MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

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JAMES F. PETERS, CSR, RPR
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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

Mr. Allan Hirsch, Chief Deputy Director

Dr. George Alexeeff, Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

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

Ms. Amy Dunn, Safer Alternatives Assessment and Biomonitoring Section

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

Dr. Ling-Hong Li, Staff Toxicologist, Reproductive Toxicology and Epidemiology Section

Ms. Cynthia Oshita, Proposition 65 Implementation

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

APPEARANCES CONTINUED

ALSO PRESENT

Ms. Sarah Janssen, Natural Resources Defense Council

Mr. Stanley Landfair, McKenna, Long & Aldridge

Ms. Renée Sharp, Environmental Working Group

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PROCEEDINGS

CHIEF DEPUTY DIRECTOR HIRSCH: Okay. I believe everyone on the Panel is here. And OEHHA staff is here, so we will start the meeting. This is the October 21st meeting of the Developmental and Reproductive Toxicant Identification Committee. I'd like to welcome you all here. My name is Allan Hirsh. I'm Chief Deputy Director for the Office of Environmental Health Hazard Assessment.

Our Director, Dr. Joan Denton, normally sits in this seat. Dr. Denton regrets that she cannot be here. She had some personal obligations that require her to be out of the area, and so as Chief Deputy, I guess I'm lucky enough to sit in this seat.

Just quickly here to introduce the Panel members. On my left is Dr. Dorothy Burk, who is Chair of the DART IC. And then going down the line, Dr. Carl Keen, Dr. Ellen Gold, Dr. Calvin Hobel. And then going down the line on my right Dr. Linda Roberts, Dr. Kenneth Jones, Dr. La Donna White and Dr. Hillary Klonoff-Cohen.

So thank you for coming and traveling the distance to be here.

Also, OEHHA staff who are sitting up in front include Dr. George Alexeeff, Dr. Lauren Zeise, Dr. Jim Donald, Carol Monahan-Cummings. And then over on the right side of the room, for most of you, left side for the

Panel, is Amy Dunn and Dr. Poorni Iyer.

So we have a list of agenda items for you. The decision item for the day is going to be consideration of methyl isocyanate as known to cause reproductive toxicity. And then we have several information and discussion items, which include a discussion of the next prioritization data screen. And then Committee meeting procedures and a petition to reconsider the designation of the NTP CERHR as an authoritative body. And then finally after that, our routine items involving staff updates, litigation updates, that kind of thing.

So we'll go through just quickly basic housekeeping items. In the event of an emergency, the audience, it's -- the two exits are behind you and then you would turn to the right and walk down the stairs and walk out of the building here.

For people on the dais, I guess it's a little more complicated. But the best thing to do is to walk out the doorway behind here and follow the corridor to the right, and that will get you to that stairway and out of the building.

Not that we expect anything, but actually today is the Great California Shakeout Day. And there's supposed to be a statewide earthquake drill at exactly 10:21 a.m., so in 11 minutes. I have been told there's

not going to be any alarm here that will interrupt our meeting. But if anyone does go outside or senses people walking around and hearing discussions about earthquakes, it's part of the drill. So there's no reason to get alarmed.

And right. Also, for people in the audience, there is a drinking fountain and restrooms are located out the doors at the back of the room. For people on the dais, there are restrooms and drinking fountains again in the back exit there. And downstairs, there is a lunch shop, if anyone needs to get something to drink or to eat.

So then with that, Carol, did you have some opening comments or should I just turn the meeting over to Dr. Burk.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. I just want to make a couple comments before -- good morning. I just want to make a couple comments before the actual agenda item starts this morning, in terms of your discussion of a particular chemical for possible listing.

So before you start your deliberations today, I wanted to just touch on a couple points and then answer any questions you might have.

I know that many of you are on a number of committees and advisory groups. And generally, this one only meets once a year. Because of that, we have included

in your general materials the guidance that this Committee adopted in 1993 to help them focus and you focus on the information that is most relevant to your decision in the context of Prop 65.

These are criteria that you should be applying to your decision today. You should note that a chemical can be shown to be a developmental or reproductive toxin based on either animal or human evidence. You aren't required to have both.

Also, the guidance can help you to determine the weight of the evidence for or against a listing of a particular chemical. If you page through the document, you'll see that consideration of actual or expected human exposure to the chemical or the effects of any possible warnings for exposures to the chemical are not discussed there. These issues are not relevant to your decision today and neither should be part of your deliberations.

You often receive comments or hear arguments from stakeholders regarding the clearly-shown standard, established in Prop 65. And I know that, at the last meeting in particular, you received a number of comments in that regard.

People may tell you that the decision you're making is a legal decision, but that's not the case. It is a scientific question that can have a legal effect.

Legal standards like "beyond a reasonable doubt" or "preponderance of the evidence" are not standards that you need to apply here. Prop 65 requires that you apply your own scientific judgment to the question whether a given chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive or developmental toxicity.

You were appointed to this Committee by the Governor because you are experts in your fields. Your scientific expertise is what needs to be applied here, and not your knowledge of the law or the economics or any other field.

I also encourage you to take advantage of the OEHHA staff's, scientific staff's expertise and familiarity with the information that will be presented to you today, particularly if something is not clear. You're always welcome to ask questions.

So at this point, are there any questions from the Committee concerning those comments?

Hopefully, all of you did receive the guidance. And I think it was like one of the first tabs in your materials.

Okay, thank you.

CHIEF DEPUTY DIRECTOR HIRSCH: Okay. So with

that, I will turn the meeting over to Dr. Burk.

CHAIRPERSON BURK: Good morning, everyone. Thanks to all the Panel members for coming today. We're all here, so we definitely have a quorum.

And thank you, Carol, for that little reminder of our responsibility.

So the next item on the agenda is consideration of methyl isocyanate as a chemical known to the State to cause reproductive toxicity. And as usual, we start out with staff presentations. And we have Dr. Poorni Iyer and Amy Dunn. I don't know which one of you, but take it away.

(Thereupon an overhead presentation was Presented as follows.)

DR. IYER: Well, so good morning. My name is Poorni Iyer, and I'm a staff toxicologist --

DR. DONALD: Microphone.

DR. IYER: Okay, good morning. My name is Poorni Iyer and I'm a staff toxicologist with the Office of Environmental Health Hazard Assessment. And this morning I'm going to be presenting the evidence on the developmental and reproductive toxicity of methyl isocyanate, also known as MIC. MIC is a highly reactive chemical, which is a carbamylating intermediate, and this is the basis for its use in the manufacture of carbamate

pesticides and other industrial chemicals. It is also found in tobacco smoke and exposure to MIC may also occur --

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DR. IYER: -- following applications of some pesticides that are used in California as it is a breakdown product.

It is a severe pulmonary irritant, and is extremely toxic to humans after acute short-term exposure. Effects of MIC on reproduction and development are based on exposures to humans and livestock Bhopal, India in 1984. And in an attempt to understand the effects of this chemical, animal studies were conducted in laboratory species, the findings of which are going to be presented today.

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DR. IYER: Following inhalation exposure, radiolabelled MIC was distributed throughout all body tissues, but the majority was retained in the lungs with detectable radioactivity in the uterus, placenta, and fetus.

MIC was cleared slowly from the blood within three days. And about 93 to 98 percent of absorbed MIC was shown to be eliminated in the urine within 3 days.

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DR. IYER: As far as the metabolism, the metabolites of MIC include methylamine, dimethylamine, trimethylamine and dimethylurea.

From in vitro data, the fetal toxicity of MIC does not appear to be exerted through the methylamines and is partly independent of maternal toxicity.

It may result from the transfer of MIC across the placenta and interaction with fetal tissues. Also, SMG, a conjugate of methyl isocyanate, MIC, and glutathione, exerted embryotoxic and dysmorphogenic effects and may contribute to systemic toxicity of MIC.

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DR. IYER: Reviewing the non-DART effects. Acute effects include bronchitis and bronchial pneumonia, respiratory tract irritation, difficulty breathing, and eye problems, which include loss of vision, loss of visual acuity, and cataracts, as well as nausea, gastritis, fever and chills.

Animal studies have reported pulmonary edema, upper respiratory tract irritation, respiratory lesions, and weight loss from acute inhalation exposure to MIC. And the LC50 levels in rodents, following a six-hour exposure were in the 6 to 12 ppm range.

Results from in vitro studies indicate that MIC has the capacity to affect chromosome structure, but not

to induce gene mutation. Chromosomal effects by MIC appear not to be dependent on any exogenous source of metabolism.

No studies in animals after chronic exposure to MIC are available. In the studies in which animals were exposed once by inhalation, no tumors were significantly associated with MIC. No other information on the carcinogenic effects of MIC in humans is available

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DR. IYER: Moving on to studies in animals. While there have been anecdotal documentation that a large number of cattle, as well as dogs, cats, and birds were killed at Bhopal, findings from the literature on studies conducted in the laboratory species are being presented today.

The experimental data available on the toxicity of MIC primarily aid in understanding the effect of MIC as a major component in the chemical cloud released in 1984. The studies that were available in the literature were conducted both in mice and rats.

No deaths among the adult mice were observed at the doses administered. The slope of the dose responsive curve for MIC-induced toxicity is quite steep, with exposures of mice to MIC at concentrations slightly higher than 3 ppm resulting in fatalities in studies where such

doses were included.

That's 3 ppm for 6 hours selected for these studies closely approaches the lethal effects in mice -- lethal level in mice.

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DR. IYER: Findings from the data on humans exposed to MIC will be presented later on by my colleague Amy Dunn.

At this point, it must be noted that there are some critical differences between the exposure of animals to MIC in these studies and the accident involving MIC in Bhopal. Some of the people in Bhopal were undoubtedly exposed to much higher concentrations of MIC than were used in these studies.

Another difference between the exposure in humans in Bhopal and the animal experiments is that the animals were exposed to pure MIC vapors, whereas the people were exposed to MIC along with other reaction mixtures from the explosion.

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DR. IYER: As far as the developmental toxicity studies, in animals, six studies reported developmental or reproductive effects, two studies did not report reproductive or developmental toxicity, and there were additional related studies.

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DR. IYER: In the study by Schwetz et al. in 1987, in this study 30 male and female mice group were mated following 4 consecutive days of exposure for 6 hours per day to MIC vapors at 0, 1, or 3 ppm.

Mating trials were conducted during weeks 1, 8 and 17 following exposure. And the females were permitted to deliver their litters, and the pups were observed until 21 days of age.

In this mating trial study, the authors noted that concentrations slightly higher than 6 ppm had caused significant lethality in mice.

As far as the findings, no significant adverse effects were observed in mating trials conducted on male and female mice exposed to MIC vapors, and there was no effect on body weight, demeanor, fertility or litter size.

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DR. IYER: In the same study in what the authors termed the perinatal toxicity study design, here, to evaluate the effects of sublethal concentrations of inhaled MIC on development in mice exposed during gestation, groups of mice were exposed to inhaled vapors of MIC at 0, 1, or 3 ppm for 6 hours a day during the gestation days 14 through 17. The females were permitted to deliver their litters and the pups were observed until

21 days of age. No effect on maternal survival, body weight, demeanor or length of gestation were noted.

Compared to controls, there was an increase in the number of dead pups at birth in both the 1 and 3 ppm MIC groups. There was also increased mortality among the neonates for these dose groups throughout lactation as well. And therefore there was an increased -- there was a significant decrease in neonatal survival with this increased mortality.

No information on the persistence or presence of MIC milk was available.

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DR. IYER: In another study conducted by Varma, et al. in 1987, to simulate the Bhopal incidence, the animals were exposed to MIC vapors only once for 3 hours on a specific day of gestation. Either on gestation day 8 to 2, 6, 9 or 15 ppm or on gestation day 14 to 9 or 15 ppm. And standard teratology procedures were conducted on gestation day 18.

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DR. IYER: MIC vapor was found to be more toxic to the mother on gestation day 14 than on gestation day 8. Exposure to gestation day 14 to MIC at 9 ppm caused higher mortality than exposure on gestation day 8. Suggesting therefore a time specific sensitivity. And whether this

is a reflection of the time of development or the stage of pregnancy it's not quite clear.

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DR. IYER: Also in the study, there was a concentration dependent decrease in body weights of pregnant mice, and relatively selective fetal toxicity. The single exposure of pregnant mice to MIC for 3 hours resulted in a concentration dependent increase in embryo loss at all dose levels of MIC exposure. There was complete resorption in more than 75 percent of animals at 9 and 15 ppm MIC exposure levels. There was an increase in visceral abnormalities and a decrease in fetal and placental weights, as well as fetal skeleton size.

There was a decrease in the length of the mandibles, about 20 percent decrease in length of the mandibles and bones of the extremities. And the observed decrease in length of bones noted in fetuses of MIC exposed mice via inhalation may be indicative the skeletal formation and may support the findings that will be presented later on.

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DR. IYER: Also included in the study by Varma et al., was in addition to inhalation exposure, there was exposure via I.P., or intraperitoneal injection. The author stated that the fetal toxicity of MIC was produced

after I.P. injections, indicating that pulmonary irritation was not essential for toxicity.

Moreover, since hypoxia resulted in a different set of abnormalities, the findings suggest that pulmonary involvement and attendant hypoxia may not be the sole cause of the fetal toxicity of MIC.

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DR. IYER: Moving on to the study by Singh et al. In this study, in the rat, females were exposed prior to mating and standard teratology procedures were conducted on gestation day 20. The rate of resorptions increase in a dose-dependent manner. Also, does-dependent was the decrease in fetal weight. And as far as teratology findings, several anomalies were observed.

However, in this study, individual data were not provided and statistical significance of the findings was also not known.

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DR. IYER: Moving on to other relevant information on developmental toxicity, embryos exposed to MIC vapor, both in utero or in vitro exhibited a concentration-dependent decrease in growth in culture. Exposure to MIC significantly decreased maternal plasma progesterone levels in mice that lost, but not in mice that retained, pregnancy.

And authors from these studies concluded that fetal toxicity of MIC is partly independent of maternal toxicity and may result from the transfer of MIC across the placenta and interaction with fetal tissues.

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DR. IYER: The authors also reported that the results from one definitive study suggest that the fetal toxicity of MIC is not exerted through methylamines, the known metabolites of MIC. However, in other cultured embryo experiments, decrements in crown-rump length, yolk-sac diameter, head length and embryo survival were observed.

Also, exposure of a conceptus in utero resulted in more toxicity than exposure of the gonadal cells prior to mating.

Other commentaries have also concluded that on the whole respiratory complication and the resulting hypoxia were bound to affect fetuses as much it did the mothers.

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DR. IYER: Reviewing the effects on the female reproductive system, MIC vapor resulted in a decrease in body weights of pregnant mice, as well as placental weight. There was a significant dose-dependent increase in the number of implants absorbed. Exposure to MIC

significantly decreased maternal plasma progesterone levels in mice that lost, but not in mice that retained pregnancy.

In the rat, no adverse effects on reproduction were noted after exposure of female rats to MIC 70 days prior the mating.

