CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

---o0o---

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986

(PROPOSITION 65)

---o0o---

MEETING OF THE SCIENCE ADVISORY BOARD'S

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT (DART)

IDENTIFICATION COMMITTEE

---o0o---

THURSDAY, NOVEMBER 4, 2004

---o0o---

HELD AT:

California Environmental Protection Agency
Headquarters Building
1001 I Street
Sacramento, California

Reported By: PHYLLIS MANK, CSR No. 5093
BALINDA DUNLAP, CSR No. 10710

APPEARANCES

---o0o---

COMMITTEE MEMBERS:

DOROTHY BURK, Ph.D., Chairperson
KENNETH JONES, M.D.
CARL KEEN, Ph.D.
LINDA ROBERTS, Ph.D.
STEVEN SAMUELS, Ph.D.

OEHHA STAFF:

JOAN DENTON, Ph.D., Director
GEORGE V. ALEXEEFF, Ph.D., D.A.B.T.
JAMES DONALD, Ph.D.
MARLISSA CAMPBELL, Ph.D.
FARLA KAUFMAN, Ph.D.
MARI S. GOLUB, Ph.D., D.A.B.T.
LING HONG LI, Ph.D.
CAROL MONAHAN, ESQ., Chief Counsel
CYNTHIA OSHITA

INDEX

---o0o---

INDEX (Continued)

---o0o---

SACRAMENTO, CALIFORNIA, NOVEMBER 4, 2004

---o0o---

DR. DENTON: Good morning. I think we will go ahead and get started. My name is Joan Denton, and I am the Director of the Office of Environmental Health Hazard Assessment, and I would like to welcome the members of the Committee as well as the members of the audience and the staff of OEHHA to the meeting.

Hopefully everyone has a copy of the agenda. And if you would like to make comments on the agenda items, our usual, our standard procedure is for you to fill out the blue cards and to give them to Cindy, who is in the back there, who will bring them up to the acting Chair.

I would like to introduce the members of the Committee. To my far left is Dr. Steve Samuels. And then next to Dr. Samuels is Dr. Linda Roberts. And sitting immediately to my left is Dr. Dorothy Burk. And to my immediate right is Dr. Carl Keen. And then Dr. Ken Jones rounds off the group there at the end.

So thank you very much to the Committee for their attendance today.

I think it is worth making a comment about the size and the individuals who are not here who were here last year. And I just want to briefly explain that during the last hours of the Davis administration, there were some changes made to

the makeup, not only of this Committee, but of our other Prop 65 Committee, the Carcinogen Identification Committee.

That was done, as I said, in the last hours of the Davis administration.

And then with the arrival of the new Schwarzenegger administration, very shortly after they arrived, additional changes were made in the Committee.

So, in essence, when all the dust settled, then the current makeup of the Committee are these individuals who are represented here today, and the other members are not -- are no longer on the Committee.

We have been working very diligently to get additional members for the Committee, for this Committee and the CIC Committee, and to bring back some of the expertise that has been lost.

And we understand that, you know, it is momentarily that there will be more appointments made. But at this point in time, those appointments have not yet been made, and we have been, as I said, working diligently to bring back some of the members, other members that we have lost as well as confirm the membership of the current Committee.

At any rate, let's see. I think the next thing is that we -- because we do not -- because we no longer have a Chair of this Committee, the -- this Committee needs to appoint -- appoint, I guess, recommend or -- an acting Chair.

Steve.

COMMITTEE MEMBER SAMUELS: I move that we appoint Dr. Burk as the acting Chair for this meeting.

DR. DENTON: The other members concur? Well, it's unanimous, unanimous concurrence. So Dr. Burk will be the acting Chair for this meeting.

Since we kind of did a concurrence thing, I would like to turn this over to Carol, the chief counsel for OEHHA, who has some comments to make on the voting, which will happen later on on these agenda items. So, Carol.

MS. MONAHAN: Good morning. I just wanted to point out since we are in a somewhat unusual situation of only having five members on the Committee today, that under OEHHA's regulations, which is Section 12302 of Title 22, the makeup of the Committee is supposed to be seven -- a minimum of seven and a maximum of 11 members.

When this situation came up in the past, there were about six members of one of the Committees, and the question was posed whether or not six members could take action that would be valid.

And the Attorney General's Office had issued an opinion in that regard that discusses State law on the question. And it's also my opinion that the Committee can act with less than seven members, but what we had to have was a vote of at least four -- an affirmative vote of at least

four of the members in order for a motion to carry.

So that means that the five of you today, of the five, four need to vote in favor of something in order for, for example, for the chemical to be recommended to be listed.

In the event that there is a vote that's maybe, like, three/two in favor, what I would -- will probably ask you is whether or not you want to defer that question to a meeting -- a later meeting of the Committee, since there would be a majority at least of the sitting members that thought that the chemical should be listed. So if that situation comes up, I'll ask you at that time.

Also, given the fact that some of the expertise that's needed for this Committee is no longer here, since some of the members are missing, I wanted also to mention to you that if you feel that you don't have the necessary expertise to make a decision today on either one of the two chemicals that will be presented to you, you do certainly have the option to request that that chemical be deferred to another meeting when that expertise is available.

Anybody have a question on that?

DR. DENTON: Okay. The last thing that I want to do before I turn it over to Dr. Burk is to just basically affirm the agenda. Because we did not have an appointed Chair, essentially if -- we need to do that now, to basically affirm the agenda.

So if the Committee has no additions to the agenda, then the agenda stands. And at this point, Dr. Burk, I'll turn it over to you.

CHAIRPERSON BURK: All right. First up, we'll start with our consideration of chemicals as known to the State to cause reproductive toxicity. And she's here, so Marlissa will begin with chloroform and our staff presentation.

DR. DONALD: Actually, if I might just make a couple introductory remarks. Jim Donald, chief of the reproductive toxicology and epidemiology unit.

Chloroform and progesterone are both chemicals which were selected through our prioritization process that we adopted in 1996 for consideration by this Committee.

Just for clarification, these chemicals were not randomly selected, as has been the case for chemicals considered by the Carcinogen Identification Committee.

Prior to 1996, we had a different prioritization process in place for chemicals that potentially caused reproductive or developmental toxicity. Chloroform and progesterone had been selected as potential candidates through that process.

So when we started the new process in 1996, we re-entered those chemicals into that process, and they were reselected as being of high concern.

The first chemical that we are going to consider is

chloroform. I should also probably clarify at this point that when progesterone's considered, it is only progesterone and not other progestational drugs that are being considered for listing today.

Dr. Marlissa Campbell will briefly summarize the evidence on reproductive and developmental toxicity in animals for chloroform, and then Dr. Farla Kaufman will present a brief summary of evidence in humans.

It will take just a moment for the projectors to warm up. I think the Committee members can see the slides on their screens? Copies of the slides are available in handout form if we are not able to project them.

DR. DENTON: Jim, it doesn't look like those projectors are on.

DR. DONALD: Yeah, they were working a few minutes ago. They seem to have turned themselves off, some sort of an energy-saving thing.

DR. DENTON: We can see them with the copies. If the public has copies, then I think we can go ahead and proceed. There we go.

DR. CAMPBELL: Chloroform, or trichloromethane, is a high-production volume chemical with over 500 million pounds produced annually in the U.S.

Chloroform is usually the most prevalent by-product formed when drinking water is disinfected by chlorine.

Exposure to chloroform may occur in the workplace or through exposure to chlorine-treated water.

Chloroform is readily absorbed by the oral and inhalation routes. Dermal absorption requires contact with chloroform in liquid rather than vapor form. It distributes widely throughout the body, and there's evidence that chloroform crosses the placenta and can be expected to appear in human colostrum and mature breast milk.

Chloroform is metabolized by cytochrome P450-dependent pathways, and any non-metabolized chloroform is excreted primarily through exhalation.

Chloroform was one of the earliest known surgical anesthetics, so there's quite a lot of acute human exposure. The use of it tapered off when it became clear that it had a higher fatality rate than newer alternatives that were coming in about the 1930s.

Chronic exposures to chloroform in the workplace have been reported to result in neurological effects, as well as affects on the liver.

Chronic exposures in animals have given evidence of cytotoxicity in liver, kidney and nasal epithelium. And chloroform is included on the Proposition 65 list of carcinogens.

In this study, the Schwetz study, in the high concentration group, the pregnancy rate was reduced. Live

litter size was decreased. Resorption frequency was increased. Fetal weights and crown rump length were decreased, and the sex ratio was altered. At a concentration of 100 ppm, the frequency of gross anomalies was increased, consisting of acaudia, or short tail, and imperforate anus. At 30 ppm, the frequency of skeletal anomalies was increased, and the crown rump length was decreased.

No maternal deaths occurred during this study. Maternal body weight on gestation day 13 was significantly reduced at all concentrations of chloroform. At the high concentration of 300 ppm, maternal weight was still reduced on gestation day 21, whereas the other treated groups had returned to control levels.

Feed consumption on the first day of treatment was significantly reduced at all three test concentrations. For the 100 and 300 ppm groups, feed consumption remained low during treatment, but subsequently increased above control levels for the 100 ppm group by gestation day 18 to 19.

In order to try to understand the contribution of maternal anorexia to the fetal effects observed with chloroform, the authors of the Schwetz study included a feed-restricted control group, which was given only 3.7 grams of food per day on gestation day six through 15.

This level of feed consumption can be compared to the 20-plus grams per day consumed by the untreated controls, and

approximately one gram per day consumed by the 300 ppm chloroform group over the days of treatment.

Feed-restricted control showed statistically significant decrements in maternal weight as well as reductions in fetal weights and lengths, but no malformations and no affect on the percent of successfully bread dams that were found to be pregnant at term.

Fetal weights in the restricted group were reduced to approximately 90 percent of ad-lib controls, whereas weights in the 300 ppm chloroform group were reduced to approximately 60 percent of ad-lib controls.

The pregnancy rate for these feed-restricted controls was 100 percent, in contrast to the 15-percent pregnancy rate found for animals in the 300 ppm group.

In another pair of studies done by the same authors, decreased weight and/or fetal length were reported for rat fetuses exposed to chloroform concentrations of 30, 100 and 300 ppm.

The number of live litters decreased with increasing concentration of chloroform, reaching a significant difference from controls at 300 ppm.

Increased skeletal variations were observed at three, ten and 30 ppm. There were no maternal deaths in either of these studies.

In the 1988 study, maternal body weight was

significantly reduced at all three test concentrations on gestation day 17, and remained reduced on gestation day 21 at 100 and 300 ppm.

Feed consumption was reduced at all three concentrations during treatment, but subsequently rebounded to a level significantly above controls.

In the 1991 study, the data on maternal body weight were not statistically analyzed, but appeared to show decreases for the three, ten and 30 ppm groups. Feed consumption was significantly reduced for all groups during the first week of the treatment period.

In the Thompson study, fetal weights were significantly decreased at 126 milligrams per kilogram per day. This is an oral study we are looking at now. Maternal weight gain during the treatment period was significantly reduced at 50 and 126 milligrams per kilogram per day.

There were no maternal deaths during the course of this study. Maternal feed consumption was significantly reduced during treatment only at the 126 milligram per kilogram per day level.

In the Ruddick study, mean fetal weight was significantly decreased in the 400 milligram per kilogram per day group. No maternal deaths were reported with chloroform exposure. And maternal weight gain was significantly decreased in all three groups, but feed consumption data were

not reported.

