21 the Office of Administrative Law and we await the Office's
22 decision within the next month.

23 Earlier this year in March, OEHHA also issued a
24 Notice of Proposed Rule-Making announcing a proposed NSRL
25 for ethylbenzene. Written comments were received, which

1 we are and will respond to as part of the rule-making
2 process.

3 Thank you.

4 CHAIRPERSON BURK: Thank you. And then we have
5 Carol Monahan-Cummings.

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Right. I'll
7 make this quick, because I know you want to get out of
8 here. But I just wanted to update you on two cases that
9 are pending currently in the California courts.

10 One I believe I mentioned to you last time is a
11 case where Exxon-Mobil Corporation has sued OEHHA and our
12 Director for listing a chemical known as DIDP, diisodecyl
13 phthalate. I don't know if I pronounced that correctly.
14 But in any event, we've administratively listed that under
15 the authoritative bodies mechanism. And they challenged
16 that decision as beyond our authority.

17 In December of last year, the trial court upheld
18 our authority to list the chemical and Exxon has appealed
19 it. The case is fully briefed. And a hearing on the
20 appeal is set for December the 9th -- I'm sorry, December
21 the 11th in Los Angeles. So the next time you meet, we'll
22 have an update on that.

23 The other case I'm not sure if I mentioned to
24 you, because it was pretty new at that time, is called
25 Sierra Club versus Schwarzenegger. A coalition of

1 environmental labor groups that have sued the Governor,
2 the Agency, Dr. Denton and all of the members of the CIC
3 Committee, your sister panel, for failure to list enough
4 chemicals under Prop 65 under the various methods of
5 listing, including the Labor Code mechanism, the
6 Authoritative Body mechanism and the CIC process. They
7 didn't sue you. And they haven't sued over the listing of
8 DART chemicals by you. Although, DART chemicals are
9 covered, you know, under Authoritative Body and Labor Code
10 provisions.

11 That case is in the trial court in Alameda County
12 and is currently in a fairly early stage. We have a
13 motion pending on December the 9th -- that's why I got
14 confused between the two. They're both in the same
15 week -- regarding whether the Court will order us to list
16 92 chemicals that have -- that the plaintiffs believe have
17 been identified under the Labor Code as required to be
18 listed in Prop 65. The rest of the case has not been set
19 yet for trial. We're in the discovery phase on that.

20 Does anybody have any questions on that?

21 Thank you.

22 CHAIRPERSON BURK: Thank you. And then finally,
23 summary of the Committee actions and closing remarks by
24 Dr. Denton.

25 DIRECTOR DENTON: Before I do that, I'd like to

1 have a clarification on what it is that the Committee is
2 recommending us to do about ozone. I didn't quite get
3 clarity on that. And I know that we may go back and
4 scratch our heads exactly what -- if we come across an
5 article, then we include it in the materials? I'm just
6 not quite sure what it is that you'd like to see on that
7 front.

8 COMMITTEE MEMBER HOBEL: Well, I just wanted it
9 to be on the radar screen, because it's listed in this
10 particular paper and it's listed in other papers as part
11 of air pollution. And so it's just something that we
12 should be aware of. I only mentioned it for information
13 purposes, because it's going to come up when we start
14 reviewing other papers.

15 DIRECTOR DENTON: So no real active product that
16 you want to see at this point in time?

17 COMMITTEE MEMBER HOBEL: No.

18 DIRECTOR DENTON: Okay. So with that, I'll
19 summarize the decisions of the Committee today.

20 The Committee decided to list chromium
21 (hexavalent compounds) but not to list chlorpyrifos. They
22 are recommending OEHHA not to prepare hazard
23 identification materials on THMs, but to continue with
24 BDCM and to include chloroform.

25 They also would like to see hazard identification

1 materials on particulate matter and particulate matter and
2 sulfur dioxide together in air pollution.

3 I think that's -- Dotty, you're looking a little
4 quizzical. Is that -- that's maybe a more quicker summary
5 than --

6 CHAIRPERSON BURK: No, no. I just wanted to make
7 sure. That's what we -- okay.

8 I'm still about the particulate matter. I think
9 we reversed ourselves on this.

10 DIRECTOR DENTON: Jim is questioning it, so maybe
11 we ought to take a moment here.

12 DR. DONALD: Yeah, clarify that.

13 CHAIRPERSON BURK: We took a second vote on
14 particulate matter. A separate set of materials.

15 DIRECTOR DENTON: Hazard identification materials
16 on particulate matter and particulate matter and sulfur
17 dioxide?

18 CHAIRPERSON BURK: No.

19 COMMITTEE MEMBER WHITE: Just the particulate
20 matter.

21 CHAIRPERSON BURK: We already have sulfur dioxide
22 in the works. And now we want a separate one on
23 particular matter.

24 DIRECTOR DENTON: Only.

25 CHAIRPERSON BURK: Only, but that encompasses

1 everything about particulate matter and it may overlap in
2 some places.

3 DIRECTOR DENTON: I misunderstood.

4 CHAIRPERSON BURK: But we want to cast a broader
5 net than --

6 DIRECTOR DENTON: See if everybody is awake and
7 still here.

8 DR. DONALD: We know that in looking at
9 particulate matter, they will include some papers that
10 also address sulfur dioxide in the analysis.

11 DIRECTOR DENTON: So let me back up. On the
12 particulate matter item, the Committee is recommending us
13 to develop hazard identification materials on particulate
14 matter.

15 Now, moving on. Of course, I'd like to thank the
16 participants at the meeting today. I'd like to really
17 thank my staff who have spent many, many, many hours,
18 weekends, vacation days working on the documents, which
19 were presented to the Committee today. And so I would
20 like to acknowledge their very hard work. Public service
21 is under assault these days, but we really have just such
22 a superb group of individuals and scientists. And I
23 really do want to acknowledge that so strongly and their
24 support of this Committee.

25 And, also I would like to thank --

1 (Applause.)

2 DIRECTOR DENTON: I would like to thank the
3 Committee for their diligence, for their commitment, for
4 their serious consideration of the matters which come
5 before you. It's always very humbling to be part of this.
6 And so I'd like to thank you all for attending it, for
7 sticking it out and, as always, wishing you, as I always
8 do, a Happy Holidays.

9 (Laughter.)

10 DIRECTOR DENTON: With that, I guess the meeting
11 is adjourned.

12 COMMITTEE MEMBER KEEN: Before we adjourn, I
13 would just like to second, by the members of the panel,
14 that I think that these were not just great reports, but I
15 think this is one of the earliest that we got the reports.
16 We actually had adequate time to review them in detail.
17 And that's not meant as a chastisement for earlier, but to
18 really say that was very much appreciated.

19 (Thereupon the Developmental and
20 Reproductive Toxicant Identification
21 Committee adjourned at 4:25 p.m.)

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1 CERTIFICATE OF REPORTER

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

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

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

15 IN WITNESS WHEREOF, I have hereunto set my hand
16 this 1st day of December, 2008.

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23 JAMES F. PETERS, CSR, RPR

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