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DR. IYER: Reviewing the effects on the male reproductive system. There was a transient decrease in mating performance of MIC exposed male mice cohabited with untreated females. There was a loss of spermatozoa and degenerative changes in spermatocytes were observed.

No effect on the incidence or distribution of resorptions in the pregnant females mated to the treated males. And the authors reported that there was no evidence of a dominant lethal effect in exposed male mice. And the data are presented in the HIM materials which show that there is a trend on week 2. However, statistical significance was not reported.

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DR. IYER: Summarizing the animal data. For developmental effects, the animal data suggests an effect on fetal loss subsequent to in utero exposure; a significant decrease in neonatal survival; adverse skeletal effects, including a shortening of bones.

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DR. IYER: As far as female reproductive system, there was a decrease in placental weight, significant dose-dependent increase in the number of implants absorbed.

And as far as male reproductive system, there was a reduction in mating performance and loss of spermatozoa, which was transient.

And now my colleague Amy Dunn will be presenting the evidence in humans.

(Thereupon an overhead presentation was Presented as follows.)

MS. DUNN: Good morning. Does this sound okay?

We turn now to the human data on methyl isocyanate developmental and reproductive toxicity.

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MS. DUNN: This slide summarizes what I'll cover. First, I'll describe the exposure to methyl isocyanate that occurred in Bhopal and forms the basis for the human studies. Then I will review the human data available on developmental toxicity and female and male reproductive toxicity. Finally, I will summarize the data available from both human and animal studies in an integrative manner.

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MS. DUNN: In December 1984, there was an accidental release of methyl isocyanate in Bhopal, India. The accident occurred at a pesticide manufacturing plant operated by Union Carbide. From a large tank approximately 30 metric tons of methyl isocyanate escaped over a one hour period. The gas spread like a cloud over the densely populated area, and an atmospheric inversion kept the cloud in place for several hours.

Approximately 100,000 people were severely or moderately exposed and more than 400,000 people were mildly exposed. In the first three days, somewhere between 2,500 and 5,000 people died from the exposure.

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MS. DUNN: The mean concentration of methyl isocyanate in the gas cloud was estimated as 27 parts per million. This is only an average. Some people were exposed to much higher levels. As a comparison, the occupational health threshold limit value, or TLV, is .02 parts per million, 1,000 times lower than the estimated average exposure.

As was mentioned earlier, there is a possibility that additional contaminants may have been present in the gas cloud. No measurements were made during the accident. However, given the extremely high volume of methyl isocyanate that was released to the atmosphere, it's

reasonable to assume that the predominant, if not sole exposure, faced by those who encountered the gas cloud was methyl isocyanate.

Individuals were exposed via the respiratory tract, skin, and through ingestion of their saliva. Because the accident happened during the middle of the night, many people were sleeping, and some awoke in a panic and ran trying to escape the extreme irritant effects of methyl isocyanate. This activity increased their exposure to the chemical.

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MS. DUNN: A number of studies are available on developmental effects associated with methyl isocyanate exposure due to the Bhopal disaster. Eight studies of pregnancy outcome and neonatal mortality were identified and are shown on this slide.

Two studies of effects after birth related to in utero exposure were also identified, and I will describe those in a few moments.

Of the 8 studies of pregnancy outcome and neonatal mortality, all found that those in the affected areas had elevated pregnancy losses. The two earliest reports by Shilotri et al. and by Varma 1987, as well as the investigation reported by Dhara and Dhara lacked robust controls or had limited reporting.

The study by Kanhere was a somewhat different type of study that looked at human placentas. These investigators found that the placenta from full-term pregnancies in gas-exposed women had significantly lower mean weight than those from unexposed women. These investigators reported a higher percentage of negative histological changes, such as calcification in the placenta of exposed women.

Four of the pregnancy outcome studies calculated specific rates or provided comparison rates in control populations. These are indicated with an asterisk on this slide.

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MS. DUNN: This table shows the four studies that calculated specific rates. The study by Bhandari et al. is the most robust study in terms of the type of information collected and published. Bhandari et al. reported the difference in spontaneous abortion rates between women in the affected and control areas was statistically significant at the .001 level.

For the other studies, results of statistical analyses comparing rates of early loss in women from the affected versus control areas are not reported by study authors. You can see, however, that the increased rates in affected women in the other studies are comparable to

or greater than those seen in the Bhandari study.

Kapoor found rates of spontaneous abortion, for example, in exposed women that were very similar to those found by Bhandari.

Varma 1991 focused on a very heavily exposed population that was living within one kilometer of the plant from which the methyl isocyanate gas escaped.

He found an extremely high rate of spontaneous abortion, 59 percent. This rate is comparable to those -- to that seen for the most heavily exposed group in the study by the Indian Council for Medical Research, which found 52 percent of those living in the severely affected area suffered an early pregnancy loss.

These investigators found decreasing rates of spontaneous abortion with increasing exposure as identified by area of residence: moderately affected, 39 percent; mildly affected, 20 percent; and 8 percent in the controls.

In this study, the differences in the rates in each of the affected areas compared to the controls were all highly statistically significant as calculated by OEHHA. The rates of spontaneous abortion in control populations in all these studies are similar ranging from 6 to 10 percent.

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MS. DUNN: This chart shows the follow up for five years after the gas disaster -- the results of the follow up for five years after the gas disaster by the Indian Council for Medical Research.

These investigators recorded spontaneous abortion rates in women in Bhopal. The different color lines on the chart correspond to women from the different areas distinguished by the severity of the effects suffered in that area during the gas disaster, as a surrogate for the exposure level.

You can see here on the left side of the graph, immediately following the gas disaster in 1984, there was a widespread in the rates that appears to be related to area of residence. We saw those numbers in the table on the last slide, 52 percent in the severely affected area.

In subsequent years, the rates in the affected areas continued to be elevated in relation to the control area with some variation from year to year that may be related to the somewhat inconsistent follow-up carried out by these investigators over the five-year period.

However, the rates in the areas severely or moderately affected by the gas continued to be significantly higher than rates in the control area, throughout the five years of follow up, with a single exception of the rate in the moderately affected area in

1988.

These findings are consistent with reports in another one of the studies of spontaneous abortion discussed in the previous slide. Kapoor 1991 also found that women in the affected area continued to experience higher rates of pregnancy loss than women in the control area in the years following the accident.

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MS. DUNN: With regard to neonatal mortality, two studies reported rates for those affected by the gas disaster.

Varma 1987 reported that neonatal mortality in those exposed -- in those born to exposed mothers was 14.2 percent, compared to up to three percent in controls. The study by Bhandari et al. found that both perinatal and neonatal mortality were significantly elevated at the .001 level in those exposed.

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MS. DUNN: As I mentioned earlier, there are two studies I'll describe of postnatal manifestations of in utero exposure to methyl isocyanate. The first, Ranjan et al. examined physical growth measured during adolescence in those exposed in utero. They used a model with multiple covariants including age, parental height and weight and family's socioeconomic status.

These investigators found significantly decreased size for males exposed in utero, in terms of weight, height, mid-arm circumference and head circumference. This study, while limited by the small number of subjects exposed in utero was well controlled for potential confounders.

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MS. DUNN: In a study published recently, Mishra et al. examined immune function in individuals exposed in utero during the first trimester of pregnancy. These measurements were made when the individuals were age 24 years. All of the blood parameters listed on the slide were significantly elevated at the .001 level in those exposed. The authors conclude that in utero exposure to methyl isocyanate during the first trimester, "has caused a persistently hyper-responsive cellular and humoral immune state in affected individuals". They intend to follow exposed individuals to identify clinical implications, if any, of this immune hyper-responsiveness.

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MS. DUNN: Turning now to the evidence of female reproductive toxicity, there are two studies of menstrual dysfunction and gynecological complaints not related to pregnancy outcome. Shilotri et al. examined gynecological complaints in exposed women soon after the accident and

reported finding cervical inflammation and dysplasia that led them to call for periodic follow up regarding potential carcinogenesis.

The brief report on the Medico Friend Circle study reported, reported by Dhara and Dhara, notes alteration in menstrual cycle duration in women exposed to the gas cloud without comparison to an unexposed population.

Of the three relatively recent review articles, two, Varma 2005 and Mishra et al., include anecdotal reports of, "menstrual problems in girls affected by the gas".

The third review article, Sharma 2005, notes that those exposed to methyl isocyanate "continue to suffer from reproductive and other disorders".

With regard to the pregnancy outcome studies described above, the increased rates of spontaneous abortions seen in these studies may reflect female reproductive toxicity, as well as or instead of direct effects on the fetus.

In particular, the finding of continued increased rates of spontaneous abortion in the two studies that followed women for years after the gas exposure both found that these women continued to experience higher rates of spontaneous abortion.

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MS. DUNN: I've included this graph again as a reminder of the spontaneous abortion rates observed in women in the study by the Indian Council for Medical Research. The women from the affected areas continued to have elevated rates throughout the five years they were followed.

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MS. DUNN: With regard to male reproductive effects, two studies are available which examined possible effects on spermatogenesis. Both of these studies were relatively small and had other design limitations. Neither study found significant differences in sperm counts or other parameters measured. Both studies collected samples too long after the exposure to detect any transient effect.

There was not adequate control for potential confounding due to tobacco use or alcohol consumption, nor was there any definitive period -- or definite period of abstinence prior to semen collection.

With these small sample numbers being used to measure parameters with large variations, the only possible effect that might have been detected would have been a dramatic permanent effect.

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MS. DUNN: In summary of the human data on methyl isocyanate, the findings all come from studies of people exposed to the gas disaster in Bhopal. There are multiple studies showing adverse impacts on pregnancy outcome. And it appears these affects persisted over years following the accident.

There are two studies showing postnatal effects seen in those exposed in utero, including effects on physical growth and on immune function. Clinicians in the field continued to report findings of gynecological problems in exposed women in Bhopal. And neither of the on two studies available on male reproductive toxicity was adequate to identify an effect.

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MS. DUNN: Finally, bringing together the findings of the animal and human studies of methyl isocyanate, I will briefly summarize the evidence.

With regard to developmental toxicity, both animal and human studies demonstrate an effect on survival of the exposed conceptus. This is seen in terms of fetal losses and resorptions in animal studies and increased rates of spontaneous abortion in human studies.

Elevated rates of neonatal mortality were also seen in both animal and human studies. There is also evidence of effects on growth postnatally, with a

shortening of bones seen in animal studies and a shorter stature seen in human studies.

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MS. DUNN: The increased rates of fetal loss and neonatal mortality, seen in both animal and human studies, may also possibly reflect an effect on female reproductive toxicity. In particular, the continued elevated rates of spontaneous abortion seen in years following the exposure in Bhopal may indicate an effect that is mediated by female reproductive toxicity.

In addition, both animal and human studies found decreases in placental weight in those exposed compared to controls.

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MS. DUNN: For male reproductive effects, the animal data show a reversible decrease in mating performance and loss of spermatozoa with no dominant lethal effects. The available human studies were not adequate for detection of a transient effect on spermatogenesis.

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MS. DUNN: This concludes our presentations on methyl isocyanate developmental and reproductive toxicity. We would be glad to respond to any questions you may have.

CHAIRPERSON BURK: Do any of the Committee

members have questions at this time?

Ken.

COMMITTEE MEMBER JONES: Thanks, Dotty. Can you say something about how much use there is of this agent in California. I know you mentioned Kern County, but elsewhere in California, and how much of a problem it is here?

DR. IYER: Well, it is a breakdown product of pesticides that are used in California. And so there's a chance of exposure. And its present in the HIM I've kind of talked about how much it might actually -- you know, how relevant it is.

COMMITTEE MEMBER JONES: Okay.

DR. IYER: And it's also present in tobacco smoke.

CHAIRPERSON BURK: Other questions?

That doesn't preclude you from asking later as we go through this.

I don't have any cards, so I'm assuming -- are there any public comments?

Oh, well, would you bring your card up, please.

CHIEF DEPUTY DIRECTOR HIRSCH: There were no written comments that were received during the written comment period.

MS. SHARP: Hi. I'm Renée Sharp. I'm the

California Director of the Environmental Working Group. And I just wanted to make a very short comment, which is I cannot imagine a situation that is more cut and dried than this one.

It is unfortunate that we -- that such a disaster, which had grave impacts on human health, would provide us the opportunity to have such cut and dried data. But since we have it, I think it's just -- I just kind of want to make the point that, you know, you have a situation here where there is clear human evidence and we know there's exposure in California. So I don't think there should be any question about listing.

Thank you.

CHAIRPERSON BURK: Thank you. That was Renée Sharp, Environmental Working Group.

And this is Sarah Janssen, NRDC.

MS. JANSSEN: That's right. Good morning. My comments will also be short. I agree with Renée Sharp from EWG that this is a pretty cut and dried case for listing. And I also just wanted to reiterate that I was quite struck from the information in the first presentation on animal studies about the differing effects depending on the timing of exposure during gestation. And I think this is another example of many of the chemicals that come before this committee where this is the case,

where fetal exposures have long-term implications and where the timing of exposure is really important.

So again, I urge you to support listing this chemical and thank you for your attention.

CHAIRPERSON BURK: Okay, thank you. And I assume that's the end of the public comments.

So we'll begin our discussion here. I would say maybe we should -- well, first, let me say, I didn't assign anybody anything this time, which I know is perhaps not unexpected, but I thought that it was a fairly digestible Hazard Identification Materials that we received, so that we should each feel free to comment on our areas of expertise. And I hope you will all chime in.

So I'd like to start with developmental toxicity, cause I think -- let's start with the human studies and see. If we can possibly use our guidance this time and speak in terms of sufficiency of evidence, human versus animal, and so forth, and try to mention specific endpoints, I think we can discuss this fairly judiciously. I use that term loosely. Remember, it's not a legal hearing. This is your scientific judgment.

All right. Could I start by asking Dr. Klonoff-Cohen just to comment on the epidemiology studies, since that I know is your area of expertise.

COMMITTEE MEMBER KLONOFF-COHEN: I actually

thought that the summary that was provided was really thorough and very well done. And I don't have much to add, to be honest.

I think regardless of what the limitations were in each of the studies. And there were certainly numerous limitations in every study, the striking thing is, in fact, that there were consistent findings across the studies. I mean, such as -- and you demonstrated this very nicely, in terms of have you looked at the spontaneous abortions in the four studies, that each and every one of them had limitations, yet they all found things. And I'm talking about the Bhandari, Kapoor, Varma and ICMR study.

If you go onto the follow-up studies after the gas leak, the same thing in terms of -- and you covered all this very nicely -- in terms of the Kapoor study and the ICMR study, which is the one that had the graph where you showed the different colors, once again supported it.

I think that if we move on -- do you want me to move on or --

CHAIRPERSON BURK: No, let's stick with those right now, and try to do this kind of systematically.

COMMITTEE MEMBER KLONOFF-COHEN: Yeah. Do you want to --

CHAIRPERSON BURK: Would you say - let's put out

a motion almost - that the human evidence would be sufficient in this case to support listing?

I'm trying to work from the guidance. We'll talk about the animal as a back-up to that.