Now we have inhalation in the mouse. And this Murray study, pregnancy rate was lower for treated animals from gestation days -- it was a single dose, and they varied the days of treatment. So pregnancy rate was lower for animals that were treated on gestation days one through seven or six through 15.

Litter size was not affected, though resorption frequency was significantly increased with treatment on days one through seven. Fetal weights and crown rump lengths were significantly reduced with exposure on gestation days one through seven or eight through 15. One of the treated dams died in this study.

Maternal body weight gain was significantly reduced for animals treated on gestation days one through seven or eight through 15. It was not clear if this was total gestational weight gain, or weight gain over the treatment period.

Oral treatment in rabbits. In the Thompson study, mean weights of fetal rabbits were significantly reduced at 20 and 50 milligrams per kilogram per day, but not at 35 milligrams per kilogram per day. Loss of complete litters was seen in all groups, including the controls, and without a clear concentration response.

Four out of 15, or 27 percent, of maternal animals

died following exposure to 50 milligrams per kilogram per day chloroform. Two out of 15 controls, and one out of 15 dams in the 20 milligram per kilogram per day group also died during the study.

Body weight gain was said to have been significantly decreased among survivors of the 50 milligram per kilogram per day group, but data and statistics were not presented.

This is an oral developmental neurotoxicity study conducted in mice. Mean litter size and body weights did not differ between treated and control groups, but weight gain over postnatal days seven to 21 was significantly lower in treated pups.

The chloroform-exposed group had reduced scores for forelimb placement on each of days five through eight, with statistically significant differences on days five and seven. These are postnatal days, obviously.

However, reflex and response test revealed no overall retardation of neurobehavioral development in these mouse pups. And tests of motor performance and learning did not show differences between treated and control groups.

Turning to male reproductive toxicity, in an inhalation study of male mice which focused only on sperm parameters, significant increases were found in the percentage of abnormal sperm for both exposed groups.

In a continuous breeding study conducted by gavage in

mice, five animals died over the course of the study. However, treatment had no significant affects on mortality, body weight, fertility or the sperm parameters evaluated in that study.

Both absolute and relative rat epididymal weights were significantly increased for animals in the F1 generation in the 41.2 milligrams per kilogram per day dose group.

Just for comparative purposes, OEHHA converted the Land concentrations to approximate doses on a milligram per kilogram per day basis. Though absorption is fairly complete from both inhalation and oral exposures, this is only a rough approximation and does not account for likely differences in pharmacokinetics by the different routes.

Turning to female reproductive toxicity, in the continuous breeding study, which we just discussed with the previous slide, there were no treatment-related changes in any of the evaluated end points of female reproductive function.

In a 90-day drinking water toxicity study conducted in rats, no changes were observed in female reproductive organs at necropsy.

In a seven-and-a-half-year study of chloroform that was given in the form of capsules to group of Beagle dogs, eight Beagle dogs of each sex, no treatment-related changes were noted in female reproductive organs at necropsy.

Now, a number of the developmental toxicity studies that I already described has information that's pertinent to female reproductive toxicity. So I'll just go through that really quickly.

In rats by inhalation, effects were seen on pregnancy rate and/or resorption frequency at a concentration of 300 ppm. Maternal deaths were not seen in these studies, but there were affects on maternal weight, body weight and feed consumption.

Mice by inhalation. Pregnancy rate and resorption frequency were affected at various times during gestation. One maternal death occurred during the study, and maternal body weight gain was affected at the certain time points.

Oral studies in rats did not provide effects -- did not provide evidence for affects on pregnancy rate or litter size.

Complete loss of litters was seen in groups of rabbits exposed by the oral route with no clear concentration response relationship. Excess maternal death was seen at the highest concentration.

And just to summarize the findings for the animal data, rats exposed to chloroform by inhalation during gestation, observations included affects on pregnancy rate, resorption frequency, fetal weight, crown rump length, as well as some evidence for increases in the frequency of

skeletal anomalies and variations.

Similar results were found for rats exposed to chloroform by the oral route, as well as for mice exposed by inhalation.

Rabbits exposed by the oral route showed affects on fetal viability. All of these studies also reported some degree of maternal toxicity, ranging from minimal decreases in feed consumption to excess maternal mortality.

Male mice exposed to chloroform by inhalation showed abnormalities in sperm morphology, while a gavage study did not detect treatment-related changes in fertility or sperm parameters.

While a study of fertility and also necropsy evaluations of female reproductive organs did not find evidence for female reproductive toxicity, several developmental toxicity studies included relevant findings. These effects included decreased pregnancy rate, decreased litter size and/or increased resorptions and whole litter abortions.

All of these effects were observed at doses or concentrations that were also associated with some degree of systemic toxicity to the maternal animals.

That's all I have for my part.

DR. DONALD: We can either take any questions you have now for Dr. Campbell, or wait until Dr. Kaufman has made

her presentation.

CHAIRPERSON BURK: Are there any questions from the Committee at this time?

DR. KAUFMAN: In this part of the presentation concerning developmental and reproductive toxicity in humans, I have included only studies that specifically determined chloroform exposure.

Studies that examined affects of trihalomethanes, of which chloroform is the major constituent, were included in the hazard identification document. However, I will not present that material here.

Concerning developmental toxicity in humans, eight studies were identified which examined exposure to chloroform, one occupational cohort study of chloroform exposure in laboratory workers, and seven studies of chloroform in drinking water.

The occupational study was conducted by Wennborg, et al., in Swedish laboratory workers with the reference group being female non-laboratory workers with the same socioeconomic background.

In the study, questionnaire data was used to assess exposure to chloroform. An increased risk of spontaneous abortion was observed for woman working with chloroform during the time before conception, with an odds ratio of 2.3, although the lower 95-percent confidence interval was just

under one. This may be due to the smaller number of exposed women. The odds ratio for previous spontaneous abortions was 2.2.

Four of the seven studies which examined exposure to chloroform in drinking water are shown on this slide. As you can see, there are -- three of these four studies found statistically significant developmental effects, including increased risk of intrauterine growth retardation, stillbirth and chromosomal abnormalities.

Two of the remaining three developmental studies, as shown in this slide, found statistically significant developmental effects, including, once again, an increased risk of stillbirth, as well as lower birth weight and small for gestational age, which is essentially equivalent to intrauterine growth retardation.

One study was located that reported on male reproductive toxicity of chloroform in the very well-conducted occupational case report. One male worker, a laboratory worker, exposed to very high levels of chloroform showed lowered percentages of total motile sperm, down to 26 percent from previously measured levels.

The lab worker was also exposed to isooctane and tetrahydrofuran. However, no animal or human studies were found which examined male reproductive toxicity of these two compounds.

In addressing female reproductive toxicity, an occupational study conducted by Dahl, et al., using questionnaire data found no evidence of an affect of chloroform exposure on fertility in female dental surgeons. However, the study had a low response rate, as well as a very long recall period for exposures and pregnancies up to 40 years.

The second study by Wennborg, et al., was described in the developmental section, and reported associations with spontaneous abortions.

To summarize the effects of chloroform exposure, the developmental effects included decreased birth weight, intrauterine growth retardation, and increased stillbirths. Developmental effects were seen in six of these eight studies.

For male reproductive effects, one case report found lower percentage of total motile sperm. This finding is in agreement with a study by Land, et al., in rats by the same route of exposure, inhalation. Decreased percent of motile sperm seen in humans is comparable to the increase in abnormal sperm morphology seen in mice.

Female reproductive toxicity included two studies. One study found no effects on fertility, while the other study reported an increased odds ratio for spontaneous abortion.

Careful attention should be given to specific strengths and limitations of these studies. These include the level of chloroform to which the subjects were exposed. In each of these studies, this varied considerably.

Evidence of a monotonic increase in risk or dose response was shown in one study for the association between chloroform exposure and small for gestational age, but only at levels greater than 20 micrograms per liter.

In certain other studies presented here, mean exposure levels to chloroform were only 11 micrograms per liter.

In addition, the ability or power of the study to detect an effect, if one is really present, is determined by the sample size. The sample sizes varied considerably between studies, as well as between the exposure levels within a study. The study that reported a dose response had the highest chloroform exposure levels, and the largest study population, and, thus, the greatest power.

This slide presents a summary of the concordance of human and animal data by outcome and route of exposure. For developmental outcomes by the oral route in humans and animals, results showed significant decreases in fetal weight and increased intrauterine growth retardation.

By inhalation route, there was increased spontaneous abortions and stillbirths in humans with increased

resorptions in animals.

For male reproductive toxicity by the inhalation route of exposure, the human case report found decreased sperm motility with the related outcome in animals of increased abnormal sperm morphology.

Female reproductive toxicity by the inhalation route again showed increases in spontaneous abortions in humans with an increase in resorptions and in whole litter abortions in animals.

That concludes my presentation. Thank you for your attention. Do you have any questions?

CHAIRPERSON BURK: Thank you very much, Farla. Are there any questions from the Committee?

I just want to say, though, while I got both of you, thank you so much for a very nice document. I always want to recognize all the effort that goes into preparing that.

Another chance, did anybody have a question now, or shall we proceed to the public comments?

COMMITTEE MEMBER ROBERTS: I have one question for you. On the slide at the bottom of page 2 of the handout, list of developmental toxicity of chloroform exposure in drinking water in humans, the Kramer, Waller, King and Dodd and King studies, those effects listed, didn't some of those also look for other affects? In other words, the one that is positive for stillbirth, did it look for small for

gestational age?

DR. KAUFMAN: In many studies they did look for other outcomes. In that study, I don't believe they did. That was strictly stillbirths.

COMMITTEE MEMBER ROBERTS: Okay.

CHAIRPERSON BURK: Are there any other questions?

COMMITTEE MEMBER JONES: Can we come back?

CHAIRPERSON BURK: Absolutely, we'll discuss it. It is just a matter of if you have a burning question now, otherwise we'll go on with the public comments. And I'll go in the order that I received the cards.

So the first one is John Ulrich, Jay Murray, Chemical Industry Council of California, Chlorine Chemistry Council. Is it both, one? Yep, both of them are coming forward.

MR. ULRICH: Dr. Burk, Director Denton, distinguished members of the Committee, my name is John Ulrich. I am a senior consultant to the Chemical Industry Council of California, a State trade association of chemical manufacturers, distributors and allied industries.

On behalf of our association and our partner, Washington D.C.-based Chlorine Chemistry Council, I would like this morning to offer some brief introductory remarks regarding chloroform and the subject matter before you.

First let me thank you, the members of the DART Committee, for your careful review on the data concerning

whether or not chloroform is a reproductive toxicant.

Chloroform is a by-product of chlorine disinfection. And chlorine disinfection is an important public health tool in preventing disease.

In fact, last month the Centers For Disease Control and Prevention noted that a number of waterborne disease outbreaks were attributable to inadequate chlorination of swimming pools.

Your evaluation today will determine whether or not California identifies chloroform as known to cause reproductive toxicity. Your evaluation will determine whether a warning of known to cause reproductive toxicity will be required for exposures to chloroform in excess of one one-thousandth of the no observed affect level.

Because the public health stakes are relatively high relating to the use of chlorine as a public health tool for disinfection, we appreciate your careful attention to this listing evaluation.

The Chemical Industry Council of California and the Chlorine Chemistry Council have jointly asked Dr. Jay Murray to review the relevant data and provide his observations today in an effort to assist your evaluation.

I understand that Dr. Murray is well-known to you. And for this reason, I will turn the floor over to him without further introduction. Thank you very much.

DR. MURRAY: Good morning. Well, first, thank you for reviewing the written comments that were submitted. And those comments were prepared by me and Dr. Robert Tardiff, who is here today. And this is Dr. Tardiff sitting in the front row.