COMMITTEE MEMBER KLONOFF-COHEN: Right. I think, as I said before, I mean, each and every one of the studies -- certainly their designs were somewhat flawed in certain ways. And yet, I think that the results all complemented one another and all showed that there was an effect. So I would think so, yeah.

CHAIRPERSON BURK: Okay. Does anyone agree or disagree with that?

I see Dr. White nodding her head. So we'll go down the row here.

COMMITTEE MEMBER WHITE: Yes, definitely.

CHAIRPERSON BURK: All right. So we get agreement. Are there any other discussion about the human studies?

Let's at least look at the animal studies as to whether they support the findings.

Dr. Roberts.

COMMITTEE MEMBER ROBERTS: Yes. Let me flip to the page again. I think it supports it for the percent dead. I'm looking at page 33.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Roberts, I

don't think we can hear you. If you could maybe put the mic up closer and make sure it's on.

COMMITTEE MEMBER ROBERTS: It's got a green light. It has a green light, so I hope it means it's on.

CHAIRPERSON BURK: Yeah. And you just have to put your mouth really close to the microphone.

COMMITTEE MEMBER ROBERTS: The animal data, especially from the Schwetz study, seems to support also by having an increase -- a dose-response type of increase in the offspring -- dead offspring, stillborns, or early mortality.

I'm not quite as convinced by the -- it looks like it has an effect upon fetal growth also. I'm not convinced I would call it necessarily specific or selective fetal toxicity, because much of what I see in the bones being shortened is what I would expect to see in a smaller fetus. But there are several other findings where ribs were absent that would be not simply a fetal growth retardation.

CHAIRPERSON BURK: Okay. Any other comments about the animal studies?

What I'm hearing is you feel it supports the weight of evidence?

COMMITTEE MEMBER ROBERTS: Yes.

CHAIRPERSON BURK: Is there any discussion of the

maternal toxicity issue, which is something that comes up periodically in our discussions. I mean, this is a situation that is a little different than our usual sort of chronic exposures to things. Most of the designs of the study seem to be more of an acute exposure, which would mimic the Bhopal incident. But I don't know how that exactly translates into, you know, a lower level of more chronic exposure.

COMMITTEE MEMBER KEEN: Yeah. That's probably the only thing that's a -- concern is not quite the right word, but sorting out is there direct teratogenic effects of the methyl isocyanate versus maternal toxicity? I don't think an overwhelmingly strong case is made. There are a few references in the experimental animal literature that says food intake wasn't affected, but the data aren't shown, and which sometimes causes a mild bit of concern, because in this case, it may have only been a single day. One day of severe food restrictions, enough to cause some of the delayed skeletal ossification. That's very clear from experimental animal literature. So one is left with the situation of having to make some assumptions.

With that said, the human data, particularly the seeming persistence of reproductive complications past the acute time period would argue that there are some effects above and beyond maternal toxicity.

CHAIRPERSON BURK: Good, thanks. Any other comments on developmental toxicity?

COMMITTEE MEMBER JONES: Yeah, just for my edification. Is there precedence for shortening of bones in an animal model correlating with short stature in humans?

CHAIRPERSON BURK: That's a good question. And I found that the most intriguing, particularly in the human study it was just in the boys.

COMMITTEE MEMBER JONES: In the boys, right.

CHAIRPERSON BURK: You know --

COMMITTEE MEMBER JONES: Are we suggesting that -- I don't think we are suggesting or anybody is suggesting this is a skeletal dysplasia that's occurring in males. So I'm wondering how that short bones in any way is consistent with short stature in -- postnatal short stature in boys, humans.

COMMITTEE MEMBER ROBERTS: I don't know of a correlation. I was wondering with only three males in the exposed group, how strong that data actually would be, even with statistical significance.

CHAIRPERSON BURK: Yeah, that's certainly an issue. The numbers are very small, but did staff have a comment on this?

MS. DUNN: Well, it might be of interest to the

Panel to know that the authors of the study human growth mentioned that one of the degradation products of methyl isocyanate is trimethylamine, which has been reported to produce selective growth retardation of male progeny of mice associated with a decrease in serum testosterone.

CHAIRPERSON BURK: So if there was a specific effect on testosterone, that would possibly explain the specific male effect.

MS. DUNN: Right. They were pointing to that as an explanation why, in the males and not the females, they found the effect.

CHAIRPERSON BURK: Yeah. I think that's intriguing, but I don't know that we can, you know, list that as an end point of concern.

All right. Any other comments about developmental toxicity?

Let's move on to female reproductive toxicity. You know, in this case, again, we have the issue of increased spontaneous abortions falling into both of these categories in our guidance, kind of potentially being an effect on the female as opposed to an effect on the fetus specifically.

And it would appear that the continuing elevated rates of spontaneous abortion might support us listing under female reproductive toxicity.

Any comments on that?

Dr. Hobel.

COMMITTEE MEMBER HOBEL: Yes. I think that one of the important things to consider here is that there is information in both the animal literature about the potential effect of stress. They did measure corticosteroid in some of the animal models that was elevated.

And in some situations, actually corticosteroid had lower levels, but again you get into the issue of stress being associated with increased corticosteroid levels, but as you have also chronic stress, the levels will be lower.

And I think one of the issues in humans is that the tremendous amount of stress that women went through with exposure with pulmonary problems, tremendous high incidence of mortality in adults. And as you know, that stress affects the hypothalamic pituitary adrenal access, and affects ovulation, and leads to permanent, sometimes, chronic stress with anovulation and problems with pregnancy.

And you know, we now are very interested in fetal programming, but we're also now interested in what happens to adult people, where you have chronic stress over time, that there's a permanent effect on one's health. So if

you have a lot of psychosocial stress, history of loss of pregnancies, whether it's abortion or pre-term birth, that that increases your long-term stress response that can affect reproduction.

So I think that the amount of stress of these people and their continuing high frequency of diseases, whether it's ocular, skin, or pulmonary problems leads to a much higher frequency of chronic stress, which can affect reproduction.

CHAIRPERSON BURK: Any other comments on that topic?

Yes.

COMMITTEE MEMBER KEEN: It's probably just worth noting that I think consistent with what Dr. Hobel has just suggested is the lack of apparent dose differences or exposure differences in the data over several years. I mean, if one had to be a little fine, something a little bit disquieting, it's why you would not see a difference between the heavily exposed versus those minorly exposed. What you would anticipate though is if they're all in the Bhopal area, that the level of stress may actually still be quite similar.

So I think that would be consistent with the fact that it may be tangential here.

CHAIRPERSON BURK: Yeah, I agree with that in a

way, if you just look at this kind of all as regressing to the same level.

Are there any -- I think what I'm hearing is we may not be able to say specifically that methyl isocyanate has caused the spontaneous abortion persistence in females and human females. But is there any data from the animals that would support or not support?

COMMITTEE MEMBER JONES: Dotty, before you get to the animals.

CHAIRPERSON BURK: Go ahead, please.

COMMITTEE MEMBER JONES: The placental weight is being placed under a female reproductive effect. I don't think it goes there, does it? I mean, isn't that a development -- isn't that the fetus?

CHAIRPERSON BURK: Yeah, I think -- I believe, and I can check in our guidance, that it probably is in there, because -- and maybe some of the others can comment, that it can be a female reproductive problem if --

COMMITTEE MEMBER JONES: How?

CHAIRPERSON BURK: Well, maybe could someone explain how they think that got into our -- and I want to read it, because maybe I am --

COMMITTEE MEMBER JONES: I mean, the placenta is the baby.

CHAIRPERSON BURK: You're right. And presumably unless the placenta is --

COMMITTEE MEMBER JONES: Unless the uterus has been affected in a way that is causing --

CHAIRPERSON BURK: Let's check that. Give me a second to find it in here.

COMMITTEE MEMBER JONES: Right.

CHAIRPERSON BURK: So I'm going to go to the part under female reproductive toxicity is defined "to include effects on the adult or, where appropriate, developing female organism, including, but not limited to, adverse effects on reproductive structure or function".

All right, so not on that one -- "or impaired reproductive performance, which includes increased pregnancy wastage, such as miscarriage, spontaneous abortion, or stillbirth, inability to conceive or adverse effects on sexual behavior".

So I don't see that specifically listed. Unless you could somehow interpret it as a -- I don't know. I really don't know.

Can anyone help me there?

Staff, since you included that under female?

DR. IYER: Well, you know, as far the female reproductive system and maintaining pregnancy, it was at that level, you know, the placenta contributing to the

female reproductive system, as far as maintaining pregnancy.

DR. DONALD: As in many cases, what was mentioned in the presentation, it's difficult sometimes to attribute an adverse outcome on the conceptus -- to a direct effect on the conceptus or effect that's mediated through the female reproductive system.

So we generally default to identifying effects under both developmental and female reproductive toxicity if it's not entirely clear what the etiology is of the effect. So since the placenta is obviously the interface between the female reproductive system and the conceptus, if there's an adverse effect on the placenta, we generally identify under both endpoints and essentially leave it up to you to decide which or whether it falls under one or both or neither.

CHAIRPERSON BURK: Does that help, Ken?

(Laughter.)

CHAIRPERSON BURK: I'm not sure if it does.

COMMITTEE MEMBER JONES: It's a little gray.

COMMITTEE MEMBER HOBEL: I think that there is information that was presented that suggests that there are certain organs that were sort of sites where this chemical was deposited during exposure. And this is true in animal models, and in humans that the placenta and the

fetus received a fair amount. And I think this is probably related to the tremendous amount of blood flow that occurs during pregnancy to the conceptus.

And therefore, it's reasonable that this chemical could affect placental function. At the same time, there was a lot of nutritional problems in these subjects that were exposed that was never well defined. But there were some comments in some of the papers about the fact that they did measure this substance in the placenta of those pregnancies that were lost. And they were able to measure it and find it. Therefore that suggests it was there and may contribute to, you know, reproductive failure.

So I think it's scientifically reasonable to assume that this chemical does play a role in reproductive toxicity. And therefore, I think it's reasonable to assume that there's probably a combination of events that leads to the poor outcome. And I think the amount of stress that these women had, and the chronic stress over a long period of time resulted in tremendous changes in the reproductive potential of these people that also contributed.

So I think it's a complex issue where there's -- it's multi-factorial, but it's scientifically plausible that there are several things going on at the same time.

I also -- there was mention in one of the papers

that the people that lived in this area continued to consume food and water that came from this area, which also was contaminated and was never really studied very well.

So there was continued exposure over time that may lead to this more chronic persistence of their diseases that were associated with this chemical.

CHAIRPERSON BURK: So would you argue that even if stress is the mechanism, that that would still support identifying MIC as a female reproductive toxicant?

COMMITTEE MEMBER HOBEL: I don't think stress was a main cause, but it contributes to the long-term effects of what we're dealing with. I think there's sufficient evidence that there is reproductive toxicity secondary to the substance.

CHAIRPERSON BURK: Okay. So how does that weigh into, you know, sufficiency of evidence for us listing it. It's tricky. I'm not trying to put you on the spot, but I do believe the long-term effect, and I do think that the stress idea is very plausible. What I'm not sure is if I can say that MIC is directly responsible for the long-term effect. Although, it's possible. We don't have any animal data to back that up, which is what I would like to see. So that's why it's a little fuzzier to me. If we can specifically identify MIC as causing female

reproductive toxicity, but I will leave that all to your --

COMMITTEE MEMBER JONES: So you would suggest that as an alternative, it's stress from being in this disaster that's leading to the -- I'm talking to you, Dotty -- that you are suggesting that it's stress due to having been in this horrible accident, over a long period of time, that explains the continued spontaneous -- increased spontaneous abortion rate years after the accident?

CHAIRPERSON BURK: No, I'm not -- I'm trying to get an argument going. What I'm hearing from Dr. Hobel is that it's long-term stress, because these people live with this every day, even though it was years ago, with the stress.

I just don't see, myself, a mechanism to say that something happened then that cause the long-term increase in spontaneous abortions that's directly related to MIC. I don't know. I would like someone to argue it one way or the other.

COMMITTEE MEMBER JONES: Well, are we discounting cervical inflammation and dysplasia?

CHAIRPERSON BURK: No. See, that's what I want to hear. So if there are gynecological problems that persist over a long period of time, then I think it's a

fair problem.

COMMITTEE MEMBER JONES: Yeah. Well, the problem is I don't think that it's really been -- I don't think the cervical inflammation and dysplasia has been followed. I may be wrong. I don't think in the Dhara and Dhara paper that the alteration in menstrual cycle duration has been adequately followed, but they certainly are both female reproductive issues that I think it's plausible that they are leading to this.

Of course, I'm not quite as worried about this stress issue as others may be.

CHAIRPERSON BURK: Good comment.

COMMITTEE MEMBER KLONOFF-COHEN: Dotty, if it was just stress, then -- I think stress certainly plays a role. But if you look at where the people were living and if you see that the distance where they're very, very close, versus where they're further away, there's different effects.

And so I don't think that the people were necessarily aware of where they were living, so the stress should have made all of those results equal. And yet, you see a difference in terms of the closer the population was, the more severe the effect.

COMMITTEE MEMBER KEEN: I think I just have to make the observation that the data are not very

convincing. And even though I think -- we're almost kind of saying, well, we think there may be there, if they'd done the studies right, but the reality is we should be judging the actual data, which has been presented in the studies had they been conducted.

And I have to echo the concern that it was not just this incident. I mean, as was pointed out, there was some severe potential, we think, dietary issues that persisted for several years. This is an area that has a lot of problems, besides this incident.

So while the developmental toxicity seems to be fairly straightforward and clear, I'm underwhelmed by the fact that we have the data saying that there's these persistent maternal reproductive effects. I just simply don't see the information provided for us.

COMMITTEE MEMBER KLONOFF-COHEN: Does anybody know what the confounders were that were adjusted for in the Bhandari study, since that's so robust, and it was the largest?

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

COMMITTEE MEMBER KLONOFF-COHEN: Do you know what the variables were that they adjusted for in the Bhandari study?

DR. ALEXEEFF: What variables were there in Bhandari.

COMMITTEE MEMBER KLONOFF-COHEN: Which confounders?

MS. DUNN: I can't really hear what you're saying.

CHAIRPERSON BURK: Let me see if I can say it. She wanted to know which of the confounders or variables were adjusted for in the Bhandari study.

MS. DUNN: That's the study of spontaneous abortion.

COMMITTEE MEMBER KLONOFF-COHEN: (Nods head.)

MS. DUNN: I can look it up. I don't know it off the top of my head.

CHAIRPERSON BURK: George.

DR. ALEXEEFF: George Alexeeff. There was a question earlier about the animal support for this question. And so there is, you know, in the information on the radioactivity studies in the animal data. And possible Dr. Iyer could mention that.

CHAIRPERSON BURK: Say that again, which --

DR. ALEXEEFF: In the animal studies, there were radioactivity studies in terms of the --

CHAIRPERSON BURK: Carbon 14.

DR. ALEXEEFF: -- the sites where MIC actually accumulates. And so maybe Dr. Iyer could mention that again.

DR. IYER: Yes. On page 10 of the HIM under the pharmacokinetic section, where they've talked about exactly where MIC was found. And as far as the females go, you know -- as far as the fetus and the uterus, in addition to all the other -- so the reproductive system was definitely exposed to MIC. So if there was any questions about whether it was -- whether the female reproductive system was targeted or it was just a general systemic effect -- if you're trying to tease that out in your head, whether it was just -- the female was -- you know, there was insult to the female as a body, systemic toxicity versus the reproductive system in particular.

CHAIRPERSON BURK: I think I see what you're saying --

DR. IYER: I don't know if that's --

CHAIRPERSON BURK: -- but I'm not sure that's a strong case.

DR. IYER: I didn't know if there was a concern for whether the female reproductive system was targeted or it was just an overall systemic effect causing the --

COMMITTEE MEMBER KEEN: I'm sorry. I'm going to have to disagree with that. I mean, all the C14 data shows is an association. There's no causative conclusion you can draw from that. So I don't think we need to over -- we shouldn't over-interpret that.

DR. IYER: No. I didn't know if there was a concern whether it had reached the female reproductive system or not. And that's why I was trying to clarify that.

MS. DUNN: So in the Bhandari study, they looked at the women with regard to their socioeconomic status, religion, something they called consanguinity --

DR. IYER: Yeah, between relatives.

MS. DUNN: -- and age of the woman, and their previous obstetric history, as well as the gestation period from which the pregnancy was lost -- during which the pregnancy was lost.

COMMITTEE MEMBER KLONOFF-COHEN: Thank you.

COMMITTEE MEMBER JONES: So I'm going to -- I would make the point here that there are three studies here on female reproductive issues.

One shows cervical inflammation and dysplasia. The comparison group is said not to be adequate, but they had cervical inflammation and dysplasia. That certainly is an effect on the female reproductive tract.

The second study has alteration in menstrual cycle duration in exposed, without same in the comparison group. That is certainly a female reproductive effect.

And then this other one that we're saying maybe "relates to stress of gas-exposed women continued to

experience increased rates of spontaneous abortions for years after the exposure". I think it's hard to say that this is not an effect on the female reproductive tract. I mean, you can suggest all kinds of alternatives, but I think that this is clearly an effect on the female reproductive tract.

CHAIRPERSON BURK: Now, Linda, did you have any comments from the animal studies that would support those endpoints?

COMMITTEE MEMBER ROBERTS: I don't think that they -- is this on?

CHAIRPERSON BURK: Yeah. I'm just talking about female reproductive toxicity. Can we say -- what I'm looking for is sufficiency. And I hear from human, there are several endpoints. Female, I wanted to know if we could back that up with anything from the animal studies?

COMMITTEE MEMBER ROBERTS: I don't think anything in the animal studies really directly relates to this in a way -- they didn't do an evaluation of issues like the inflammation of the vaginal area or cervix that isn't typical in a study. The mating study didn't have effects. That would be the closest I think we could come to a comparison to normal female cyclicity.

They do have the increase loss, you know, either the resorption, stillborn, perinatal death. So that would

be similar to the spontaneous abortion portion.

CHAIRPERSON BURK: Okay. Any other comments about female reproductive toxicity?

All right. Let's take a look at male reproductive toxicity.

I'll allow you to discuss this as long or not as you want, but ultimately your vote will be your vote. So I think we've heard the discussion.

All right, would the male repro tox -- in summary, the human data, I would say, is inadequate and in no way sufficient to make any conclusions.

So then we come to the animal data. And I'm, you know, particularly intrigued by the effect on spermatozoa disappearing, and then coming back.

Is that sufficient evidence of male reproductive toxicity?

Dr. Hobel.

COMMITTEE MEMBER HOBEL: Yes, I would think so, because it was very dramatic. There was almost complete destruction of the cells within the epididymis. And then that recovered after the exposure. So that is fairly clear to me that it had an effect on spermatogenesis, but it's not permanent.

Now, the big question is, it's mentioned in the literature, is that is there some effect on the genetics,

on the genes. And you know, there has been reported some chromosomal changes, but there could be some epigenetic changes that are permanent that could affect reproduction later on in the lifecycle, but that has not been studied.

So we don't know if there's any permanent effect from that very short period of time, when there was marked alteration in the amount of spermatozoa.

So I think that suggests there is evidence there that MIC does have an effect on spermatogenesis, but it's short term.

COMMITTEE MEMBER ROBERTS: A question for staff, can you -- in looking at the Arora and coauthor, 1989 study, can you translate for me the 134 milligram per meter cubed into ppm's, just so I'm looking at it consistently. I think that's in the HIM study.

DR. IYER: I think it comes up to about 27 or 28 ppm, but I'll have to go back and run the thing. I think I did it when I was reviewing it, but it was at a higher level.

CHAIRPERSON BURK: So that's a very high dose.

COMMITTEE MEMBER ROBERTS: But similar to what I guess they had in Bhopal.

One of the reasons I'm asking is that I know we've talked about stress and such, and we were seeing some of these effects appear and disappear. I know there

was a study years ago, in which -- and it was an industry study. And I'm not exactly sure who all was involved with it.

But they were finding decreased male organ weights and histology findings following dermal application of a material that was progressively corrosive. So it's, you know, an irritant, severe irritant. You're applying the material on the same skin. The skin gets more damaged and more damaged. And these organs got smaller and there were male reproductive effects.

And in order to determine if it was a direct effect of the material or if it was related to stress on these rabbits, there was a follow-up study using a variety of different materials that were very severe skin irritants, and they found the same finding.

So I'm not as convinced on this one, if the dose was that high, that that might not have been sufficient effect, stress-wise, to be secondary to be causing an effect on males, that as the stress goes, you know, the finding may go.

It wasn't as quite as convincing to me as some of the other findings we have.

CHAIRPERSON BURK: Any other comments on male reproductive toxicity?

I think the problem in this chase, is there's just not a lot of evidence to look at, and you will need to decide if what we have is sufficient.

COMMITTEE MEMBER WHITE: In looking at the criteria for male reproductive toxicity, I just again read through the criteria, and I don't believe we have enough -- we have enough information to really conclude that there is male reproductive toxicity.

Sure, there was a significant decrease in the spermatozoa. But then after, what, 14 days or so, they begin to see the spermatozoa. And the head of the sperm actually did change shape, but there was nothing significant with that.

So I'm not sure, based on the studies that we've seen, that there is genetic damage to the spermatozoa or its precursors. Even just looking at that, I didn't quite see that, based on our criterion.

Impaired sperm and/or seminal fluid production or impaired or altered endocrine function. Everything that we saw in those studies were very transient. We could say perhaps there was a transient toxic effect, but that was it. It was transient.

So I'm not quite sure how that would fit into our criteria. I don't know if someone can tell me. Otherwise, I would appreciate the education.

CHAIRPERSON BURK: Yeah, I agree. I think the problem -- I mean, I believe it. And I think it's one study that does show an effect. I would just like to have more than one study, I guess that's --

COMMITTEE MEMBER JONES: So what if you get hit with this thing every 15 days?

CHAIRPERSON BURK: Yeah.

COMMITTEE MEMBER WHITE: Well, yeah, then that might change.

CHAIRPERSON BURK: Well --

COMMITTEE MEMBER JONES: What if you're a worker in the state of California or in Kern County and you're getting exposed to this agent every 15 days, then certainly you've had an effect on your reproductive.

CHAIRPERSON BURK: Sure, yeah. No, I am not arguing one way or the other. I'm just trying to get a good discussion going. So I can see that -- the problem is I'm looking at it as sufficiency of evidence, based on what we have. And I say we have no human unfortunately. They just didn't do the studies adequately.

But we do have at least one animal study that clearly, to my mind, shows spermatozoa disappearing. It's reversible, because of, you know, the way they did the dosing.

Other studies too had no dominant lethal, so

there weren't, presumably, chromosomal anomalies in there. It's not mutagenic. Well, I think you'll have to make your own decisions about it, but you could certainly argue that there is one very clear study.

COMMITTEE MEMBER WHITE: That there was an effect, sure.

COMMITTEE MEMBER JONES: Well, what about the Agarwal and Bose study, or however you say the names, in which there was this reduction in reproductive performance, so it was transient.

CHAIRPERSON BURK: Right. It's transient, and the authors attribute it to general stress, not specifically to the chemical. So I'm just playing the devil's advocate here, just to have a thorough discussion.

Any other comments from this end on that? I really appreciate everyone chiming in here though. It's much more interesting this way.

(Laughter.)

DR. DONALD: Dr. Burk, if it would be helpful to the Committee, we have Dr. Ling-Hong Li in the audience who's our expert in male reproductive toxicity, who could perhaps give you some additional information on the transient nature, or otherwise, of the effect, if you'd like.

CHAIRPERSON BURK: I think we would welcome that.

DR. LI: Yeah. My name is Ling-Hong Li. This is on, right?

And I just want to make a few comments. You know, this is -- I didn't work on this project. I heard your discussion. Several issues.

One is, is the effect secondary to stress or general toxicity? Well, if you look at the study, the morphology or histopathological changes sloughing of germ cells from epithelium. You'll kill all the animals you won't see -- you would not -- see those kinds of effects.

There are several chemicals that cause this effect and been observed, phthalates, hexanedione, glycol ethers. So I want to make that point.

And this is very severe is dramatic. It has been shown by chemicals and other general toxicity. Go to the lethal reaches as has been shown.

Secondly, you're talking about the reversibility, the transient. If you look at the exposure, you have three studies, four studies, 8 minutes, 4 hours, 4 days. If you use the other chemicals, phthalates, glycol ethers, give them a 1 hour, 2 hour shot, you would see the same thing. It's a general phenomenon with the male repro system. It's a dynamic system. If your exposure is chronic, repeated, you don't ask the question how about you have 15-days exposure, what could happen? You give it

one shot, then the system will recover. If you give it chronic, repeated exposure, who knows, we don't have the data on that. So I want to make that point.

The third thing is dominant lethal studies. What you do is you expose the animals one time, then you mate the treated males to the control females week by week. Now, you have one exposure, right, 8 minutes, 4 hours, what would you expect?

You would not expect a reduction in performance or in pregnancy mating trial or implantation loss every week. You would only possibly see reduction in the week that is corresponding to the damage in the window, right. That should be the window week 2 or week 3 -- or late week 1 until early week 3.

Now, if you look at those two studies, look at just week 2, there's a reduction clearly there. If you look at the studies, it's clearly there, but it's not statistically significant. Now, you go back through the studies again, you have one study, you have 3 pregnancies in week 2. That's a small number. How could you detect that -- detect a change with that three numbers, but you already see the trend of reduction.

Go to the other study, let's use 3 ppm, very low dose, it's for 4 days, compare it to the other one more than 13 ppm.

So what I'm saying is that you have a limited number of studies, but if you look at the nature of the studies, I think the evidence is right there very clear to me.

Thank you.

CHAIRPERSON BURK: Thank you. That was very helpful, I think. Does anyone have any other questions about -- before he gets away?

COMMITTEE MEMBER ROBERTS: I do have one. If I'm looking at page 57, Table 21, the number of pregnant animals for the dominant lethal. And I see you had, in week number 2, the percentages of pregnants from the control 1 ppm and 3 ppm were 93 percent, 93 percent, and 83 percent. And I believe that was the week you were mentioning that had a finding in your opinion?

DR. LI: Yes, that's one. If you look at it, you have 1 ppm, you have 3 ppm, right? You compare 3 ppm to the control, whether it caused a reduction. It's less than 90 percent to compare the two. More than 95 percent pregnancy.

Now, you look at the resorption, also in week 2, you'll see the same thing. This is low dose, 3 ppm. Because there is another study that also I call it a dominant lethal study. It is a mutagenicity study, right, with a positive control.

Now, you look at week 2, you look at it as a high dose exposure, the reduction is obvious.

DR. IYER: I think that's the right table you were looking at, the 83 versus 93, yeah.

COMMITTEE MEMBER ROBERTS: The reason why I'm wondering is if we go down to week number 3, the percentages across from 0, 1, and 3 ppm were 97, 83, and 97.

DR. IYER: Yeah, it goes back up, but at 83, which is the --

COMMITTEE MEMBER ROBERTS: So do you feel that the --

DR. LI: Let me look at this.

COMMITTEE MEMBER ROBERTS: Okay.

DR. LI: Yeah. Okay, this is one study. What this is a 3 ppm, or one 3 ppm study. There's another study. I don't know which it -- that used the higher dose. I think it's 30 minutes exposure. It's a much higher dose than this one.

COMMITTEE MEMBER ROBERTS: That was the 27 ppm one approximately?

DR. IYER: Yeah.

DR. LI: Yeah. I look at that one. I look at the week 2. By week three, basically, the animal has already -- the spermatogenesis has already recovered,

because if you think about germ cells is just one week, just one liter take 4 to 7 days to reach the epididymis, then the mating.

So by week 3, you already have the new sperm coming in. Also, if you look at the other study, 27 ppm study, it's very interesting. You look at the morphology, the sperm morphology, they're okay. If you look at the sperm density, it's increased. Why? Because you have all the sloughed-off sperm, you know, stored in the epididymis.

I would bet the motility would be down, but it's also not reported in the studies the motility of the sperm in the epididymis.

Okay, so if you really look at the data, it's consistent. It's consistent. What I'm saying is the pregnancies, the index, the resorption, I mean, you have small numbers of the low dose. I hope you have -- people have done, you know, a better job. You know, increases in animals or look at it more carefully, or even analyze it -- do the analysis week by week, not just line them up. You have 7 weeks. You put everything together. You're going to lose any difference, yeah, that's what I'm saying.

Ultimately, it's your opinion that matters. This is my observation, personal, you know.

Thank you.

CHAIRPERSON BURK: I don't think we have a table for that other one. And I don't think that's one of the articles that I printed out, so we will take his word for it, I think.

But thank you again. That was very helpful. And particularly that bit about the morphological changes in the sperm, not just that they were missing. That stress wouldn't likely cause the morphological changes.

Okay. Are there any --

DR. IYER: I have the two articles in case you're interested.

CHAIRPERSON BURK: Okay. Well, so could you verify that -- or is there a table in there that shows that the resorptions by the week after --

DR. IYER: The resorptions you have in the HIM. That's the table that Linda was looking at.

CHAIRPERSON BURK: Okay. So what's the other --

DR. IYER: The other two articles were the articles by Arora and the other one by Bose, I believe.

CHAIRPERSON BURK: Agarwal --

DR. IYER: Agarwal and Bose, yeah.

CHAIRPERSON BURK: That's the one I think he was saying was the higher dose.

DR. IYER: Yeah, that's the one with the higher

dose.

CHAIRPERSON BURK: Okay.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk, would you like to take a short break so that the Committee members could look at that information --

CHAIRPERSON BURK: I would.

CHIEF COUNSEL MONAHAN-CUMMINGS: -- or do they feel like they need it?

CHAIRPERSON BURK: I think it's time for one anyway, so why don't we take 10.