Dr. Tardiff, for those of you who may not know him, headed up U.S. EPA's toxicology drinking water laboratory where some of the major risk assessments of chlorine disinfectant by-products were conducted, including chloroform.

He also ran the first Environmental Health and Toxicology Department at the National Academy of Sciences. And for those who are familiar with that nine-volume drinking water and health series, that was Dr. Tardiff's responsibility. And today he's the founder and principal of the Sapphire Group in Bethesda, Maryland.

I have two sets of handouts. I wonder if I can figure out how to get up there, if I can bring those to you. Thank you, Cindy. Next slide.

Well, we have all been here before. These are the three issues before you. I am going to cover them in this order, and I am going to focus mostly on developmental toxicity, because that's where most of the data are. Next slide.

One of the first things I did is I looked at what

summaries were available on the epidemiological data. And what you see on this slide is a quote from U.S. EPA's toxicological review of chloroform that was done in 2001. Says, "Although epidemiological studies of this type are useful in evaluating whether chlorinated drinking water can increase the risk of adverse reproductive effects in exposed populations, the studies are not adequate to establish a causal link between ingestion of chloroform and the occurrence of adverse reproductive effects in humans, because chlorinated drinking water contains many different potentially toxic disinfection by-products."

And I emphasized the section in the middle, and that was my emphasis, not EPA's. Because as you know, the standard for Proposition 65 is causation. It has to be clearly shown through scientifically-valid testing, according to generally accepted principles, to cause reproductive toxicity. So an association isn't enough. Association doesn't meet the listing criteria, in part because an association can be due to other factors. Next slide.

So on the epidemiology developmental tox studies, there is no causal link established with respect to chloroform. As you heard in OEHHA's presentation -- by the way, OEHHA did a very nice job of reviewing these studies, both in the hazard identification document as well as in the summary presentations this morning.

So in some cases I'll be able to breeze through these slides, because it's already been said, and this is one of those things.

You heard correctly that all but one of these are drinking water and THM studies. They are not chloroform alone studies. Some of the studies included an evaluation of chloroform. But where there's chloroform, there are other disinfectant by-products.

There was also the one occupational study of laboratory workers, the Wennborg study that you heard about. One of the difficulties there is you have all worked in laboratories. You know that chloroform is not the only thing you're exposed to in the laboratory.

The association that was sometimes seen for THMs is interesting because many of those -- not many, but in a subsection of those studies, also looked at chloroform.

And in the summary slides that you saw in the epidemiology this morning, the good part is what you saw were the data specifically for chloroform. But it's also important to keep in mind that for a lot of those studies, the primary focus was total THMs. And they would see an association for total THMs in some of those studies, but then when they looked at chloroform, either there was no significant association for chloroform, or the association was weaker than it was for total THMs, suggesting that

chloroform is not the culprit.

The limitations of the epidemiologic studies, you heard some of that this morning, and it was also in the hazard identification document, no dose response problems with exposure misclassification. So I am not going to go into any detail on that. Next slide.

Animal studies. First there have been no developmental effects seen in the absence of significant maternal toxicity in those studies. The HID said that, and Dr. Campbell, I believe, also said that this morning.

When maternal toxicity -- and probably also important to point out that these studies did not demonstrate any teratogenic activity of chloroform. So the issue is embryotoxicity and fetotoxicity.

And what the study showed is that when maternal toxicity was excessive and then -- by "excessive," what I am talking about in these studies, we had studies where there was a very high rate of maternal deaths, around 30 percent. There was another study where there was -- the rats virtually starved themselves throughout the exposure period, and lost a good bit of their body weight. And I'll talk a little bit more about that.

Under those circumstances, what was seen was a decrease in fetal weight and/or a decrease in viability, mostly early resorptions or showed up as animals that weren't

pregnant because the resorptions occurred very early during pregnancy.

And that's not surprising, given that excessive degree of maternal toxicity. That's maternal toxicity that regulatory agencies would not like to see people use, that would not like to see at the high dose in any developmental toxicity study. That's beyond what today would be considered scientifically-valid testing.

Now, when maternal toxicity was not excessive, the developmental -- but still significant, still significant statistically and biologically, what we had seen were developmental effects that were not seen consistently among studies. And the effects that were seen can easily be explained by the degree of maternal toxicity that was present. And I'll show you a slide in a couple of minutes that supports that.

Also, in some cases, some of the studies that were in the HID, but were not presented this morning, are not scientifically-valid testing, because they are abstracts. They are pilot studies, range finding studies, studies of that nature. Next slide.

This is a quote from the same U.S. EPA toxicological review of chloroform. And this is a summary of the animal studies that EPA provided. And it says, "Developmental effects occur only at the same or higher doses as those which

cause affects on the dam, suggesting that most of the effects are secondary to maternal toxicity. No studies were located that demonstrate that the fetus is more sensitive to chloroform toxicity than the mother. This is supported by findings that the enzyme responsible for chloroform metabolism is low or absent in the fetus."

Now, I was reassured by that quote. But one thing that gave me a little pause was the phrase "suggesting that most of the effects are secondary to maternal toxicity."

And I wasn't sure why they said it that way. I didn't know if they were just being especially cautious or if they had seen something which I hadn't seen. Because all the studies that I had seen, effects were always associated with maternal toxicity.

So I contacted the author of that EPA document, who is Dr. Julie Dew, and asked her about that. And she confirmed that at the present time, there is no indication that any of the developmental effects occur in the absence of maternal toxicity. And she said that it would be correct to drop the "most" and simply say "suggesting the effects are secondary to maternal toxicity."

So the important thing is that they are not studies that we don't know about that EPA had that suggested there are effects in the absence of maternal toxicity. Next slide.

Now, one of the handouts you have are a couple of

tables. And what this slide is -- and the first one is a summary table of the developmental tox studies by the inhalation route.

What the slide is that you are looking at right now is really a summary of the summary. And the reason I had to do this is I couldn't fit everything on here. So this slide is missing some of the information that's on the more detailed table.

But I color coded this so that you could at least see, differentiate the studies. The green -- the three green rows is the Schwetz study. The light blue rows are the two Baeder and Hoffman studies, and the last column is the mouse inhalation study by the illustrious Dr. Murray.

And what I want to point out here, the reason this is a little different from the other tables that you have seen on this is what I was trying to do is match up maternal toxicity with developmental toxicity. Because it was harder to do on some of the other summary tables which I had.

And, again, all of these are rat studies except for the very last row.

First thing I want to point out is that there's maternal toxicity at every single concentration that's been tested. If you look at the top value in the Schwetz study, the 300 part per million, I labeled that as excessive maternal toxicity because the animals lost nearly 100 grams

of body weight during the first week of exposure in that study. So between gestation day six through 13, they lost nearly 100 grams. These are rats that weigh less than 300 grams. We are talking about a third of their body weight in one week. We are not talking about decreased maternal weight gain. We are talking about a third of their body weight lost in a week.

If you look at the food consumption data in that study, it's not surprising. They didn't eat.

But that is truly excessive maternal toxicity. And what we have seen is a decrease in viability and a decrease in fetal body weight, and no wonder.

There was consistency between the Schwetz and the Baeder and Hoffman studies at 300 parts per million. Also saw a lot of maternal toxicity in Baeder and Hoffman, but not quite as dramatic as the weight loss, still decreased viability and fetal body weight.

Those were the consistent effects in rats. If you look at Schwetz at 130, you'll see an increase in fetal anomalies at one dose, and at 30 an increase in delayed ossification that was not seen in higher doses in that study.

But then look at the same concentrations in the Baeder and Hoffman study where they saw no affects. And these were -- the Baeder and Hoffman was essentially a repeat of the Schwetz, et al., study. Same concentrations, same

days of exposure. So there should have been more consistency there.

You'll also see that in the second Baeder and Hoffman study they saw a decrease in fetal body weight, but it was not seen in the first study at 30 or even at a high concentration in that study.

So there are some inconsistent effects seen at levels less than 300, but they are inconsistent and always seen in association with maternal toxicity, and enough maternal toxicity to explain the effect.

In the Murray study there was a decrease in viability and decreased fetal body weight, again, associated with significant maternal toxicity.

So as noted by EPA, no study demonstrates that the fetus is more sensitive than the mother. Next slide.

This morning you saw a slide on the Schwetz, et al., study dealing with maternal toxicity. What's unique about this study is that this was the one study that attempted to take a look at one part of the maternal toxicity issue.

And Schwetz, et al., had a -- what's been described as a starved control group, which was designed to look at what effect food deprivation would have in that study. And that starved control group showed an affect on fetal body weight, but did not show an affect on viability.

Now, the slide that you saw earlier made that point

and made the second bullet as well, and that the starved control group in the Schwetz study was not really a pair fed control group. They were given 3.7 grams a day of feed.

If you look at the high-dose group in the Schwetz study, which is in the HID, I think, on page 31, there's a big difference in the so-called starved control animals, actually ate four times more food than the high-dose chloroform group. So it is not truly a pair fed control group. It is not a great comparison.

Because if you are really trying to do that, they would have gotten about a gram a day of feed. And that fourfold difference alone can make a big difference.

Also, Schwetz did not measure water consumption. And one of the things we know from other inhalation studies of chloroform is when the animals stop eating, they also stop drinking. So that study did not deprive the animals of drinking water, the same way they were affected in the high-dose -- in the chloroform study.

And then, obviously, in a study like this, you're really looking at one aspect of maternal toxicity, food consumption. You can't really control for all the other aspects of maternal toxicity. You can't control for liver effects, kidney effects, central nervous system effects, nausea associated with exposure to chloroform.

So, you know, you can't draw conclusions from the

Schwetz study that maternal toxicity is not the most plausible explanation for the effects that we're seeing. Next slide.

This is similar to the slide that you saw, and this corresponds to the second table that I gave you. Again, it's a summary of a summary. And the three studies you see depicted here in green is the Thompson rabbit study. Light blue in the middle is the Thompson rat study. And the one on the bottom is the Ruddick rat study.

And what you see in all of these is -- let me start with the 50 milligram per kilogram per day on the top row in the Thompson study. That study had excessive maternal toxicity, and that's the study that four out of 15 dams died during the course of treatment with liver effects.

They also had anorexia, diarrhea, but four out of 15 dams dying tells you that that's a very high dose. Anorexia and diarrhea are some of the acute symptoms of overexposure to chloroform.

At that high dose there was a decrease in fetal body weight, which is what you'd expect with that.

And as you look at the high dose in all three of the studies, what is consistent is a decrease in fetal body weight. The one at the bottom, it was associated with an increase in variations of the sternebrae having to do with rate of ossification. But in every case, it was also

associated with significant maternal toxicity.

The only -- and it was only at the high dose where an effect was seen, with the exception of the low dose in the Thompson rabbit study. That's the 20 dose up in the third row. The authors reported a decreased fetal body weight. But you also have to remember that that study was published in 1974.

Thompson was still using the fetus as a statistical unit, not the litter. So it is questionable whether that is truly an effect. It obviously wasn't seen at a higher dose, and there's no dose response.

So the pattern is at the high dose in these studies, significant maternal toxicity, some evidence of embryotoxicity.

At the next lowest dose, there is typically still significant maternal toxicity, but less than at the high dose and no developmental toxicity. So that in these studies, you can see even when you have some maternal toxicity, there's still no effect on the fetus. It is not until you're having a more severe affect on the mother that an effect shows up. Next slide.