CHIEF COUNSEL MONAHAN-CUMMINGS: We can get you copies and then leave some for the public, if they're not already in the back, okay.

CHAIRPERSON BURK: Okay, thanks. We'll resume at say 10 of.

CHIEF COUNSEL MONAHAN-CUMMINGS: No discussion among yourselves.

CHAIRPERSON BURK: No, we're not discussing it among ourselves. We're taking a break for the court reporter.

(Thereupon a recess was taken.)

CHAIRPERSON BURK: Okay. Everyone is back. I think we'll continue our discussion of male reproductive toxicity. And we have received copies of two papers.

The Arora and Vijay... whatever, which was the

one on testicular histomorphology. And we've also received a copy of the Agarwal and Bose, which is an assessment of germ cell mutagenicity and reproductive effects in rats.

So has anyone had time to kind of digest these and reach any conclusions?

I know Linda made a comment.

COMMITTEE MEMBER ROBERTS: Yeah. The comment was just in the first paper the Arora and coauthor from 1989. Dr. Iyer has the calculation that it wasn't 27 ppm exposure, it was 57 ppm. So very, very high. And in their discussion of the paper, the authors noted that exposure to methyl isocyanate might have affected this stage elongation of the nuclei in the spermatid, due to stress and hypoxia because of the severe respiratory disturbance induced by MIC.

And I am not clear if -- it doesn't look like they actually evaluated respiratory disturbance or any microscopic changes to the lungs in this particular study. It looks like they only looked at the male organs. Is that a correct or is that the same interpretation you all have?

DR. IYER: They didn't look at anything else that they reported. I guess they focused on the male repro.

CHAIRPERSON BURK: But Dr. Li told us that the

type of changes that we're seeing with the morphology and so forth did not suggest stress, but were more in line with several other came chemicals --

DR. LI: Yes.

CHAIRPERSON BURK: -- that have been --

DR. LI: Yes.

CHAIRPERSON BURK: Tested.

DR. LI: If you look -- I don't have the paper, the paper that showed the histopathological evaluation. I think there are four figures. The first one is a control. The second one is the day 3 after 30 minutes exposure. And if you look at the middle of the tubule, that's a chunk of the tissue. That does not belong to this tubule, okay.

That's the epithelium sloughed off from somewhere else washed over here. Sloughing of germ cells is one of the most severe damage in the testes. It has been shown by several very leading researchers in the world, Kim Boekelheide, Bob Chapin, it will be caused by chemical insult.

And the stress, let's say you have 80 percent of food restriction conducted by a group by Carni et al. -- what was his name Eddy? -- and the further restriction or severe, you know, stress, you could cause a reduction in sperm, but not sloughing of germ cells. That's what I'm

saying.

CHAIRPERSON BURK: Okay. Is everyone okay with that? I take you -- I think you are an expert in this and I agree, that severe stress might cause a reduction in sperm, but probably wouldn't cause sloughing of tissue in this manner. That's what I'm hearing.

Okay. And then the -- any other comments on that paper?

Sorry.

And then we have Agarwal and Bose, which also did a dominant lethal study. The table we have in our materials is from the Schwetz. So what we're looking for in Agarwal and Bose, I think would be their Table 1, where they have untreated controls, EMS exposed and then MIC exposed. And what I heard Dr. Li say before is that we're seeing the implantation rate go from 8.4 to 6 and then back to 8.7. Was that what you were referring to before, so that it's a specific timing kind of thing --

DR. LI: Week 2.

CHAIRPERSON BURK: -- in a way sort of thing.

DR. LI: Yes, by the timing of spermatogenesis, what you have this one in a 30-minute exposure, what you look for is a reduction or damaging in week 2 or 3, depending on the time, you know -- I mean, it's continuous. It's mated -- the animals were mated every

day, every week.

CHAIRPERSON BURK: Right.

Well, that one does seem to me to be consistent with the Schwetz table that we have, just seeing that drop at one point.

Again, I don't know how statistics work on this, but, you know, anyway.

COMMITTEE MEMBER ROBERTS: And I guess I still have the question with the Schwetz paper that if 83 percent is a significant drop at week 2 for 3 ppm, why isn't 83 percent considered a significant drop at 1 ppm the following week. To me, it just -- that makes it look like there's some variation in mice. And having worked with mice before, they're --

DR. LI: What I'm saying is that I don't know if that paper did it week by week in a statistical analysis, but what I'm saying is that, in that study the exposure is much lower one at 3 ppm, right. And then if you postulated there is an effect, the hypothesis is the effect should be small.

I don't know if the drop has reached a statistical significance. But what I'm saying is there's a trend, and it's consistent with the histopathological change. That's what I'm pointing out, yeah.

COMMITTEE MEMBER KEEN: If I could comment

though. I'm still a little uncomfortable. We do statistics and that's how we test a hypothesis. There was no statistical difference here. They clearly state that. And so I'm very uncomfortable with us saying well, you know, maybe if -- we're almost torturing the data set by saying well maybe there's a trend, because I could just as easily say, well, the trend that I see is that implantation frequencies are higher in the MIC exposed animals compared to untreated controls, because the untreated controls are 7.2, 7.6, 7.2. And the MIC-exposed are 8.4, 8.7, 8.0. I mean so --

DR. LI: You are talking about --

COMMITTEE MEMBER KEEN: That's why we do statistics. I really -- I find to talk about a trend when if I do slightly different comparisons, the trend is, is that the MIC actually had more implantations than the untreated controls.

DR. LI: I totally agree with you the statistical analysis is necessary, is essential. What the trend that I'm talking about is not that one study week by week. What I'm talking about is different studies observed the same direction of the effect.

COMMITTEE MEMBER KEEN: Yeah, I agree. I just think that we can't -- we can't be that selective about data which are not statistically significant. If we're

going to talk about trends, then we have to look at the whole picture, so I would hesitate as to go down that road personally.

DR. LI: It's your call.

CHAIRPERSON BURK: All right. Any final comments on any of the issues before we vote?

Dr. Gold.

COMMITTEE MEMBER GOLD: I should have just probably said this when we were talking about developmental toxicities, but -- and maybe this is just a little bit of icing on the cake, but in the early sixties the Surgeon General established criteria for assessing causality in epidemiologic studies, and there have been other people that have done it since then. And I think we can apply it to these data, particularly in the human studies, to sort of make the case. And since we're here to assess the science, I thought I would just sort of do one minute on that.

And so in terms of looking at the strength of the association of the exposure to the outcome, I'm talking particularly about the spontaneous abortions now. I think that even if you look at the sort of modestly affected and the low affected and the moderately affected, you see really sizable differences from the control group. And by the way, the loss rates in the control groups are sort of

what you would expect, which says they probably pick pretty good control groups.

And I agree with the comments that were made about the limitations. I tell my students there's no such thing as a perfect epidemiologic study. I haven't seen it in over 30 years of doing this kind of work. But I think the strength of the association -- I think the fact that we see sort of a dose response that helps build the case of causality, the fact that the exposure came before the outcomes helps build the case, and then the consistency across the study.

So I just thought I would bring in those kinds of measures that we use when we're assessing causality in epidemiologic study. I think it helps build the case of a causal effect here of the exposure in relationship to pregnancy loss.

I think the things about female reproductive toxicity, you know, maybe those arguments are not as clear cut there, but I think very -- if we're going to talk about pregnancy loss, and particularly spontaneous abortions, I think those criteria are petty clearly met in the studies that we have before us.

CHAIRPERSON BURK: Thank you. Are we ready to vote?

All right. I will read the votes separately for

each endpoint.

Has methyl isocyanate been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity?

All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: All right 1, 2, 3, 4 -- I see 8. So 8 yes.

Five votes -- five yes votes are required to add a chemical to the list.

Okay. Has methyl isocyanate been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity?

All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: Okay, 8. So I don't have to ask for the no's.

And finally, has methyl isocyanate been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause male reproductive toxicity?

All those voting yes, please raise hand.

(Hand raised.)

CHAIRPERSON BURK: Okay. I see one.

All those voting no, please raise your hand.

(Hands raised.)

CHAIRPERSON BURK: All right, 7.

So we have voted to add methyl isocyanate to the Prop 65 list for developmental toxicity and female reproductive toxicity.

Okay. If I can find my agenda. We will move on.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Burk.

CHAIRPERSON BURK: Yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: I just wanted to note that the agenda for the meeting that was published on the web and sent to the public is different than the one that you received today on this next subject, the discussion of the next prioritization screen.

And, in fact, we hadn't publicized that there would be any public comments on that. When we've had those discussions before, for example, at the CIC Committee more recently, it was just a discussion among the Committee and the staff to giving the Committee's advice to the staff about the prioritization.

So I just want to make it clear that that item actually is a discussion item. There's no decision that needs to be made and no public comment is necessary.

CHAIRPERSON BURK: Let me make sure, it's a discussion item only, and there will be no public

comments?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. It wasn't on the agenda that was published, and so we shouldn't take public comment on it.

(Thereupon an overhead presentation was Presented as follows.)

CHAIRPERSON BURK: Okay. So I guess we will start with a staff presentation and then a discussion of the next prioritization data screen.

And Dr. Jim Donald is speaking.

DR. DONALD: Thank you, Dr. Burk.

I'll begin by reiterating briefly. In 2007, we had developed a list of candidate chemicals for consideration by the Committee, based on our prioritization process published in 2004.

Using that process, OEHHA applied an epidemiologic data screen to chemicals in our DART tracking database. The screening criterion was identification of at least two analytic studies of sufficient quality.

Use of that criterion resulted in a list of eight candidate chemicals. Three have previously been brought before the Committee and a fourth has been presented today. Hazard identification materials are almost completed for a fifth chemical. And one chemical has been

added to the Proposition 65 list through an administrative mechanism. So that leaves only two additional identified candidates.

Since all of these candidates were selected because they had substantial epidemiologic data, much of the workload, both of prioritizing chemicals and preparing hazard identification materials has fallen on the relatively small number of our staff who are experts in epidemiology.

In order to give us flexibility to use our resources in a more efficient and timely way, we'd now like to propose a screening process that's based primarily on animal data.

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DR. DONALD: So again, just to refresh everyone's memory, this flowchart shows the various steps we follow in prioritizing chemicals for consideration by the Committee.

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DR. DONALD: Our starting point for this round of prioritization would be the same tracking database as used previously. From that, we identify chemicals that pass the initial screens for the availability of some relevant toxicity data and for some potential for exposure in California.

For this round of prioritization, the tracking database has been updated with a substantial number of additional chemicals that have come to our attention since the last round of prioritization.

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DR. DONALD: So as I mentioned, we previously screened for chemicals that had relevant epidemiologic data in humans, and we anticipate potentially using that screen again in the future.

For the next screen though, we'd propose using a process that would identify chemicals that are known to occur in humans, but which were not found by a previous screen to have at least the specified amount of epidemiologic data.

We'd also propose using a subsequent screen to select a subset of chemicals that also have a substantial amount of relevant toxicological data from animal studies. And our goal would be to identify important chemicals that have direct relevance to humans, but at the same time allowing us to use our staff resources more efficiently.

--o0o--

DR. DONALD: For the exposure screen, we would begin by reviewing compiled data sources, such as the National Health and Nutrition Examination Survey. Depending on the number of chemicals identified through

this approach, we may also use computerized searches of the open literature. We would expect this screen to identify most chemicals that occur in humans, though it would potentially omit chemicals with human exposures that have not yet been identified or chemicals for which human is known to occur, but which have not yet been measured in human tissues.

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DR. DONALD: Since the goal of the process is to identify a manageable number of candidates for consideration by the Committee, we will chose a cutoff number of studies that will yield approximately 8 to 15 candidates. We expect that this can likely be completed in a relatively short period of time. We do recognize that it may miss chemicals of emerging concern that have not yet been included in these databases or which more recent studies have not been added resulting in chemicals not reaching the number specified in our criterion.

And I'd be happy, at this point, to take any questions the committee might have.

CHAIRPERSON BURK: Go ahead.

COMMITTEE MEMBER ROBERTS: So in the toxicity screen, you'd be looking for studies -- or for chemicals that have at least six repro developmental publications or tests?

DR. DONALD: Right. As I said, we're trying to take a very large number of chemicals and get down to quite a small number. So we'd like to leave that a little bit open, so that we can adjust the number of studies to end up with the sort of range of chemicals that we're looking for. We're guessing it's somewhere in the range of 6 to 10 studies as a cutoff would probably achieve that.

COMMITTEE MEMBER ROBERTS: I'm thinking that some of the more popular chemicals might have a very long list of references to take a look at, and some of the others, particularly the ones that might have come out and had testing more recently through like the high production volume chemical testing program, might only have two or three, but they might be very good studies that could be used.

DR. DONALD: Yes, and we --

COMMITTEE MEMBER ROBERTS: I like the flexibility.

DR. DONALD: We recognize that. Whatever criterion we apply, obviously we're going to eliminate the vast number of chemicals. That's the purpose of the process. So there are, as you know, provisions in our prioritization process for bringing other chemicals to Committee that have a compelling public health reason to

do so. So we're hoping that if there are any really obvious cases where we missed something that should come forward, we do have an alternative way of bringing it to you.

CHAIRPERSON BURK: Any other comments?

Ken.

COMMITTEE MEMBER JONES: So Jim, could you just clarify some things here. This is what --

DR. DONALD: I can't hear you --

COMMITTEE MEMBER JONES: I'm sorry. So you have said that we have really exhausted all of the chemicals for which there is good human epidemiologic data, is that correct, did I understand you correctly?

DR. DONALD: Not exactly. I said that we have pretty much exhausted the list of chemicals that past the screen the first time we ran it, which was several years ago.

COMMITTEE MEMBER JONES: Yes.

DR. DONALD: There are a couple of chemicals left that haven't come before the Committee yet, and we recognize that there are ongoing studies that will probably identify additional chemicals that would pass that criterion. And that's why we've proposed to run that screen again in the future.

COMMITTEE MEMBER JONES: Right.

DR. DONALD: But for practical reasons, because we still have a couple of candidates that are primarily based on epidemiologic data, and we only have a relatively small number of staff with expertise in that area, we think it would be more efficient if we could also identify some other candidates where the bulk of the data are from animal studies, so that we can use our staff resources more efficiently to bring chemicals to the Committee in a more timely way.

COMMITTEE MEMBER JONES: All right. Thanks.

CHAIRPERSON BURK: Any other comments?

Linda.

COMMITTEE MEMBER ROBERTS: This wouldn't preclude or push pharmaceuticals out of the way, would it, from the exposure screen?

DR. DONALD: There's nothing explicitly in the process we've proposed that would do that, no.

COMMITTEE MEMBER ROBERTS: Okay.

DR. DONALD: The criteria would be applied equally to any chemicals.

CHAIRPERSON BURK: That was a good question.

I think the --

DR. DONALD: I'm sorry. Can I add one thing to that answer? Part of our process is that if there are other mechanisms for listing chemicals, administrative

mechanisms, that the chemical appears to be applicable to, then we would generally use those mechanisms to save the Committee's time for chemicals that do not fall under those mechanisms. So for some pharmaceuticals potentially there would be other mechanisms that they could be listed through, that would not result in them coming before the Committee.

COMMITTEE MEMBER ROBERTS: The question kind of came out of my ignorance about part of NHANES, because I typically get drawn in on it, if there are concerns about industrial chemicals, and exposures and I've never really looked at it from whether or not it gathers any data for pharmaceutical type materials.

So thank you.

DR. DONALD: Okay. If that's a matter of particular concern, I can have our staff who are most familiar with NHANES address that for you.

COMMITTEE MEMBER ROBERTS: I'm actually pretty much okay with what you've told us. So thanks.

COMMITTEE MEMBER KLONOFF-COHEN: So I just wanted to clarify something, so then are there only going to be animal studies that we're reviewing now or is this just a process in order to identify further, yeah?

DR. DONALD: It's the latter. As the chemicals that we bought before you that were identified based

initially on epidemiologic data also generally have animal data. There may be cases where chemicals for which there are predominantly animal data have some epidemiologic data. It's also possible that the data maybe entirely in animals, but you know we won't know until we've run the screen.

CHAIRPERSON BURK: All right. I don't see anybody else wanting to comment. So I guess --

DR. DONALD: So I think, at this point, we're asking for a recommendation from the Committee as to whether we should employ this screen that we've suggested to you.

CHAIRPERSON BURK: All right. So you want us to vote or just a consensus.

CHIEF COUNSEL MONAHAN-CUMMINGS: No. No. It's not a -- it's just a -- if you could generally give advice. Does this seem like a good approach or would you rather that we looked at something else? That's generally what we're looking for. It doesn't have to be a vote.

CHAIRPERSON BURK: Well, what I'm sensing from the group is that it's fine, we support that, particularly the effective use of resources and time and so forth.

I personally would like to have you run the human data screen again at some point, because I still think that we -- I think we appreciated the prioritization

process, you know, that we've just been through, and wouldn't want to lose that ultimately, but I think we understand how you need to use staff time more effectively.

DR. DONALD: Thank you.

Okay. The next agenda item I believe Allan Hirsch will introduce Items 4 and 5.

CHIEF DEPUTY DIRECTOR HIRSCH: We can do that, but just a question for you. Given it's 20 after 12, it would be your decision, as a panel, if you wanted to take a lunch break or if you wanted to proceed.

CHAIRPERSON BURK: Well, let me ask. I believe the next two agenda items are Committee discussion only with no public comment. So I don't expect that to take a great deal of time. So I guess I'll ask, is anyone really famished or would you rather just push on?

I think we push on. I think we're in agreement there.

CHIEF DEPUTY DIRECTOR HIRSCH: All right. That's our first discussion, great.

Okay. So for Item 4. This item has its origins in a letter that Dr. Denton received from several non-governmental organizations, NGOs, on July 22nd, 2009. That was a week after your last meeting. And the letter contains several specific criticisms of the way that the

meeting was run.

OEHHA and Dr. Burk met with representatives of these groups in April. And the attitude that we had was not that we needed to rehash last year's meeting, but simply that we're always willing to listen to constructive criticism, and, you know, and see if there are ways to improve our processes.

So Dr. Denton responded to the NGOs in a letter dated September 1st, 2010. And in it Dr. Denton said, we cannot do some of the things that the NGOs asked for, but she did say that OEHHA would make some changes to improve the clarity of the information that we present to you.

And specifically to the item before you, Dr. Denton also conferred -- she conferred with Chairwoman Burk and Dr. Burk wanted to bring three specific items relating to meeting procedures to you today for discussion.

These are items that would affect the Committee's deliberations at future meetings. So Dr. Burk felt it would be desirable for you to discuss those.

Lastly, just to be -- just for the sake of completeness, Dr. Denton last week received a letter from the NGOs with some further thoughts on meeting procedures, as well as a letter from the American Chemistry Council that rebutted the NGOs' original July 2009 letter. And

you should have copies of all of that correspondence and it's on our website as well.

So again, this is a discussion item only. And our Chief Counsel, Carol Monahan-Cummings, will give a short presentation on the three items concerning meeting procedures.

(Thereupon an overhead presentation was Presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you. We're going to just get a couple slides up here. It's unusual for a Chief Counsel to do slides, but I thought it might be more interesting for you than just listening to me.

As Mr. Hirsch has mentioned, there's two discussion items -- two other discussion items, besides the prioritization item we already had, on the agenda today. And I know this is a relatively unusual thing for this Committee to have discussion items, rather than decision items, but it's not that uncommon for other groups, you know, city councils or other groups that are subject to the open meeting laws to have discussions that are giving advice or just kind of kicking around some ideas that don't really require public comment and are really just advice items.

In this particular case, on the procedures, what

we're looking at is I think that Dr. Burk wanted some discussion among the Committee members about some potential changes you could make to your procedure if you think that they'd be useful. You could always try them out and if they don't seem to be comfortable then you could go back to something else, but these were issues -- procedure issues that were brought up in the NGOs' letter.

And again, we're not asking you to make a binding decision or make a vote or anything today, we'd just like some discussion and then Dr. Burk can take that and perhaps discuss it also with Dr. Denton, in terms of conduct of the future meetings. And we can help support any changes you might want to make.

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CHIEF COUNSEL MONAHAN-CUMMINGS: Some of the issues that you might want to consider today have to do with the format of presentations; some discussion around public comment periods; and your voting protocol. Some of the -- as Dr. -- or Mr. Hirsch -- anyway, we've got so many doctors around here.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: -- mentioned, we did have a couple of discussions with the individuals that sent the letter to Dr. Denton. And there's a mention in there that sometimes Committee members may -- it may be

difficult to go through a lot of data first and then go back and vote on individual endpoints. It's not an issue so much for the CIC, since they only have one endpoint to look at.

One of the suggestions that we had is that we might -- we usually present our information endpoint by endpoint like we did today. For the most part, we'll go through developmental and then female and then male, given that -- if there's some data to discuss. And in some circumstances, if there's a lot of information on any of those, it may be useful to you to have a presentation of the information on one endpoint, and then go to the public comments and then your discussion and your decision on that particular endpoint before going to the next one.

It's certainly not a requirement. You wouldn't have to do it in every case, and it might not be appropriate in every case, where there's not a lot of data to consider, but it's a suggestion you might want to consider.

We think that it could allow the members to assess the evidence for each endpoint separately, and you know, may be more -- in more detail. The con to it is that it could result in some redundancy, because some of these things overlap, as you can see from the meeting today.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: In terms of public comments and public comment periods for the meetings, you all when you first started on the Committees, and maybe periodically since then, have heard me comment on the Open Meeting Act. And we gave you a copy of it, the Bagley-Keene Open Meeting Act sometime ago. I was kind of considering putting it in your materials, but it's kind of a long document.

But in any event, the Open Meeting Act does require a public comment period either during or -- during the Committee's discussion or prior to its decision on items that are -- you know, if you're actually making decisions, say you're voting on something.

The Open Meeting Act also allows you to limit public comment. And in certain circumstances, you may need to do that just based on the volume of -- or the number of people wanting to make comments and the rest of the items on your agenda.

I checked with other boards at CalEPA, there's only two left now, the Air Board and the Water Board, and both of them place time limits on public comments. The most common is three minutes. That is variable depending on some of the issues that are being presented, number of

people that want to comment, that sort of thing. But the most common is three minutes.

The Water Board often publishes notice in advance that comments will be limited to say three to five minutes, so that people know that they, you know, they don't spend a whole bunch of time on a 20-minute presentation and then they come in and have to compress it.

As far as I could tell, there's similar rules with federal advisory committees, like the CDC or U.S. EPA. They do limit the comment periods on their committee meetings and often it's about three minutes.

If you're familiar with the legislature, it can be one minute or less. And so, of course, they have different issues than the ones that you all tend to look at.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: We do have some suggestions in terms of -- and I think we've done this in the past for both committees is keeping related speakers together. Sometimes a particular industry group or a particular group of NGOs need to speak together to just present a coherent presentation. And in terms of logistics, that seems like a good approach.

There are a couple questions that we wanted to present in regard to that, and you saw it at your last meeting, and that is should individual speakers be allowed to cede their allotted time to others. And that is not allowed by most other groups that I had spoken with. There's a bit of room for manipulation on that, depending on the number of people that a particular group brings to a meeting. You can send in a whole bunch of cards and then combine them all together and let somebody speak for an hour, which is really not the intent of a three-minute limit on comments.

So from our perspective, I'm not going to recommend anything on any other ones, but I would you recommend that you not allow the ceding of time.

And then I had already mentioned about whether or not we should let the -- you know, at least let the public know that there will be time limits set in advance, but that there would be certainly variability, in terms of, you know, if you have a hundred commenters versus two. And lastly is just kind of an item of interest that I just ran across relatively recently.

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CHIEF COUNSEL MONAHAN-CUMMINGS: And that is in terms of voting. Most groups still do the type of voting that you do here, where the chair asks the question, and

there's a voice or hand vote, in terms of what the answer is. And each of the Committee members can look at the others and see what they're doing right then.

There's been a change at FDA on some of their advisory committees to go to a ballot vote, which is one where the Chair would pose the question, but you would check off a box, you know, yes or no, on the ballot. And then those would be collected and announced by the chair.

Their stated reason for doing that is that they think it allows panel members to cast their votes without an immediate influence by other member's votes, you know, particularly if someone is more forceful than others.

But it's certainly not, again, anything that you have to do, but I just wanted to bring that up as an interesting recent development in some advisory groups. So with that, I know we showed a number of different items up here, but I'd turn the meeting back to Dr. Burk and you all can have a discussion on it. If you need me to go back to any of the slides, just let me know, or if you have questions at this point.

CHAIRPERSON BURK: Thank you, Carol.

Again, this is strictly for Committee discussion. Any input that you have would be great. We're not going to vote on these things, but I'd like to get your input.

So there's three things that have been proposed.

The first one would be that we take each chemical by endpoint, hear the presentation, discuss, you know, hear public comments and vote. I think the advantage, I agree, would be that, you know, we could perhaps focus more on each endpoint by endpoint and not be overwhelmed with everything at once. So just anybody have any input on that, pro con?

COMMITTEE MEMBER KEEN: Yeah, I actually disagree. I like it the way we do it, and for a very specific reason. If we do it endpoint by endpoint, you lose the possibility -- what do we do if we suddenly find, for example, in endpoint number 3, it's clearly demonstrated that we're having maternal toxicity, but that wasn't shown for endpoint 1. Do we go back and suddenly say, "Oh, I want to change my vote or rethink my vote."

I personally don't think it's that difficult for us to keep the facts straight for a period of an hour to two hours. So I like the current system, because many of these endpoints they're not singularities. They really do cross over each other and we should be able to look at the totality, in my opinion.

CHAIRPERSON BURK: Okay. Any other comments on that?

George.

DR. ALEXEEFF: Excuse me. George Alexeeff.

Yeah. One of the things that came up and it's going to come up in the next meeting for the next chemical, sulfur dioxide, the study design for some of the studies are very complicated. And, you know, it's in our mind we're not sure if it's helpful for us to, for example, bring someone to explain how these studies are conducted, these air pollution studies with multiple variables and how they calculate it and stuff like that. Some of you may be familiar with it, others may not.

And so if we started to do that kind of thing, and we kind of ran out of time towards the end of the day, what would be the best way to kind of carry it over, like to the next meeting?

So that's why we thought maybe on certain chemicals, endpoint by endpoint may be appropriate, if it seems like there's going to be a lot of discussion about how they came up with that endpoint. And we wanted to bring -- make sure we had other experts available to explain the details of the study design, which may be kind of different from what you're normally used to seeing. That was one thought that we had.

And the next one, sulfur dioxide, could go more than a day, because there's a lot of studies. I forget how many. Many, many, many epi studies, and they're all very complicated. Not all, but many of them are very

complicated with multiple exposure chemicals. So part of it was just to lay all that out.

CHAIRPERSON BURK: Well, hearing that, does anyone have any other -- I have to say, if something is going to go for two days, I think we would have to break it up. I just can't imagine us listening to a whole presentation and then all the comments and then trying to sort it out. So that's just my take.

COMMITTEE MEMBER ROBERTS: This is not to address sulfur dioxide, because I'd be recusing myself on that anyway. But in situations where we have a huge amount of information, that might be a case where you try to bundle at least all the developmental tox parts of it together, all the female -- almost in sort of a mega-way of what we're doing right now, where we try to at least discuss one of the voting endpoints at a time, as opposed to within a developmental tox or within a female repro, which endpoints seem to be affected.

It seems to me like that's something where we can be kind of flexible on, and really do whatever makes the most common sense.

DR. ALEXEEFF: I couldn't quite hear everything you said, Linda, so could you say it again, what your concept of the bundling was, just so we can understand it. Because part of it is as the staff prepare their

presentation, that would affect, you know, how the thing is kind of laid out.

COMMITTEE MEMBER ROBERTS: I'll reiterate. This is a comment in general for those situations where we might have a very large amount of information, that I could see how being able to focus the presentation and focus the discussion on one of the voting endpoints at a time. So we can get through all of that before proceeding to the next one, so that all of the information pertinent to development tox might be in one period of hours, female reproductive tox in the next period of hours, male reproductive tox going on to midnight or whatever, you know, that that would be fine.

And I really do like the idea if each of us is familiar with different types of standard studies, and particularly some of my academic colleagues here are familiar with the more complicated research approaches, but if in situations where you come across where test design is pertinent to understanding it, and it almost always is, and if it's not likely to be familiar to the eight of us up here, I think it would be very useful to have somebody who can explain that to us, so that we can understand how that impacts the biology.

COMMITTEE MEMBER WHITE: So then in that respect, would we still vote on that endpoint or would we just --

we wait or how would that work? I mean, I agree, to reduce as much confusion as possible when we have lots of data for a significant chemical, if we do it endpoint by endpoint, we want to reduce the risk of cross-over information that may compel us to want to go back to change a vote. That increases confusion. It reduces efficiency, and then we -- that's a nightmare.

So then my question would be, if we do it endpoint by endpoint, based on the chemical, would we want to vote at that time or would we want to vote the second day or however long it takes us to get through those endpoints.

COMMITTEE MEMBER ROBERTS: My preference would be voting when we're done with all discussion at the end of it.

I find I often will be swayed by something that I near in a different part of the discussion.

CHIEF COUNSEL MONAHAN-CUMMINGS: Question. If you were to do it that way, would it be helpful, particularly if it's a two-day meeting, to have a short summary of each of those endpoints just before the vote, so that you can kind of remember what was presented, you know, the prior day or would that be too redundant?

CHAIRPERSON BURK: I don't know. I think what I'm hearing is that when we have a chemical like today, we

are happy to get it all at once and vote all at once. If we have something with many, many studies, we might like to have the presentations bundled by endpoint. But I think what I'm hearing is we would still vote at the end, in order to have the big picture.