There were some other studies, and these were mentioned, the neurobehavioral study. And the HID concluded chloroform showed no overall tendency to retard neurobehavioral development of mouse pups. There were the

two in vitro studies, which are really of limited value for your purposes. Next slide.

Shifting gears, male and female reproductive toxicity. Epidemiologic studies provide no evidence of male or -- no consistent evidence, I should say, of male or female reproductive toxicity.

And by the way, I meant to mention earlier, and let me do it now while I'm thinking about it. There is yet another epidemiology study that just came out. It's a study by Tolidano, et al., which was published on October 21st of this year. It is on-line in "Environmental Health Perspectives."

This was one that looked at THMs in drinking water and low birth weight and stillbirths. And my understanding is that there were no significant findings in this study. Dr. Tardiff, who is here, has reviewed that study. And if you would like additional details on that study, he's prepared to review that with you.

But back to male and female reproductive toxicity, no consistent effects in the epi studies. We have a negative NTP continuous breeding study, and this is important. That's the study where if you're going to see affects on the male and female reproduction, it generally shows up in NTP continuous breeding studies. This was a study done by Dr. Bob Chapin at NTP. This is a guy who knows what he's

doing in the field of male and female reproductive toxicology. Saw no effect attributable to chloroform.

We also have negative 90-day rat and seven-and-a-half year dog studies. They looked at the pathology of reproductive organs. Saw no effect due to chloroform.

So what it really comes down to is we have the developmental toxicity studies in animals where there was decrease in viability, which sometimes manifests itself as a lower pregnancy rate. And we have already been through all of the issues having to do with maternal toxicity and those studies.

And when you think about the fact that you have all these negative studies that were really designed to look specifically at male and female reproductive toxicity, it is not really convincing.

And then for males we have the mouse sperm morphology study by Land, et al., which, in my opinion, is truly inadequate. And I will go into detail on the next slide.

You heard that Land was actually published in '79 and then again in '81.

In '79 it was an abstract only. So it is hard to get the details of that study. But one of the things that leaps out is that the mortality rate in that study was greater than 20 percent, which is not something you want to have in a study assessing semen.

And the authors did not specifically report what the mortality rates was, but from the materials and methods section by their choice of dose levels, you can figure out that the mortality rate had to be more than 20 percent, otherwise they would not have chosen the second dose level that they chose. There was no dose response for abnormal morphology, no details of the statistical analysis.

Then in 1981 they republished the results of the study with a key difference. What they did between '79 and '81 is added five mice to the two chloroform-exposed groups, the low and the high groups. But they did not add any mice to the control group.

So if you look at the two papers and compare them side by side, the controls are exactly the same for the two studies, but the exposure group gets bumped up by five mice. So there's really no concurrent control. The results are very different between the first and the second study, even though this was just an add-on to the original study.

And probably most important is remember the NTP continuous breeding study, Chapin's group did a full semen evaluation in that study. They did sperm count, motility, morphology, saw no effects attributable to chloroform in their semen evaluation.

So it would be very surprising if chloroform had an affect on morphology of semen, and it doesn't show up in the

NTP continuous breeding study. So last slide.

So in conclusion, the epi data, at most, suggests an inconsistent -- I'd say at most they suggest an association. And that association is not consistent. It certainly does not indicate a causal link.

The association is generally stronger for THMs than it is for chloroform, and that's important to take into consideration. In the animal studies, the effects seen in animals studies are easily explained by maternal toxicity. There were never any effects seen in any animal study that were not associated with significant maternal toxicity.

And you also saw a slide earlier dealing with the concordance of the evidence between the animal studies and the human studies.

And I want to make just a couple of points on that. One is to remind you that the concordance is only as good as the underlying studies that form the basis there.

And in the case of the animal studies, saying that these are effects without taking into account the degree of maternal toxicity is inappropriate. And a table like that doesn't really look at all of the evidence. It looks at what effects were seen. It doesn't weigh what studies didn't see an effect.

For example, I'm looking at the last slide in OEHHA's presentation. If you look at the column for "male

reproductive effects," in the animal there was an increase in sperm morphology. That's the Land study that we just reviewed on the previous slide. So that's the basis for that. Doesn't say, "Oh, by the way, the NTP study that looked at semen and looked at semen morphology more recently was negative."

And then the decrease in motile sperm that you see in the "human" column, that was the Chang study, one person. One person in a case study. So the concordance is only as good as the underlying data.

But even if there were consistent suggestions, and I don't think we do have consistent suggestions, that doesn't translate to causation. So is this an issue we ought to keep an eye on? Yes, I think it is. Is it clearly shown to cause? I don't think so.

So in conclusion, chloroform has not been clearly shown to cause reproductive toxicity, not developmental, not male repro, not female repro. Thank you.

CHAIRPERSON BURK: Thank you, Jay. Does anyone have any questions? Carl.

COMMITTEE MEMBER KEEN: Okay. Jay, as always, I kind of enjoy your presentations. There is one thing I would like to get clarified in my own mind, and perhaps also for the record, though. As you were indicating, you made the statement that in all the cases there was evidence of

maternal toxicity, rather severe maternal toxicity.

There seems to be one paper that stands out from that, and it is by the illustrious Dr. Murray. As I read your paper carefully, it seems as though there was only very modest reductions in the maternal food intake and modest reductions in body weight.

And the reason I have some pause here is, again, I think in contrast to what you stated, in that paper there was a significant increase in the incident of cleft palate. So there is one paper where malformations are observed. Happens to be your own paper.

If you could, perhaps, elaborate a little bit on that, because it is the only one where I can see where there is malformations outside of reductions in birth weight and skeletal ossification abnormalities, which are consistent with maternal toxicity. Cleft palate is not as consistent with maternal toxicity, particularly when it seems to be kind of mild. So I am a little confused on your statement.

DR. MURRAY: I'd be happy to address it, and I have read the study. First, on the issue of maternal toxicity, I have gone back and read it a couple of times recently. And one of the difficulties in that study is that it doesn't read -- it summarizes the food consumption data, but it doesn't present that data.

And my suspicion, I know back in that era, we always

recorded food consumption and had tables on food consumption. And my suspicion is that we submitted that as part of the publication, and back in that era, that was -- if a paper was too long, that was usually the first table that goes.

So all we really have is a description that I had on food consumption. And I wish I had the numbers. I don't have the numbers, and I sure don't remember the numbers to this day.

One of the other limitations of my study is that there was only one exposure level. So it is hard to evaluate dose response and know what's going on.

But in the case of cleft palate, I have gone back and looked at that. And the one thing that really leaped out at me is remember there were three different groups exposed to 100 part per million in that study. And cleft palate was increased in one of those three groups.

Now -- and it was the eight through -- gestation day eight through 15 group. Now, the one group was gestation day one through seven. Not surprising that you don't see an increase in cleft palate on those days, because cleft palate happens later.

But the other group that didn't see an effect was the six through 15 group. So if chloroform exposure was causing cleft palate, it should show up to the same degree in the six through 15 group that it does in the eight through 15.

I have a theory, and it is just a hypothesis, is that from now having had the benefit of reviewing lots of chloroform studies that have been done after my study was done, is the pattern seems to be one of the typical affects of chloroform on the mother is this decrease in food consumption. And it's particularly prominent on the first few days of exposure.

If you give really high dose levels like Burn Schwetz did in the rat study, they just stop eating. They never eat through that exposure period, or they virtually stop eating.

From my description in the mouse study, I don't think they -- I don't think they stopped eating through that whole period, but I think it's likely that they stopped eating, particularly on the first few days of exposure.

Okay. If you're starting exposure on gestation day eight, guess what time that is? Think about how that is in relationship to the time when you can induce cleft palate in a mouse.

So it is the perfect time, if you are going to take the food away, and we know food deprivation causes cleft palate in mice.

On the other hand, the six through 15 group, my guess what was going on is they stopped eating on day six through seven, but by day eight and nine, they were getting pretty hungry, and the food consumption started to pick up. That's

a guess. It is a hypothesis, but I think it is the most likely explanation based on everything I know today.

COMMITTEE MEMBER JONES: Jay, I know you discounted the epidemiological studies, and to a certain extent I think that's probably appropriate, given the fact that there really aren't studies that look specifically at chloroform ingestion. I would just like to get one thing straight, and it is for my edification.

DR. MURRAY: Dr. Jones, your microphone may not be on.

COMMITTEE MEMBER JONES: Well, it is, but maybe I am not close enough to it. You say on your fourth slide that the enzyme responsible for chloroform metabolism is low or absent in the fetus. And yet in this study by -- I am not going to pronounce it right -- Infante-Rivard in 2004 that was reported by OEDA, is stated that the growth deficiency in newborns was effected significantly by the CYP2E1 variant.

This was a study that was looking at polymorphisms and their affect on growth in human babies who were -- whose mothers use -- drank various amounts of water that were allegedly contaminated with chloroform.

Can you comment on what seems to me to be a disparity between what you have said and what was stated in this paper?

DR. MURRAY: Rather than me take a stab at that, can I pass to Dr. Tardiff, who is even more familiar with the

epidemiologic studies than I am?

DR. TARDIFF: Dr. Jones, we think that the -- we don't have any empirical evidence for the following, but it seems very reasonable to believe that the maternal metabolism is really what is happening here. The maternal individuals which have the deficiency in the CYP2E1 are the ones who also produce lesser amounts of oxidated metabolites in the process.

The others who are -- who have full complement of the enzyme on the other hand do have it. The active agent, while it's relatively short-lived, does get through the placenta.

So the fact that the developing fetus doesn't have an active metabolic enzyme dealing with the conversion of chloroform is overwhelmed by the fact that the mother is generating those metabolites and could be having an influence.

Now, that still remains to be demonstrated in more sophisticated experiments that I understand are being considered now at places like NIEHS.

COMMITTEE MEMBER JONES: So what you are suggesting is that the fetus does not have this, despite the fact what was stated in this paper, and that it is the maternal polymorphism that's important?

DR. TARDIFF: That seems to be the case.

COMMITTEE MEMBER JONES: Okay. Thank you.

CHAIRPERSON BURK: Question from Linda.

COMMITTEE MEMBER ROBERTS: One comment first about cleft palate. Mice, I don't know if this was an anaesthetic level, 100 ppm, that was used in the studies or not, but mice, when they go down, apparently it causes a lot of stress, and they release a lot of corticosterone. And that's been known to cause cleft palate, and that may be the mechanism in this particular case for the cleft palate that was from eight to 15.

Because you'd also assume it could be a feed issue, but you also assume that after a few days of going through this, they're getting used to the routine. They are less stressed out by it.

And, actually, I don't put a whole lot of weight in cleft palate in mice anyway. If you see it in another species I do. And I say that having done my graduate research in cleft palate in mice.

But I did have a question about the rabbits. And the table is on page 46, the rabbits treated orally. Significant effects were noted at 20 and 50, but not 35 milligrams per kilogram per day.

But I also noticed that that had the smallest number of live fetuses as well. And I wondered if that might not have been a factor in why there isn't a finding on fetal weight, given that they had two less pups in the litter.

DR. MURRAY: Dr. Roberts, you are talking about page 41, in the HID?

COMMITTEE MEMBER ROBERTS: It is my page 46, bottom of the page, table 22. If I misspoke and said rats, I'm sorry. I meant rabbits.

DR. MURRAY: You talking about at 50 or at 20? I see it now.

COMMITTEE MEMBER ROBERTS: 50 and 20 both have statistically significant differences, but the number of live fetuses in the 35 group, which is negative for effects on fetal weight, also has the smallest litter size, which can have an impact on fetal weight.

DR. MURRAY: No, that's right. I see it, the highest dose had a higher litter size. I don't know what role, if any, litter size is playing in that study. But what I do know is that when Dan Thompson did that study, it was before that lab was doing statistics on the litter.

This was an analysis of fetuses, and it looks like there might have been 12 litters in total there. So this could be a -- could well be a false positive. I don't know what these results would look like if this were a mean of litter means.

But clearly what this is is a mean of individual fetuses. So that's why I questioned whether that is a real statistically significant effect.

COMMITTEE MEMBER SAMUELS: May I ask Dr. Campbell if you can confirm that? Because in some cases I know you have reanalyzed data, if it were available.

DR. CAMPBELL: No, we didn't reanalyze this. It is hard to say how big of an affect litter size would have. You would think it would have some. But without really doing a specific analysis, can't partition it out.

DR. MURRAY: And part of the difficulty is we don't have all the data that you would need to really reanalyze it.

DR. CAMPBELL: To do that.

COMMITTEE MEMBER SAMUELS: I ask because the title in the document states it was a litter mean instead of an animal mean.

DR. CAMPBELL: I did say that, didn't I?

COMMITTEE MEMBER SAMUELS: So I just want to clarify.

DR. MURRAY: Also, Dr. Jones, Dr. Tardiff just informed me he had another comment in regard to Infante-Rivard, if you are so inclined.

DR. TARDIFF: Sorry for the disconnect in that regard. There was one other element to the analysis that you need to keep in mind, and that is all of the trihalomethanes, or at least three out of the four are metabolized through the same pathway, the same oxidated pathway. The epidemiological association was for total trihalomethanes and not for the chloroform. And bromodichloromethane is known to be a

reproductive toxicant in some experiments.

So the expectation is that the same statement that's made about the enzyme is correct, but it is probably another surrogate of that group of compounds that may be responsible if, in fact, we can show that the same association can be repeated.

COMMITTEE MEMBER JONES: Okay. I appreciate that. Again, just for my edification, are you still suggesting, then, that the enzyme is not in the fetus?

DR. TARDIFF: That's my understanding, is that the evidence indicates that there's little or no metabolic specific activity for that particular enzyme.

COMMITTEE MEMBER JONES: Okay.

DR. TARDIFF: It is not unusual for many of the enzymes --

COMMITTEE MEMBER JONES: I'm well aware of that.

DR. TARDIFF: -- that are dominant in the liver to develop after birth.

DR. KAUFMAN: Dr. Jones, may I make a clarification on the paper? For the maternal, the risk estimate in the mothers with that specific polymorphism was elevated. When looking at the newborns with that polymorphism, the estimate was doubled that of the mother's, suggesting that there is, indeed, an additional affect of -- in fetuses.

DR. DONALD: Sorry to jump around between topics so

much, but with regard to the Thompson, et al., rabbit study, just to clarify for the record, the mean number of live fetuses in the high-dose group of 50 milligrams per kilogram per day group is 7.4 fetuses, and the mean fetal weight, whether on an individual or litter basis, was 30.3 grams to 35 milligrams per kilogram per day.

The number of live fetuses was 4.5 on average compared to 7.4 in the high group, and the fetal weight was 32.4 grams. So bearing in mind the well-established inverse correlation between litter size and fetal weight, it may well be that there's at least a possible explanation there for the lack of significant affect on fetal weight at that dose group.

COMMITTEE MEMBER ROBERTS: That was my concern, that this might be a false negative in that particular case. Although, I guess we have statistical questions about that, too, that may linger.

CHAIRPERSON BURK: Any more questions of Dr. Murray? Okay. Thank you. And we'll go to the next speaker, which it looks like GG Ferbrick, Burbrick. And I'll let you say what organization you're representing, because I can't read it.

MR. VERBRYCK: Hi, my name's George Verbryck, and I am representing the Spa and Pool Chemical Manufacturers Association.

We have a Dr. Susan Rice here who is going to make

our presentation. I am going to make a few introductory remarks.

The Spa and Pool Chemical Manufacturers Association is a trade association, and it is composed of manufacturers, distributors of chemicals which you use in spas, pool, hot tubs and what we call recreational water. I explain that as being waterparks, waterslides, that sort of thing. Some people don't know what that is.

Many of our companies also provide inorganic hypochlorite solutions for water, wastewater and general disinfection purposes.

Chlorine and chlorine-containing chemicals are the water disinfectants of choice throughout the world as well as in California. Most of our products are based on chlorine-containing chemicals, the chlorinated isocyanurates, inorganic hypochlorites, and brominated and chlorinated hydantoins.

In California in the year 2002, according to the most recent report for the Department of Pesticide Regulation, 147 million pounds of these products were sold which were registered as pesticide products.

If we include chlorine gas as a chlorine-containing compounds, the total number of pounds sold is well over 250 million.

While we have no firm data, we believe at least

another 250 million pounds of chlorine-containing chemicals are sold for non-registered uses, such as bleaching and cleaning.

Under use conditions, miniscule amounts of trihalomethanes, including chloroform, may be generated as by-products. Listing chloroform under Proposition 65 for developmental and reproductive toxicity has tremendous implications for public health and our industry.

Undermining public confidence in chlorine disinfection is not in the public interest, unless, of course, it can be demonstrated that chloroform causes reproductive and developmental harm in humans.

Dr. Rice received her Ph.D. in 1976 with the University of California, Davis, in comparative pharmacology and toxicology. She was a professor at the Department of Anesthesia, Stanford University School of Medicine with a joint appointment for the Palo Alto VA Medical Center for a total of 14 years, 11 as assistant and associate professor. She's performed research related to the toxicity of the anesthetic agents, primarily the volatile inhaled halogenating anesthetics.

She received NIH and VA grants related to the neurotoxicity effects of anesthetics. For 14 years she's been involved in a large program investigating the reproductive and developmental effects of these agents. She

has personally performed and overseen reproductive developmental and non-developmental testing. She was coauthor of several chapters on reproductive and developmental toxicity of anesthetic agents, and several on overall anesthetic toxicity, which included reproduction development and metabolism.

She's been consulting since 1990 and been an independent consultant since September of 1993. She assists pharmaceutical companies with toxicology training, testing, including design and interpretation of reproductive and developmental studies. She's met with and presented to FDA on behalf her clients.

Last month she gave a presentation titled "Introduction to Developmental Neurotoxicity" at a combined meeting of the Northern and Southern California chapters of the Society of Toxicology.

Gary Shaw, the author of one of the papers included in this draft HID, was also a presenter. She's a member of the Teratology Society, and a member and past president of the Neurobehavioral Teratology Society, and a member of several other associations. She has a DABT. Without further adieu, Dr. Rice.

DR. DENTON: Before you begin, Dr. Rice, I wanted to tell the Committee that we did receive written comments from Dr. Rice several days ago, and we did not have time to supply

them to you. So they are in your binder behind the last -- they are at the back of the binder.

DR. RICE: Good morning. I wanted to thank the Committee very much for considering our comments. And at a later date, I presume you'll have a chance to read my complete report. I know several of the people on the Committee, so it is wonderful to have a chance to talk to you.

I planned for a longer presentation, but the presentation that Dr. Murray has given and that from OEHHA has obviated the need for me to go through all of the studies that I had initially planned to talk about.

So what I would like to do is to hit some high points, comment on a few specific studies, and give you an idea of the summary for the comments that are provided in the report. If I could have the first slide, please.

Just to remind everyone, although I know all of you are very well aware of this, the criteria for evaluation of causal association with epidemiological studies is related to the strength of association dose response, specificity of association, appropriate temporal association, consistency across multiple species, biologic plausibility and coherence of the evidence. Next slide, please.

As far as epidemiological studies that were presented in the draft HID, I would say the strength and direction of

associations of chloroform in DART outcomes are not consistent across studies. A dose response for chloroform is not present in the majority of studies. Where it is, it is very weak. Misclassification of subjects in exposure categories is a major weakness of the majority of the studies. Next slide, please.

And the types of misclassification could result from chloroform concentrations in the home drinking water that were not measured directly in the majority of studies, and that exposure categories were used, such as the water source, differentiating ground and -- ground and water -- ground and surface water. Other exposure categories were concentration at the distribution source and not necessarily for the area in which the woman resided.

And at best, the metric was created that measured concentration times reported home tap water consumption.

We do not have contributions from other sources evaluated in the majority of these studies. Next slide, please.

Additionally, there is great possibility for misclassification of gestational weight, which would significantly affect weight-related outcomes, and I'll have a specific comment in regard to one of the studies later on.

Confounding factors were not consistently controlled across the studies. And we have already talked about the

total trihalomethanes as not being an appropriate surrogate for chloroform.

And then finally, there's no causal link stated by the U.S. EPA, which Jay presented earlier. Next slide, please.

Actually, if you could go back one. I think this time it would be a good idea for me to make comments on the few studies that came into question or weren't covered well.

And the first one, I'm on page 2 of the OEHHA summary of human studies, for the Kramer study, there was an inconsistency in evaluation of the intrauterine growth retardation, in that when the authors looked at the associations with water source, that is surface water or groundwater, but they did not find an association for surface water, but they did for the groundwater, and this would be wells of varying depths.

With a surface water, in general, we would expect much higher levels of chlorination than we would at the groundwater sources.

So this in my mind is an inconsistency, and there were no measurements of the two sources to give us any direction.

For the King study, a number of other trihalomethanes were examined, and BDCM was shown by the authors to be a stronger, independent predictor of risk than was chloroform.

In the Dodd study, which is on the next page, 2004, the mid-dose group was not statistically significant. Although, we did see associations with the lower-dose group and the higher-dose group.

And with the Wright study, the authors themselves commented that the order of magnitude for lower birth weight and small for gestational age was less by an order of magnitude than one would expect to see with confounding by smoking.

They also said that there was a great likelihood of errors in the estimation of gestational age, which would obviate a number of their findings.

So the authors themselves did not think that their findings were very strong. Now, if I could go on to the next slide.

As far as the animal studies, and, again, these were very well summarized, the majority showed no affects of chloroform on development or reproduction. When there was a dose-dependent relationship, the results were not consistent. I need to back up here.

When statistically significant effects were seen in these studies, in general, there was not a dose response. There was also a lack of consistency among the outcomes between the studies. Maternal toxicity, as Dr. Murray explained, can take care of most of these toxic effects. May

I have the next slide, please.

I think we need to keep in mind, of course, that the pilot and range finding studies are inappropriate for our evaluation. Abstracts, as Dr. Murray mentioned, are inappropriate also. And as OEHHA said, the in vitro studies are essentially irrelevant. And I'd like to point out that those studies were conducted at chloroform concentrations that would be lethal to humans. And the next slide, please.

What I would like to concentrate on is the effects on sperm. When I was reviewing material last night, I was trying to think of what sorts of things might stand out to the Committee and what sorts of things I identified myself when I was first reviewing the comments.

And so I'd like to start with the occupational case report study by Chang. First of all, this was a laboratory worker who was exposed in the laboratory to concentrations of chloroform as high as 450 parts per million. And this was due to a lack of ventilation system.

And this concentration may have been this high for as long as two hours a day, 5.5 days per week for up to about eight months. He appeared in the clinic with the problem that his wife was unable to conceive.

When they explored his background, they found that a year prior he had had some reproductive tests, and they were deemed to be normal. No data was given in this particular

study for that.

When they did present the data, they showed that there was reduced sperm motility. Morphology was not evaluated, and that as his time away from the exposure increased, the motility also increased.