And I would have to assume that everyone would be forming their decisions as they went along, but still potentially open to changing them. You know, whether we'd need a summary from staff, I don't know. I would think it might be nice to have a summary perhaps from Committee members as to, you know, why they're voting the way they're voting, let's say, i.e., sufficiency of evidence in the various categories and so forth.

DR. ALEXEEFF: George Alexeeff again. One comment.

So as Carol alluded to, and probably, as you recall, when we surveyed you for time for this meeting, we were trying -- if we were going to bring that chemical, we thought it would be a two-day meeting, so we would try to structure it the days next to each other or close to each other, depending upon people's calendars, if they could get two days next to each other, that's the best way to do it. That's what we did also for the CIC, when we thought it would go over to two days. So that would be one way, so that it wouldn't be a long time between the

information.

The other thing that was brought up in the comment letters from the petitioners was the concern for discussion. And this morning, you had a great discussion, of course, after going through everything. But the concern was that if you were up to, you know, a five o'clock time point and we had spent all day presenting this stuff to you, then you felt like you had a little bit of -- not enough time to discuss, but you had made it up in your -- you had your thoughts, so you're maybe able to vote, but the discussion wasn't clear to your thought processes, because we ran out of time.

So one of the concerns -- one of the thoughts would be that if you went through each endpoint, you could begin some of the discussion, at least, after the presentation of that endpoint, maybe without voting. So maybe that's something to discuss, if that makes sense or not. So that it's clear that you've had your questions answered, you've thought about it maybe, in your mind you've made some preliminary thoughts and then we could move on to the next endpoint, if that's helpful.

CHAIRPERSON BURK: Yes. Does that sound reasonable? I would say so. I think we would want to -- when we're talking bundling the things, that would include our discussion, that's the way I'm hearing it. It just

wouldn't necessarily end with a vote.

Now, the issue again, I would assume, it would include public comments on the topic, but that's another thing, unless I --

CHIEF COUNSEL MONAHAN-CUMMINGS: I think --

CHAIRPERSON BURK: You know, in other words, we'd focus on each part at a time, but would not necessarily vote until the end on each of it -- each of the endpoints.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. So you're required to either have public comment during your deliberations or prior to the vote, so whichever one would be most helpful to you. You know, if you leave all the public comments to the end, there again going to go back to some other stuff. But you know, it's entirely up to you guys.

And it could be that, you know, this is just something that needs to be decided on a case-by-case basis on each agenda. But I think that Dr. Burk just wanted some input on what you all might want to see for future meetings.

CHAIRPERSON BURK: Okay. Well, that was good.

On the topic of public comments, again, I mean, I have to speak for myself. At the last meeting, I know we tried to make it fair. So I'm just saying the idea of allowing pro-listing and anti-listing to get equal weight

is certainly acceptable and actually something that, you know, we tried to facilitate.

But from the Committee's point of view, I'm just more interested in your feedback on the length of time that we should allot to comments and so forth.

Dr. White.

COMMITTEE MEMBER WHITE: Having commented before a Senate committee hearing previously, which I think landed me here, it got such rave reviews, I suppose, three minutes was all we were allowed. And in three minutes, I was able to give my comment with much passion and clarity. My recommendation would be that we do keep it to three minutes. I think if -- or a short amount of time. I was shocked myself that I was able to give my comment in three minutes. And I finished at three minutes and the timer was shot.

So I know if I can do it, and I'm not anymore brainy than anyone else, then I know that those who are passionate about what they're commenting on can do the same. You can say a whole lot in a short amount of time, and you can say nothing in an extended amount of time.

So that would be my recommendation is that we keep the time very short, because if we have -- we have had chemicals where we had large numbers of commenters. And I think that whether we have two people or a hundred

people, I think we should keep the time consistent. And I also think that time should be published. That's just my humble opinion.

CHAIRPERSON BURK: So time published ahead of time as to how --

COMMITTEE MEMBER WHITE: Yes.

COMMITTEE MEMBER KEEN: And I agree, but of course there is the devil in the details, in the sense that we just had a scenario painted for us where a meeting might last over two days, where we do endpoint by endpoint. And so I think we'd have to up-front say, does that mean there's three three-minutes, or one three-minutes, I mean, because it would be, in my mind, inappropriate to have one three-minute and then expect somebody -- it may not even be a two-day meeting that's next to each other. So I think we'd have to have that as a caveat, but state it up front, so it doesn't surprise people and we have bricks thrown at us.

COMMITTEE MEMBER GOLD: This actually partially reflects back to what the previous discussion about whether to group them. And I like the idea of grouping the endpoints, but I can envision a study, one study, that's looking at one agent and looks at multiple endpoints. And what I would like to see avoided is sort of redundancy in reviewing the study designs and

limitations and all that three times, and then having commenters, both on the Panel and from the public repeated three times.

So I think -- I support the idea of flexibility, but I think we ought to avoid redundancy to the extent possible.

CHAIRPERSON BURK: What I'm hearing so far is keep the comment period short, and announce it ahead of time, you know, depending. And I suppose it could vary. I would also like to suggest that the Committee always has the prerogative to ask questions to a commenter, particularly if they're presenting some scientific evidence that we don't know about. That doesn't count on their time. That's our time.

Some mechanism for avoiding redundancy. And I know, in some ways, I think I've heard that, at least in the state, it's often done that if someone agrees with someone all they have to do is get up and say I agree with so and so, and they don't have to talk for three minutes, but they get on the record that way.

You know, my personal feeling is I spend more time reading the things that are submitted ahead of time. And as far as I know, there's no limit on it that, so I would encourage somebody, if they have something to say, to send it in writing.

But am I hearing anything on the concept of ceding time?

COMMITTEE MEMBER KEEN: Opposed to it.

CHAIRPERSON BURK: Okay.

COMMITTEE MEMBER WHITE: He said he's opposed to it?

CHAIRPERSON BURK: He says he opposed to it.

COMMITTEE MEMBER WHITE: I'm opposed to it.

COMMITTEE MEMBER JONES: I'm opposed to it.

CHAIRPERSON BURK: All right. So that one is pretty clear.

The other comment that was presented in the letter was about asking each presenter to state their financial interests. And my understanding is that isn't required by any law. But I would say if any of you want to know that, you know, I'd be happy to ask. They don't have to answer, I guess. But is that something you want me to try to do more of?

COMMITTEE MEMBER GOLD: I'll just say in the medical school setting, where I am, this is increasingly the case, so that any seminar, any presentation, there's usually disclosure at the beginning. And I'm also accustomed to seeing it in other sort of advisory panel settings as well, and also professional meetings now. Well, for a long time I think there's been disclosure of

whether you have support from, you know, certain -- wherever. You know, whether it's just federal support or whether it's industry support.

So I'll just say that there is an increasing trend to this sort of form of disclosure. I'm not sure I feel strongly one way or the other at this point about this panel.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just for clarification, the Open Meeting Act specifically says you cannot require someone to state their name, affiliation, or any other information if they want to speak in front of the group. It doesn't say you can't ask.

So if you want to ask a question or follow-up, you know, on a particular study, you know, who was that funded by, that sort of thing, it's entirely up to you whether you ask that. But you can't say well then you need to sit down, if you're not going to answer the question or something, because we can't require it.

CHAIRPERSON BURK: And then the other item was the idea of taking a paper ballot vote. The idea being that each person it would be read out by their name, but their vote might not be specifically influenced by looking around and seeing how other people were voting. So there would be more independent voting, I guess.

Any thoughts on that one way or the other?

I heard it just adds time.

COMMITTEE MEMBER WHITE: It just adds time.

CHAIRPERSON BURK: Okay.

COMMITTEE MEMBER JONES: What would be the idea, you would put your name down on the vote.

CHAIRPERSON BURK: Yeah.

COMMITTEE MEMBER JONES: You would put your name down and your vote or you'd just do it anonymously or what?

CHAIRPERSON BURK: No. It wouldn't be anonymous. The idea would be everyone would just have a ballot. And when it called for the vote, they'd check yes, no or abstain, pass it in, with their name on it, and it would be read out. So the only idea there really is that instead of the appearance of looking around to see, you know, how other people are voting, you would be voting individually, but still on the record.

Again, you didn't have any problem voting differently, and I have done it in the past. You know, I personally feel confident in the way I vote. But some of this is the appearance that we're giving to others, and that's why this was brought up. You know, I'd say it's perceptions that --

COMMITTEE MEMBER JONES: Perception is always important.

CHAIRPERSON BURK: Yeah, I know, and that's why we're bringing it up.

So I'm not hearing anyone strongly for it or against it.

COMMITTEE MEMBER WHITE: My question is -- has this in the history of this body, has this come up previously how we vote?

CHAIRPERSON BURK: Not that I'm aware of.

CHIEF COUNSEL MONAHAN-CUMMINGS: No, not the process itself.

COMMITTEE MEMBER WHITE: Not the process.

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't know what perception people have had before of whether or not people change votes based on who's, you know, next to them or whatever. But I brought it up, primarily because, you know, it was FDA and they had, you know, this idea that it might help people be more independent, in terms of their approach. I don't know if it's larger groups, or, you know, they've had some issue that we haven't here or whatever, it's just kind of an interesting concept. And so it hasn't come up to my knowledge specifically before.

COMMITTEE MEMBER WHITE: Okay. Thank you.

CHAIRPERSON BURK: I think we've -- it's just a proposal to address a perception that there might be someone that's kind of driving everyone else in a

particular direction. I would like to hope that we could all have our own opinions and feel free to express them.

All right, so I'm not hearing anything much on that, one way or the other.

Okay. So I think that pretty much covers Agenda Item number 4. Did you want to address number five or -- go ahead.

CHIEF DEPUTY DIRECTOR HIRSCH: So if we've finished Item number 4, we'll move to Item number 5.

In this item, on August 5th, OEHHA and specifically Dr. Denton received a petition from the American Chemistry Council asking you, your Committee, to rescind the designation of the NTP CERHR as an authoritative body. Dr. Denton conferred with Chairwoman Burk who decided to place this item on the agenda as a discussion item.

So this will give you an opportunity to discuss whether you wish to reconsider the designation of the NTP CERHR as an authoritative body at a future meeting. So we have provided you with copies of the petition, as well as various letters that we have received, both in support and opposition to the petition. And we have placed those on our website as they have come in.

So I just want to clarify, because of the letters, we did not announce a written comment period on

this item. But since this is America, and people have a First Amendment right to send you anything that they wish to talk -- that they wish, we felt that in the interests of transparency that it was important to make sure that you received those letters, and to ensure that they're available to the public on our website.

So, you know, these letters give you a sense of the interest in this item among certain stakeholders. But again, this is strictly a discussion item for you today.

So with that, Carol Monahan-Cummings had a short presentation on this subject.

(Thereupon an overhead presentation was Presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: This is more talking than I've done in any previous meeting I think.

As Allan noted, this is the discussion of the American Chemistry Council petition on NTP CERHR. That group was designated as an authoritative body by a unanimous vote of the DART Committee back in 2002.

By regulation, this Committee can revoke or rescind the designation of an authoritative body, if the Committee no longer considers the body to have expertise in identifying chemicals as causing reproductive toxicity.

The Committee Chair and OEHHA are seeking your advice as to whether or not we should consider putting

this petition on a future agenda. Obviously, we don't -- we haven't had a public comment period yet. There's -- we would want to do that and also spend a fair amount of time putting together materials, perhaps inviting speakers, if you wanted to consider it.

And so we didn't want to do that work if there wasn't interest in the group on reconsidering this. So what we -- what we don't want to do today is have you consider the merits of the petition, so much as just the concept of whether or not it's something that you'd like to consider at some point in the future.

We do have, at this point, plan to have a meeting of the DART Committee in spring, because we should be ready with sulfur dioxide by then, and we may be able to link this up with that one, depending on the amount of work involved, and that sort of thing.

So essentially, that's all I wanted to say and answer any questions you might have regarding the approach here. I do apologize for the -- again, for all of the reining in of comments that you received, but I think it came a bit from the fact that for this Committee at least, there's not usually a discussion item, so much as there's decision items. And so people are used to sending in comments. And so they did, even though they weren't solicited.

CHAIRPERSON BURK: So the question is for us, do we wish to consider the request to rescind NTP CERHR as an authoritative body at a future meeting. Does anyone have any feelings on it one way or the other?

COMMITTEE MEMBER ROBERTS: I'm very reluctant to rescind them, but I'm kind of concerned that after we voted, what, 7 to nothing that it didn't meet listing, that there would be a portion of the report that would be interpreted as indicating that it did meet listing. That part I have a concern about. I'm not sure it's using the CERHR in an appropriate manner.

CHAIRPERSON BURK: Well, you know, I will remind you of what our responsibility is in the code. "As an advisory body to the Governor and the lead agency, the DART Identification Committee may undertake the following activities:" And number 2 is "Identify bodies which are considered to be authoritative and which have formally identified chemicals as causing reproductive toxicity".

So we decide who's authoritative, but we don't necessarily get involved in the process that follows from that. And I think that's what you're expressing concern about, understanding how OEHHA then uses that designation to --

COMMITTEE MEMBER ROBERTS: Well, I guess what I would like to -- am I loud enough, I hope?

I guess what my concern about is, is that CERHR writes a really nice thorough report after putting together experts. And they identify chemicals as having some degree of concern. And those are somewhat subjective form of identification. And as I looked at it, previously, my feeling was that it was not really identifying a chemical in a listing type of format at all of those levels. That negligible concerns should be something that is not a listing conclusion is minimal. You know, I'm not sure that that would fit with the -- yeah, either the intent of Prop 65 or our intent as identifying them as an authoritative body. I'm not sure if anybody else --

CHAIRPERSON BURK: Yeah. So what are you recommending, that we discuss it as an authoritative body or try some other approach to --

COMMITTEE MEMBER ROBERTS: I'd like to have a clear understanding of what they mean when they say that they have identified something as having, say, minimal concern? I forget their other criteria, but they've got five of them I believe.

CHAIRPERSON BURK: All right. So is that a possibility, Jim, that --

DR. DONALD: Well, as a matter of clarification, while CERHR does identify levels of concern, that is not

what OEHHA uses in identifying whether formal identification has occurred. We never have and we have no intention of doing it in the future.

What we use is their weight of evidence identification. And we only use cases where they have identified clear evidence of adverse developmental or reproductive toxicity. So the level of concern is essentially hazard -- excuse me, not hazard, risk characterization. They're comparing the hazard they've identified with the potential exposure and coming up with a level of concern.

We only deal with the level of hazard that they have identified based on their weight of evidence evaluation.

COMMITTEE MEMBER KEEN: Yeah.

CHAIRPERSON BURK: Well, again, we don't want to debate the merits of the petition. I guess what we really just want to know is, is this something we should put on the agenda for a future meeting?

COMMITTEE MEMBER KEEN: Yeah. I think it's difficult for me to envision removing them. But with that said, given the flurry of letters from both sides that have come in, even when they weren't solicited, suggests that, as far as the public is concerned, it's an issue that perhaps does merit some discussion.