Now, the problem with this -- one of the problems with this study is that this worker was also exposed to multiple other solvents. None of them were identified as having other developmental effects, but I don't believe they have been studied either. If I could have the next slide.

Now, I would like to compare this to the effects on sperm that were seen in the Land study. And one of the reasons it stood out for me is the potential highest exposure level seen in the Chang study was approximately the same as seen or used by Land.

Now, in 1979 Land first presented this information at a meeting of the Society of Anesthesiology. I was one of the members of the audience at that time. And the reason that there are differences between this study and the 1979 study, at least the abstract, are because a number of us in the audience objected to the study design, including the number of animals, the high mortality and such.

Now, when it was published in 1981, since I was not one of the reviewers of the article, I have no idea if he just added additional animals to the groups, which it looks

like very much, as Dr. Murray talked about, or if he did completely different studies. From reading the methodology, it does not appear as if he conducted a completely new study. So I would say that these are add-ons.

With the add-on animals, he had a 10-percent mortality in each of the exposure groups, and they were exposed for four hours per day, five days per week in early spermatogenesis.

Now, these concentrations are very high for the mice, and you would expect some toxicity as he saw.

Now, when we come to the results, he saw in his control population about 1.4 percent abnormal sperm. This is a number that has been seen by a number of other authors working in the area for mice. At 400 parts per million, the percentage increased, and it increased again at 3. -- at 800 parts per million to about two and a half times what we saw in the control group.

Well, my question to myself, and I'm sure you're asking the same thing, is: What is the relevance to fertility for these findings in mice? The next slide, please.

Well, if we review again the male reproduction studies, the NTP continuous breeding protocol study saw essentially no effects, normal sperm motility, normal sperm density, and percent abnormal sperm were essentially normal.

Next slide, please.

And in the U.S. EPA study of rats, the 90-day subacute toxicity study, essentially there were no affects, also. Next slide.

Heywood is one more study, and this was in the Beagle dogs for 7.5 years, and essentially there was no affect on the testes or prostate. May I have the next slide.

So, now, if we get back to humans, this is something I looked up myself last night, because I was -- I was concerned, well, what does an increase of 1 or 2 percent abnormal sperm in mice mean to humans?

Well, generally for humans, if we look at morphology, greater than 12 percent normal sperm morphology could be predictive of fertility. And this is far, far below what we saw in the animal study.

So a normal -- a normal sperm morphology could be as -- as much as 50 percent abnormal or 50 percent decreased in motility, and you would still be able to conceive. Could I have the next slide, please.

In conclusion, I'd like to say that there is no evidence for developmental effects, either male or female reproductive effects. The epidemiological studies show no causal association. The case report is uncontrolled. And for the animal studies, the developmental and reproductive toxicity is only seen in the presence of chloroform that

causes significant maternal and paternal toxicity.

Excuse me. I had a note here written to myself I can't find. Just a comment on the Schwetz study. Dr. Murray covered this quite well, but just to point out again, this was not -- this was on page 3 of the OEHHA summary. It is not a pair fed. The starved control was not pair fed controlled. So it cannot be considered to really control for the stress effects that were -- that were seen.

As far as Murray's study goes, I think it needs to be taken into consideration, as Dr. Roberts pointed out, that these halogenated agents do cause significant stress to the animals, especially at the beginning of studies.

Myself conducting many studies of the anesthetics agents, the halogenated anesthetic agents, we would see significant stress, which I would relate as the animals being extremely active, running around the cage for extended periods of time during the first several days of exposure.

And we do know that maternal stress can significantly increase the incidence of cleft palate, especially in mice. And mice is the one tricky species here, because they have cleft palates at a very high rate anyway.

And the next. I don't know if I have another one. Okay. In conclusion, I believe that there is insufficient evidence to classify chloroform as a developmental or reproductive toxicant.

And I will leave it there and ask if the Committee has any questions.

CHAIRPERSON BURK: Anybody have any questions for Dr. Rice? No.

COMMITTEE MEMBER SAMUELS: I'll ask.

CHAIRPERSON BURK: Okay. Steve.

COMMITTEE MEMBER SAMUELS: Dr. Rice, the difference between the Thompson -- one important difference between the Thompson and Land studies is that in the Land study the route of administration was by inhalation, and in the Thompson study by oral administration.

And I think as it turns out, it was for the single man who was exposed in the laboratory. The evidence seems to show, by and large, that inhalation is a more sensitive route, given all the other problems that are involved. Do you think that might be a reason for the difference between the findings?

DR. RICE: I don't believe so in this particular case. When I first looked at the Land study, and I haven't looked at it in 20 years, I was thinking, well, you know, this looks very suspicious, if you can put it that way.

But as I reviewed the paper more carefully and went through the methods and remembered this present -- the initial presentation anyway. And I did know Dr. Land. I haven't had contact with him for years, but it was definitely

my feeling that this was not a very good study overall. And the main -- even if this were to be a valid effect, a 1- or 2-percent increase is an extremely small increase. And you would really have to push it much higher, I would believe, to get anything more.

Now, remember, even at this increase of 1 or 2 percent, they had a lot of deaths, or at least 10 percent, one per group of ten animals in both studies.

So I don't know how much toxicity is playing a role here. Poor study design certainly is a role in that the controls weren't necessarily concurrent and the exposures were done at different times.

So I personally do not have any confidence in the study. Does that answer your question?

COMMITTEE MEMBER SAMUELS: It does. I have one more comment. Again, the study may not be well conducted and the circumstances of the publication and the addition of one group are certainly of concern, but my impression is that animal sperm, rat and mouse sperm, show very little variation compared to human sperm. So that the doubling at least of the percent abnormal might be of concern, simply because they are not as variable as you have shown in the presentation of the human figures. So I am not --

DR. RICE: I understand where you're going. I had misunderstood. Yes, the mice and rats are not all that

variable, especially when you're looking at these F1 breeds.

So from there I agree with you, that if there is an increase, there is one. But I am not 100 percent sure that it is valid in this study.

COMMITTEE MEMBER SAMUELS: Thank you.

COMMITTEE MEMBER ROBERTS: I have a question, if you don't mind. I was just going back trying to compare the Chapin NTP study and the Land study in terms of how long they were exposed. And in the Chapin it was 98 days, and in the Land it was five days with 28-day postexposure, if I am reading correctly. Would they be getting spermatozoa in that study?

It would not be exposing the whole period of the spermatogenic cycle in that study. I do wish we had Marian Miller.

The last one was that I wish we had Marian Miller at this point. But I was noting that there was a difference in the duration of the exposure period in the Chapin and Land study. One was for 98 days, and the other was for five days with a 28-day period, and that didn't happen the entire spermatogenic cycle.

DR. RICE: I don't think anyone could hear the last part of your comment. Would you like to repeat it?

COMMITTEE MEMBER ROBERTS: Not really, but I will. I was noting that there was a difference in the exposure

duration for the two studies. Chapin looked like it was 98 days, or perhaps 98 plus seven pre-pairing. Land's was five days with a 28-day post dosing period before they took the samples. Marlissa; is that correct?

DR. GOLUB: Yeah, I think so.

DR. RICE: Yeah, it is correct.

DR. ALEXEEFF: Dr. Roberts, we have with us Dr. Ling Hong, who is on our staff, and his expertise is specifically in this area of male fertility. So I think he can add a little bit of light on this maybe.

DR. LI: I am Ling Hong Li, staff toxicologist at RCHAS, and Marlissa review the study I helped her on this study of the male repro issues.

Regarding the Land, et al., study, the animals were exposed for five days, and waited for 28 days. If you put those duration and compare that to the spermatogenicity in mice, I think what Dr. Rice is pointing out, that the exposure had been in the earliest spermatogenicity, which means the early packaging genes from spermatocides are neither packaging spermatocides.

So in theory, in theory, it could cause abnormal sperm in the epididymus, but probably not by genetically effect. Because if you think about the spermatocides, they going through spermatogenicity, shedding all the cytoplasm and the only maintenance they had. And the Land, et al.,

study only observed the abnormal sperm in the head, not in the tail, not in the middle piece of the sperm.

I mean, it is a bizarre study to not observe the motility, to not attempt to evaluate the motility.

If that study had looked at the motility, then you can have the direct comparison of that study to the human study.

I also want to point out in the human, the morphology, the sperm morphology has a lot, a lot of variation. And Dr. Rice pointing out lower than 10 percent, 15 percent. Most of the time it depends on which criteria you use.

If you go to the WHO manual, it will say 50 percent, and higher and lower. Some people will use straight criteria, like, say, 10 percent of the human sperm are normal in a normal healthy man.

So a variation in human might be biologically significant as largely as we see in here, but the difference in sperm motility in mice or rats, most the time, I think it is generally established that it is a biologically significant. That's all I have.

COMMITTEE MEMBER ROBERTS: Thank you.

CHAIRPERSON BURK: Farla, did you want to make a comment?

DR. KAUFMAN: Yes, I just wanted to address one of

the comments that Dr. Rice made, and also was one of the comments in the comments submitted by Dr. Murray. So I wanted to clarify that. It pertains to the Kramer, et al., study and the issue of surface water and not seeing an effect when they looked at surface water.

Well, the authors looked at -- stratified the wells or the source of water because they wanted to look at the issues of pesticides or herbicides, other contaminants, to see if that was a confounding factor.

And so when they did that, they had to -- what happened was they didn't find any non-detectable levels for the sources in surface water. So as you can see, there's zeros there.

So in the comparison, they had to make a comparison between the greater or equal than to ten micrograms per liter versus the one to nine micrograms per liter. And the numbers are very, very small.

They did see an increase in risk of 1.5, but as you can see, the confidence intervals are very wide. The estimate is unstable. But it wasn't because they were looking at chlorination. It was more to look at the pesticide issue. And they saw that there was no difference between the shallow and deep wells, and so they were pretty confident there was no confounding by contaminants.

DR. RICE: If I may make a comment. I did misspeak

when I had mentioned and said that the groundwater was significant, significantly different.

I think the comment I did make still stands from this -- from this point, that one would expect the level of chloroform in the surface sources to be much greater. We just have greater than or equal to ten, and it is across all of them. But we would expect the surface sources to be much higher than we would expect for the shallow wells and the deep wells.

Again, I don't have any information. The numbers are small, but I don't think the conclusions in this study are really supported.

CHAIRPERSON BURK: Carl has a question.

COMMITTEE MEMBER KEEN: Excuse me. It is more of an observation or a comment. Clearly our role here is to assess whether or not different agents pose reproductive risks. Part of that we evaluate the quality of papers as they're reported. We try to infer whether or not maternal toxicity could be complicated in the data, etcetera.

I just feel that, perhaps, and I am sure it was unintentional, but we should not be in the position of impugning a researcher who is not here to defend themselves. A number of kind of statements were made about Dr. Land that, frankly, may be inappropriate or incorrect to make an assumption that an individual did something and then that

assumption almost became fact.

I personally am comfortable with -- and I am sure that's not what was intended, but I think we should stick to an evaluation of the data which is actually presented in the papers and not begin to draw other information that would really cast doubt on it.

If it turns out that either we revisit this particular agent again in the past, it would be useful, certainly to me, if OEHHA could follow up with Dr. Land, if Dr. Land is still available to ask questions to, and solve the issue.

I am not disturbed by the data which were presented, but we spent an awful lot of time talking about how it was received at a meeting 20-plus years ago, and also making certain assumptions about how subsequent experiments were done. I think that probably is not appropriate or fair to that individual.

DR. RICE: If I may say, there was no intention to disregard Dr. Land's work or to impugn his integrity. There are just questions that I have about the experimental design.

CHAIRPERSON BURK: Are there any other questions of Dr. Rice? I have one more card. Thank you. Thank you very much. Donald C. Burns, do you still wish to speak? No. Okay. You were part of the last group.

All right. So that is it for the public comments. I

guess we'll begin our discussion. Does anyone have a preference for how they'd like to begin or how to organize our discussion? Steve.

COMMITTEE MEMBER SAMUELS: I'd like to begin. The epidemiology studies came first in the Committee document. I would like to ask in the future that the staff presentations, as far as they can, follow the order in the document. Because we have made notes to ourselves, and it is hard to track our notes.

First of all, I have -- I think the epidemiological evidence is stronger than some of our commenters have indicated, and perhaps even than the investigators themselves concluded. And I reviewed the Wennborg documents, in which the laboratory workers were asked retrospectively about their exposures to specific agents.

And the assumption is, though, there was no validation, that they would know what they had worked with, and chloroform was a specific agent named.

And the odds ratio in that study for the relation between spontaneous abortion with chloroform was 2.3 with a confidence interval 0.9 to 2.5, not significant at a two-sided level. I didn't do the calculation to see whether a one-sided test would be significant, but it would be close.

And this -- I have two comments on this study. First of all, I believe that the investigators improperly included

prior miscarriage as a risk factor in the model. And there were only a few miscarriages, prior miscarriages, but the effect of including an outcome, prior outcome in the model, is that if that outcome were itself affected by the occupation, that you're asking, then, whether there is additional association of occupation in the current pregnancy after an outcome is in the model which in part may have been caused by that occupation.

So it is an over control, and I would judge that omitting prior miscarriages as a covariant in the model might have increased the odds ratio to the point of clear statistical significance. And, of course, that's speculation.

The second thing I want to point out is if you read the paper carefully, in their assessment of the association, though their table says that they adjusted for maternal age and prior miscarriages, in fact, they apparently included all exposures simultaneously in their multiple logistic regression model.

So, again, given potential for misclassification, nonetheless, this is, the association, the odds ratio of 2.3, was in the present and adjusting for the other exposures which were ascertained and present in the model.

So my conclusion is that that is certainly a stronger finding and might have been even stronger if analyzed

differently.

To balance that out, there were multiple pregnancies per woman in the analysis, and the author stated that if they had presented the standard errors appropriate to the analysis of possible correlation between pregnancies, the confidence intervals would have been slightly wider.

So it is, in a way, a frustrating paper to read because it is so tantalizing. And I wish they had come to us first before they published the data.

The second paper I'd like to discuss is the paper by Jay Michael Wright. That is a paper that examined mean birth weight as a continuous variable and small for gestational age.

And the figures in that paper were reproduced in the draft document provided to the Committee, and they certainly do provide with -- I think, five or six groups, I don't recall. They certainly do provide evidence of a clear dose response for both outcomes, both mean birth weight and small for gestational age. And these were among term births.

Now, Dr. Murray in his comment stated that, yes, there was a statistically significant response in mean birth weight, but the difference in average birth weights between the lowest and highest groups was about 18 grams. And that is a very, very small difference, and probably due, in my opinion, to the very large sample size.

So we are left with a kind of dilemma that this may well be a real difference, but it may, in fact, be a trivial difference.

The odds ratio -- the maximum odds ratio for small for gestational age in these term infants was 1.1, and Dr. Murray commented that this is a small and transient effect, and certainly it is an effect that is not as persistent as would be small for gestational age in pre-term infants, but I do believe there is literature which supports that there is, indeed, a detriment to being very small in a term birth.

So I disagree with Dr. Murray, but it is certainly not as severe a predictor of any kind of morbidity. And that was also a clear dose response, and, again, a fairly strong one.

The third study that I'd like to comment on is the study by Infante-Rivard in Montreal, and that is a study in which the gene polymorphisms were studied. And the comment was made that the odds ratio for trihalomethanes, which was the only statistically significant finding in the presence of the gene polymorphism, was 13, which was higher than the odds ratio for chloroform, which was only 5.62 and did not include the -- did not include one, I believe, in the confidence interval. Somebody can correct me, because I didn't have that figure.

First of all, I believe, in fact, that the chloroform finding is stronger than the trihalomethane finding. The confidence intervals width for the trihalomethanes, the total trihalomethanes is, in fact, so wide that it's -- the confidence interval for chloroform is much narrower if we take this on a log scale or a ratio scale.

So I actually think it is more precise in that sense. If you notice, the upper limit for the trihalomethane finding is very, very high. Just a very wide and imprecise estimate.

I think, however, that a more serious problem, and one which leads me to believe that this is a stronger finding, again, than published, is that there were only 45 cases and 37 controls with the CYP2E1 variant. And Dr. Infante-Rivard used the 90th percentile for chloroform as her definition of high exposure, and compared these to -- compared risk in that upper 10 percent to the bottom 90 percent.

This was a very conservative approach in general. Many times you see in epidemiology people comparing upper quintiles to lower quintiles. And clearly there's misclassification when you have a cut point exactly at the same point. But more seriously, this effectively meant that only 10 percent of her subjects could be considered exposed.

And when she defined -- tried to use the 95th percentile, her estimates broke down and were clearly non-

significant.

But if you consider the subgroup of subjects with a variant of CYP2E1, that means that, perhaps, only four or five would have been considered exposed in -- among the cases in the controls, so that sample size became a serious problem, in my estimation.

And, again, the finding near significance with that small a subgroup to me is evidence of an actual clear affect. That if she had loosened her definition of exposure, again, this is speculation, might have become clearly significant. So I actually judge this as a positive effect.

So my summation is that while there are certainly weaknesses in the epidemiology studies, and I think that they have been pointed out, that these three studies at least do present reasons for thinking that there are effects in humans, including one with a dose response, but they are, of course -- and it is going to be up to us to judge whether they are persuasive in light of all the other evidence.

It is rare that we have so many human studies to investigate. So I was -- and I was kind of happy to see that not all of them were at least bad or irrelevant.

I have one other question, but I am going to leave it to my other Committee members to comment, which is that we have been repeatedly -- it has been repeatedly told to us that in the presence of maternal toxicity, and I have had a

conversation with Dr. Burk about this, that we can't find any evidence for reproductive harm.

But I am wondering if Dr. Jones may have a comment. But I can certainly think of drugs, alcohol, and there may some other teratogens which may have known toxicity in the primary recipient, but certainly the additional harm in the fetus would not be considered due to maternal toxicity. So I don't really buy the complete requirement that there has to be an absence of maternal toxicity to find reproductive harm.

COMMITTEE MEMBER JONES: I was just going to say certainly not in humans, there's no question it's true. I would agree with you.

CHAIRPERSON BURK: You would agree that --

COMMITTEE MEMBER JONES: You don't have to have maternal toxicity in human in order to show.

CHAIRPERSON BURK: But I think you were kind of going the other direction.

COMMITTEE MEMBER SAMUELS: You don't have to have the absence of maternal toxicity, is my point.

COMMITTEE MEMBER JONES: No, I agree.

CHAIRPERSON BURK: Do any Committee members have any more comments about the epidemiology? I think Steve did a lovely job giving us his perspective. Shall we move -- what about you, Ken.

We can move on to the animal discussion.

COMMITTEE MEMBER JONES: Maybe I would like to. I don't understand quite the significance of these disinfection by-products studies. Can somebody comment? That's what the Wright study apparently was, it was a disinfection by-product study, and I don't quite know what that means. Can anybody?

CHAIRPERSON BURK: Do you want to give the definition, Farla?

DR. KAUFMAN: Disinfection by-products encompass all of the products produced by chlorination. The trihalomethanes are a major class of those disinfection by-products, but there are certainly other things. Haloacetic acids are included in numerous -- I think there's a table in the beginning of the HID that shows all of the products.

But because of the predominance of the trihalomethanes and because of the predominance of the chloroform within those trihalomethanes, a lot of the studies are now focusing on the chloroform.

COMMITTEE MEMBER JONES: Yeah, so aren't you concerned that we are a long way off from the chloroform when we are talking about disinfection by-products?

COMMITTEE MEMBER SAMUELS: Well, I am discounting -- my comments were only about the findings of chloroform and the fact that there was a THM, or trihalomethane, finding. As I say, I think that unlike some of the studies where

certainly chloroform had a weaker affect than other of the chemicals studied in this case, it seemed to me to actually have sort of paradoxically a stronger, at least a more precisely determined effect.

So we are not regulating all the other chemicals. So only those studies which specifically studied chloroform, I think, are relevant. It is tempting to say, "Well, chloroform was the majority of the trihalomethanes, therefore, we should use the trihalomethanes." But I don't agree, and I think that was properly -- the distinction was properly made in the document.

CHAIRPERSON BURK: I certainly support that we are just looking at chloroform. I am just kind of curious in the database and so forth when this was prioritized, was there ever a thought to look at a group of, you know, look at disinfection by-products? Or what about the other one, like, say, bromodichloromethane, is that in the pile somewhere.

DR. DONALD: There was some consideration to looking at trihalomethanes or disinfection by-products in general, but it was decided that since chloroform had been specifically identified in the prioritization process, that it was more appropriate to look at chloroform at this time. That doesn't preclude looking at other trihalomethanes in the future.

CHAIRPERSON BURK: Dr. Jay Murray would like to make

a comment.

DR. MURRAY: Can I just respond to the question that was just asked about kind of definition of disinfection by-products? Probably most of you know this, but just in case, the disinfection by-products are chemicals that are formed as a result of water treatment. In the case of chloroform, as a result of chlorination of water.

And it is a combination of two things: It's the method of chlorination, or disinfection, that determines the by-products; and the presence of organic material in water.

So it is not as simple as, you know, when you chlorinate the water you get, you know, certain levels of disinfection by-products. It is also a function of what the organic material is, dirt, if you will, in the water.

And when you chlorinate and get chloroform as a disinfection by-product, you also get dozens of other disinfection by-products. Some are more toxic than chloroform. Some are less toxic than chloroform, but they go hand in hand.

When drinking water has more chloroform than other drinking water, that same drinking water that has more chloroform is likely to have more of the dozens of other chlorination disinfecting by-products.

So even if you have a study that is looking at chloroform and looking at the relative risk of chloroform, in

the real world, you have all those other disinfection by-products there.

So that if you see an association where you see an elevated risk, it could be because chloroform's there, but it could be because any of the other disinfection by-products are there. That when one goes up, the others go up.

CHAIRPERSON BURK: Thank you for that clarification. Does that answer your question, Ken?

COMMITTEE MEMBER JONES: Yeah, I think so.

CHAIRPERSON BURK: Are we clear that we are trying to look specifically at chloroform? So some of the studies, you know, lab workers, that's one way of looking at it. Products of water chlorination's another way, and then we have animal studies where it is a little more controlled as to what the actual exposure is.

Are there any more comments about the epidemiological studies? I am not anxious. Shall we move on to the animal studies? Anybody that wants to start, feel free. Okay. Carl.

COMMITTEE MEMBER KEEN: I'll start. It is not a question on the epi -- I will point out that I find the epidemiology papers that we reviewed provocative, though I don't find them definitive.

When I come to the experimental animal studies, I am impressed by the fact that severe maternal toxicity is a

complication of most. And I agree with Steve's point that clearly in some cases you can have an agent that causes maternal toxicity, that independent of that, still has a direct embryo or fetal toxic effect. I think that was your point. There's no question about that.