CHAIRPERSON BURK: Okay. Do others agree? I mean, it will involve, and I would ask, you know, what sort of information we would like to have to carry out this discussion or in the future. And, I mean, information that we would request beyond what public comments would bring in, I'm sure. I don't know.

CHIEF COUNSEL MONAHAN-CUMMINGS: Could I also clarify, in particular for Dr. Keen, are you concerned about the process OEHHA uses in the authoritative body process or are you concerned about the conclusions or the process that NTP uses to develop their documents? Because, you know, the presentations would be entirely different in those two cases.

COMMITTEE MEMBER KEEN: I personally don't have any concerns. And I'd be very surprised to -- if I were to change my opinion of how I view them and their documents right now, which is in a very positive fashion.

My comment was more that this seems to be an issue that folks have not sorted out in their own mind. And I think the Prop 65 process is critical. And just as we, in the previous discussion, were dealing with the perceptions of many NGOs and how they thought the process -- if this is a significant point, then I think it perhaps merits some discussion.

It's not because I personally have a concern for

them. So I'm giving you a bit of an evasive answer, because I'm quite satisfied with the process that they use, though I think for some Committee members and certainly some members of the public to have a better understanding of how they arrive at it, may be beneficial to the whole Prop 65 process.

CHAIRPERSON BURK: Well, I hear that as two different things though, because if we decide to hear the petition, what we're deciding is, are they an authoritative body or not. And we've already determined that they are. And I, you know, personally am only hearing everyone say yes they are authoritative, so without making any kind of decision.

The discussion, is there a way we could do that in a more informational way, you know, more educational way as opposed to having huge amounts of pro and con public comment on the authoritativeness of NTP CERHR. I don't know. I don't know. I personally am trying to avoid a huge amount of work for some inevitable, maybe, decision. But I'm open to anyone that has an opinion on this?

Dr. Hobel.

COMMITTEE MEMBER HOBEL: Yeah. I think that we, as a Committee, have the right to look at anything we want to look at, in terms of making a decision. And I brought

the document from our last meeting. I've been through it. I think it provides reasonable information. I made a lot of notes last time. And I think it's information that we use in our decision making. So I think we have that right to look at it.

And the source, I think, is good. And if there's biases in it, that's up to us to decide whether there's a bias or not. But I think it has tremendous value for us to use in our deliberation and assessment.

CHAIRPERSON BURK: Well, I agree, but I think the actual petition is to remove them as an authoritative body, which is a separate listing process than the DART Identification Committee process. So there's several ways that a chemical can get on the list.

COMMITTEE MEMBER HOBEL: It's a resource.

CHAIRPERSON BURK: And us using their information, I don't think anyone is disputing that. I think maybe it is unclear how this works, but there's a separate listing mechanism that OEHHA can use, where they take chemicals formally identified by bodies that we designate as a authoritative and then they can list on that mechanism.

CHIEF COUNSEL MONAHAN-CUMMINGS: You know, and also, it sounds like there may be some confusion about that particular process more than, you know, questions

about this particular authoritative body. And so a suggestion would be that we would be happy to give the Committee, you know, an overview of each of the processes -- there's four -- for listing chemicals and you can -- you'd be able to see where they are similar, where they're different.

You all are actually -- have been involved in the authoritative body process in a number of different ways. You identify the chemicals -- or I'm sorry, you identify the authoritative bodies. You also can -- we can refer chemicals to you if they don't seem to meet the criteria in the regulation that we've adopted. You had a lot of input, in terms of what the regulations says about the criteria for listing chemicals, and so -- for authoritative bodies.

And so it might be useful for you to see that, in terms of understanding the process. It also would be an educational process for the public, because I think that they may have a certain level of misunderstanding of how those documents are used. Each authoritative body has a little bit different approach, and a different format, and things like that, that our office has to kind of sift through. And we've got, you know, procedures for doing that.

So we could -- we'd be happy to do a presentation

like that for you, either before or whatever, if that would be more helpful or something, in terms of the process rather than the actual designation of an authoritative body.

COMMITTEE MEMBER GOLD: So maybe it was my confusion when I read the petition, but it sounded to me --

DR. ALEXEEFF: I couldn't quite hear you.

COMMITTEE MEMBER GOLD: It may have ben my confusion when I read the petition, but it seemed to me that there was confusion in the petition between requesting that they be -- you know, reconsideration of this authoritative body versus how OEHHA uses the authoritative body. And so I think those two things are getting confused.

And I'd like to try and separate them. And I think the educational process that you're suggesting would perhaps help to clarify that, and -- but given that con -- I just don't see the reason for the petition, per se -- I mean, for reconsidering the authoritative body. I think having some education about how it gets used might be helpful.

CHAIRPERSON BURK: Any other comments?

COMMITTEE MEMBER WHITE: I would just like to say I agree. I'm somewhat ignorant with respect to the

various -- the four various ways that chemicals get listed. And I couldn't even imagine thinking about rescinding anything without having enough education. Thank God I don't practice medicine that way.

(Laughter.)

COMMITTEE MEMBER WHITE: Without enough information. So I too agree, we need an education. We need to be educated, and then go from there. I think that would be fair.

CHAIRPERSON BURK: So I think what I'm hearing is we would defer our decision on whether to hear the petition or not until we get some education.

COMMITTEE MEMBER WHITE: Yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: You can basically table the discussion on the NTP petition, and then, you know, we can work on -- and if you all today or if you think about kinds of questions that you would like us to address, we'd certainly put some materials together for you in advance.

And are you interested in all of the other listing mechanisms or would it be your reference just to look at authoritative bodies at this point?

CHAIRPERSON BURK: Oh, I think a quick overview of the four listing mechanisms would be useful, and then maybe more information on specifically the authoritative

body mechanism. And I personally can think of some questions that I have, so I would hope that we could submit those.

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. That would be fine. You might want to -- don't send them to anybody else, but say to me. And then we won't be having any problems with reply to all. Although, it just would be a discussion item once again, in terms of, you know, the Committee understanding the process and kind of an educational session, rather than any decision making.

MR. LANDFAIR: Dr. Burk, will the Chair entertain comment on this?

CHAIRPERSON BURK: No, sorry. We decided to have this discussion. And I can see a lot of people out there chomping at the bit. So I know that even if we do this as an educational process, there's still going to be folks that are going to want to comment on it.

MR. LANDFAIR: Well, what I have to state for the record is that the petitioner has placed before the Committee a formal legal petition asking, in essence, for adjudication of its right --

CHAIRPERSON BURK: A formal legal --

MR. LANDFAIR: This is a formal legal petition.

CHAIRPERSON BURK: There will be no public comment and we're not a court of law.

MR. LANDFAIR: And we are being denied the opportunity to be heard.

CHIEF DEPUTY DIRECTOR HIRSCH: This is a discussion item only. And maybe Carol can clarify this, but we've run into legal problems if we start taking public testimony.

MR. LANDFAIR: We recognize it's been placed on as a discussion item. However, you were presented with a formal petition to, in effect, decide an important matter which affects the rights of parties who have an interest before the Board. So by placing it before the Board as a discussion item --

CHAIRPERSON BURK: Yeah, I understand that, but we've decided to table it.

MR. LANDFAIR: -- and then deciding not even to entertain comment from those affected, you have effectively denied us an opportunity to be heard and due process of law.

CHIEF DEPUTY DIRECTOR HIRSCH: What the Committee is discussing here is having an informational item at a future meeting prior to making a decision on whether they want to hear this petition. So, in my opinion, there's been no -- not hearing public comments, there's always the opportunity to present that later.

MR. LANDFAIR: Then it seems as our petition has

just been deferred ad infinitum and effectively denied.

CHIEF COUNSEL MONAHAN-CUMMINGS: No, it's been tabled for the moment.

MR. LANDFAIR: That's kind of what I said.

CHIEF COUNSEL MONAHAN-CUMMINGS: And, Stan, there is no public comment right now. So I'd appreciate if you would --

MR. LANDFAIR: Well, I recognize I'm extending beyond the limits of courtesy, and I recognize that and I will yield.

Thanks very much.

CHIEF DEPUTY DIRECTOR HIRSCH: All right.

CHAIRPERSON BURK: George.

DR. ALEXEEFF: Dr. Burk, just to get back to where we were, in terms of understanding the authoritative body process, as Carol had mentioned, each authoritative body that you've designated kind of comes with different kinds of reports and kind of puts together their level of evidence differently.

So what we could do, if you'd like, we could either just focus on NTP and say how we interpret their information, in terms of the authoritative body listing process, or we could give you information about the other authoritative bodies as well on how we interpret their documents, like EPA, and et cetera, FDA whatever.

So I just kind of -- we would do it briefly. We wouldn't try to -- but it would just sort of give you a sense as to the types of things we look for in the documents as to whether they've made a decision and what type of decision they've made.

CHAIRPERSON BURK: Yeah. I think I'm hearing that we would like to hear that briefly.

All right. I think that's the end of our discussion.

So the next agenda item is staff updates. And Cynthia Oshita is coming forward.

MS. OSHITA: Good morning -- or good afternoon, I guess now.

Since the Committee last met in July, OEHHA has administratively added 29 chemicals to the Prop 65 list, 19 were added as chemicals known to cause reproductive toxicity, and the other 10 were added as chemicals known to cause cancer.

And I will not recite all 29 chemical names, but instead we've included a summary table with the latest additions, and the respective effective dates. And they're in your meeting materials behind the staff updates tab.

There presently are three chemicals that are under consideration for administrative listing, being

methanol as causing reproductive toxicity, 4-Methylimidazole and metam potassium as causing cancer. And each of these chemicals are in the Notice of Intent to List phase. We've received comments on each of the chemicals, and those comments are under review.

In addition, on three separate occasions since last July, OEHHA announced the proposed administrative listing of yet some other chemicals. One of the chemicals as causing reproductive toxicity, that's BPA. Comments were received on BPA and those are under review.

The other two chemicals were under consideration for causing cancer. Those are epoxiconazole and DEF. Those two are in the Notice of Intent List phase right now. Comments were received on epoxiconazole. We are reviewing those comments. And then an extension to the public comment period was granted for DEF and that will be closing on November 15th, 2010.

Today, OEHHA will also post a notice announcing the proposed administrative listing of yet six more chemicals, that they are under consideration for causing cancer. And the public comment period will close on December 21st, 2010.

Turning to the safe harbor levels. Since last July, OEHHA has proposed to adopt two new Maximum Allowable Dose Levels. Those are for DIDP, and hexavalent

chromium. The rule-making package for DIDP is currently with the Office of Administrative Law for review and approval.

We did receive one comment on the Maximum Allowable Dose Level for hexavalent chromium. And so its rule-making package will be finalized and submitted to the Office of Administrative Law in the near future.

We are also proposing -- we have also adopted two No Significant Risk Levels, one is for para-chloroaniline and the other one is for para-chloroaniline hydrochloride. These levels became effective on August 12th, 2010.

And then currently we have also proposed two new No Significant Risk Levels. Those would be for 2,4,6-Trinitrotoluene, or TNT, and glycidol. We did not receive any comments on either. And so their rule-making packages will be finalized and submitted to the Office of Administrative Law as well in the very near future.

Thank you.

CHAIRPERSON BURK: Thank you. And now Carol Monahan-Cummings will talk about Prop 65 litigation.

CHIEF COUNSEL MONAHAN-CUMMINGS: Here I am again.

We have three pending cases related to Prop 65 listings or proposed listings. Two of them are in the Court of Appeal different districts. One was a case brought by the California Chamber of Commerce challenging

our authority to list chemicals under, what we call, the Labor Code mechanism under Prop 65, which I'll explain to you at the next meeting what those are.

And then there's another case that is pending in the Court of Appeal that relates also to Labor Code listings under a little different process, and that has to do with styrene and vinyl acetate. And those are fully briefed and ready for the courts to hear, but we haven't had a briefing schedule issued by the courts yet.

The one case that's pending in the trial court is the Sierra Club versus Schwarzenegger case, which I've mentioned to you a number of times. It's been pending, I think, since 2007 perhaps. And we are in the discovery stage of that case still. It mostly affects our other listing processes, including authoritative bodies, Labor Code and CIC processes. But this Committee -- and actually the CIC members have been named in that action not you.

But it affects this Committee to the extent that it also discusses the prioritization process that we adopted in 2004.

That case, as I mentioned, is in the discovery phase. There's some motions that should be decided shortly on discovery issues that may result in our office taking a writ to the Court of Appeal. And so we may have

all three cases in the Court of Appeal at some point in the future.

There are always other cases that are pending Prop 65 issues, but those are the ones that directly affect our office and potentially affect this Committee.

Does anybody have questions on those?

I don't believe that you are -- any of you are part of the litigation hold that I have on documents, and so you don't have to worry about that. That's the CIC.

CHAIRPERSON BURK: Thank you. Thanks, Carol.

Before I let Allan close, I just want to thank everyone for coming today. I particularly want to thank the staff for all the hard work they put into preparing the materials for us. And, of course, I want to thank the Committee for, I think, excellent discussion today and participation.

And I'll turn it over to Allan Hirsch for final comments.

CHIEF DEPUTY DIRECTOR HIRSCH: Thank you, Dr. Burk. Well, just to quickly summarize what took place today in the one action item, the Panel voted to list methyl isocyanate on the Prop 65 list for developmental toxicity and female reproductive toxicity. That was both unanimous notes. You voted not to list it on the basis of male reproductive toxicity.

And so then on the other items, the sense of the Committee was the approach we suggested for prioritizing chemicals in the future you seemed comfortable with.

On the meeting items, in terms of how you wish to split your Committee discussions and votes, the sense of the Committee was certainly maintain flexibility. So on chemicals without, you know, a substantial volume of information like today's, you could certainly keep doing it the way that we did. But for large chemicals, to keep open the option of having separate presentations and discussions for each of the three endpoints, but wanting to withhold your votes until the end.

On comment periods, the sense of the Panel was to keep the comment period short. Three minutes was the only number given, but to keep the comment period short, while noting that if you have separate presentations on each endpoint, that would probably connote three separate comment periods too. And that OEHHA would do its best to avoid redundancy in our staff presentations.

And you also, you know, oppose speakers ceding time to other speakers.

You also -- the sense of the Panel was, yes, that the Chair or any of you could ask a speaker for attribute -- to state their affiliations and any financial affiliations or disclosures that you would like them to

make.

And the sense of the Committee was also to keep voice voting the way that you have been as opposed to paper voting.

And then last, but certainly not least, the sense of the Panel was to have us come back with an informational presentation probably at the next meeting about the four listing mechanisms, and then that would proceed any further discussion that you would have about whether you want to consider the petition to de-designate or rescind the designation of the NTP CERHR.

So unless anyone thinks I've misstated anything, that's certainly my summary of what happened.

We don't have a firm date for our next meeting, but, as has been said, we're thinking in terms of next spring. It's a little -- I guess you've had meetings in the spring in the past. They tend to be in the fall, but we are thinking of having you back next spring.

And that's it.

CHAIRPERSON BURK: All right. I think we're adjourned. Safe journey home to everyone.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 1:28 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 1st day of November, 2010.

JAMES F. PETERS, CSR, RPR
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