I am impressed with the exception of one paper that we reviewed, and that's the Murray paper, the level of embryo -- level of maternal toxicity in the rat, mouse, rabbit is so severe, that by definition, it will give mills to the effect, in fact, all of the effects that were reported. From my -- I do a lot of work in maternal toxicity. And looking across the board, if anything, I was impressed by how few problems that we saw. I would have anticipated more.

So the only paper that I can even remotely pull out of this where I did not find maternal toxicity to be an overriding concern was one, and I -- I find that less than definitive. Because I think that it was done prior to a time point where we have good day-to-day variation on food intake.

I concur that if it turns out that there was an abrupt effect on food intake, which seems to be typical of this particular agent, on that day, cleft palate is exactly what you predict that you would get and about that frequency.

So my read of the -- of what we were presented is that it seems to be secondary phenomena that we are looking at rather than direct embryo or fetal toxic effects.

CHAIRPERSON BURK: Okay. Anybody? Linda, do you have any comments? We are talking, I guess, right at the moment about developmental tox animal studies.

COMMITTEE MEMBER ROBERTS: No, I don't have any -- I don't have any disagreement with that. I was flipping back just to take a look at what the rabbit toxicity was in the does.

CHAIRPERSON BURK: I am still personally sort of in a quandary, because I do think -- I do agree that the epidemiology studies are provocative, and I would like to see something solid in the animals that we could really, you know, I guess hang our hats on and really sharpen it up.

I'd like to talk about the male reproductive toxicity. I still -- speaking for myself now, I still find the Chang case study very -- and I don't want to use the word "suspicious," but actually, I thought it was really effective. However, it is only one case study, and that's not the way to make a decision.

So then we come to the issue of whether the Land study supports it. And, I mean, I do see there is some concurrence there in that sense. So this is the one area where I'm really in a quandary.

I do, of course -- NTP studies that are done in looking at fertility always get heavier weight with me just because they are designed for regulatory purposes, I think,

at least in my opinion. They are the kind of things we want to look at. But I can't lose sight of the sperm effects.

I too wish that Marian was here, and I want to know how you all feel. Do you feel comfortable making a decision on the male situation? Would it be something you'd want to defer until the Committee got larger? It is just an option that we have, so I guess I am just asking everyone what they think.

COMMITTEE MEMBER JONES: I would just like to comment on the Chang case report for a second, because I must tell you, I was struck by the fact that six months prior he'd had a study to determine why there was a problem with infertility. Or at least most people don't go around getting sperm studies unless there's some problem.

So I'm wondering -- and, again, this is speculation. There's nothing in the study that would tell us the answer to this, but I'm wondering if this guy had a problem with fertility to start with and had absolutely nothing to do with his exposure to chloroform.

And I don't think we have any way of saying that except to say, "Why in the world is this guy having a study, a sperm count motility study?"

COMMITTEE MEMBER SAMUELS: Well, this study -- I think the unfortunate kicker in this study is that there were two or three other chemicals that were prominent, and you

cannot -- we did have one study a few years ago where -- well, irrelevant. But in this case, while I really do think this was a chemically-caused effect, I couldn't pin it on chloroform, and I don't think we'll ever be able to do that.

CHAIRPERSON BURK: I agree. It was very intriguing. But in the absence of some other supporting data, you know, one case study just isn't sufficient.

Although, I guess, in our actual criteria, I was sort of reading along, one good study would be sufficient if we were thinking that way, but I don't think this qualifies.

COMMITTEE MEMBER JONES: This isn't it.

CHAIRPERSON BURK: Okay. Any comments on female reproductive toxicity? Again, I think, you know, most of the studies that were presented are essentially the developmental ones, but here we're looking at systemic toxicity of the mother and the effects, but there is the -- I guess it is the spontaneous abortion in the lab workers would be another potential study that could be used on the female side. What's your thinking there? Would that be strong enough for listing for female repro tox?

COMMITTEE MEMBER SAMUELS: This is the Wennborg study, and my judgment is that it is a -- what I look for is whether there was any concurrence in the animal studies, and I am not sure what would be the parallel effect in animals. We did have increased resorptions in some studies, and the

argument has been that these were all in the presence of maternal toxicity.

So I do find a parallel there on the basis the other two studies that -- however, it is the only study that found a significant association with spontaneous abortion, and one study by myself which has not as many problems as it's been criticized for, very difficult for me to state it should stand alone as indicating an effect on spontaneous abortion. If we reanalyzed, it might well be stronger, but it is not reanalyzed. So I cannot -- I don't want to make a conclusion based on that alone.

CHAIRPERSON BURK: Okay. I guess I have been mixing the human and the animal, but any other comments about the animal studies relative to female repro tox?

COMMITTEE MEMBER JONES: Steve, what about the Windham study?

COMMITTEE MEMBER SAMUELS: This is the one I'm talking about. What I really should have done, though I didn't think about it, was to do a new calculation to do what's called a one-sided statistical test, which I'm guessing probably would have turned out to be significant at the .05 level, which might then elevate it somewhat to our -- to important status.

And then if my belief is correct that they over controlled, they would have had even more significance.

So my personal belief of that is a statistically significant study, if analyzed in the proper way, but, again, it's not --

COMMITTEE MEMBER JONES: They needed you, Steve, on all these things.

CHAIRPERSON BURK: A good statistician really is important.

Well, I am not trying to rush anything. Are there any more comments? I want to make sure we have a chance to say anything that's on our minds before we take a vote. I sense we're ready. Let me find the script.

All right. We will vote separately on each end point, as we have always done, and recall that it would require four yes votes to list in any of these circumstances; is that correct?

MS. MONAHAN: Uh-huh.

CHAIRPERSON BURK: Okay. So first, has chloroform been clearly shown through scientifically-valid testing, according to generally accepted principles, to cause developmental toxicity? A show of hands if you say yes. I see one. So that will not be listed for developmental toxicity. I am supposed to record these, so I am writing them down.

All right. Secondly, has chloroform been clearly shown through scientifically-valid testing, according to

generally accepted principles, to cause female reproductive toxicity? Again, a show of hands. I see zero yes.

I haven't been asking for abstentions. I guess someone should tell me if they want to do that, because I am just assuming the other votes are no.

Okay. All right. Was it important that I actually ask separately for the yes and the no? Because if so, I will start over.

MS. MONAHAN: I think it would be more helpful. It will make the record more clear.

CHAIRPERSON BURK: All right. We will start over. We are back on developmental, and I asked has chloroform been clearly shown through scientifically-valid testing, according to generally accepted principles, to cause developmental toxicity, and we had one yes. All those voting no, could you raise your hand. All right. I see four. Any abstentions? No.

Okay. So now I'll do it again the same way. Has chloroform 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. Okay. I see zero. All those voting no, please raise your hand. I see five. And any abstentions? Nobody's left. Okay. So zero.

Okay. And third, has chloroform been clearly shown

through scientifically-valid testing, according to generally accepted principles, to cause male reproductive toxicity? All those voting yes, please raise your hand. Okay. I see zero. All those voting no, please raise your hand. I see five. All those abstaining? Again, zero.

Okay. So do I make a conclusion here, or do I leave that for you later?

DR. DENTON: Just move on.

CHAIRPERSON BURK: Great. All right.

(Whereupon a recess was taken.)

CHAIRPERSON BURK: I think we are ready to begin again, and the next item on the agenda is the discussion of progesterone. So first we will hear the staff reports, and is it Mari.

DR. DONALD: Yes, Dr. Mari Golub will present a summary of the data both for human and animals. But Dr. Kaufman also worked on the human data, so we will be available to answer any questions.

DR. GOLUB: Welcome back, and I am going to just present an overview of the hazard identification document for progesterone. Next slide.

Progesterone is an endogenous progestational hormone. When administered exogenously, progesterone has low oral bioavailability, which has limited its use for therapeutics. Bioavailability by the vaginal, nasal and dermal routes is

adequate for therapeutic use.

Recently a micronized progesterone has become commercially available, which has improved oral bioavailability. The low bioavailability of progesterone is due to its extremely short half-life, which in turn is due to a very rapid and extensive first-pass affect in the liver.

In target tissues, progesterone activates specific nuclear and membrane receptors, and it can also act as a modifier of signal transduction.

Progesterone exposure is primarily through therapeutic uses, as a female contraceptive, in an IUD preparation, as a luteal support for in vitro fertilization pregnancy, for treatment of a variety of gynecological disorders, and as hormone replacement therapy for postmenopausal women.

In addition, progesterone is marketed directly to consumers as a supplement and cosmetic. Some of the suggested benefits from internet advertisements are improved sexual libido, enhanced serenity, prostate support, opposition of estrogen dominance and production of healthy and more intelligent children.

Progesterone is one of five hormones that is approved by the FDA as a growth promoter in livestock and anabolic steroid. Progesterone can also be a contaminant of environmental media through animal and human wastes, and also

through commercial progesterone production.

Early studies evaluated progesterone as a potential male contraceptive. An intrasubject design was used in a small sample of prison volunteers. A dose of 50 milligrams per day administered intramuscularly lead to azoospermia, reduced libido and testicular size and fewer mature sperm in the seminiferus tubules in a testicular biopsy that was done at the end of ten-week study.

A more recent study administered progesterone at the same dose to ten young men. The purpose of the study was to look at circulating levels of gonadotropins, testosterone. In addition, a gonadotropin-releasing hormone response test was done, and reduced levels of gluetinizing hormone, follicle-stimulating hormone, testosterone and gonadotropin, and reduced gonadotropin response was seen in the study.

A similar suppression of spermatogenesis has been demonstrated in monkeys, rabbits and rats. Those studies are described in the HID.

Reproductive track maturation, a sensitive male reproductive toxicity endpoint has also been shown to be influenced by postnatal progesterone administration in animal studies.

For female reproductive toxicity, early studies also evaluated progesterone as a female contraceptive. Using a 300 milligram oral dose, progesterone was found to suppress

ovulation during cycles when it was administered as compared to control cycles in the same women.

A later study also evaluated the progesterone IUD inserted shortly after birth. Postpartum menstruation and a greater production of milk with an altered composition was found in this study.

A similar suppression of ovulation and reduced fertility have been demonstrated in a number of animal species. Altered sexual development has also been demonstrated in female rats exposed to progesterone in utero and postpartum

Finally, parturition and maternal behavior, which depend on endogenous progesterone, can be disrupted by exogenous progesterone in rats.

Human developmental toxicity studies. The therapeutic use of progesterone led to concern about adverse affects in the fetus, since many of the applications were for pregnant women.

Studies of malformation incidents were generally for drugs classified as progestogens, which includes progesterone as well as other drugs designed to have progestational activity, but better oral bioavailability.

We were able to find six studies that contained small numbers of women treated only with progesterone, in which a malformation incidence was studied. There was no association

of malformation with the progesterone administration.

There were three prospective random studies of progesterone administered for threatened abortion in the literature. No effects on pregnancy outcome were reported in these studies.

Because of the androgenic potential of some progestogens primarily the nor-testosterone derivatives, concern was raised about virilization of the female fetus when progesterone is administered during pregnancy.

Female virilization was confirmed for several of the progestogens, by case studies and population studies. But only three case reports are available for progesterone itself, and this precludes any estimate of the risk of female virilization for progesterone.

A large number of large-scale, case-controlled studies for hypospadia have been conducted for progestogens. Hypospadias are caused by insufficient testosterone during early embryonic development. And as mentioned earlier, progesterone can depress androgen production.

The only two studies of progesterone itself, however, contain no control groups, and this is not possible to evaluate the incidence of hypospadia related to progesterone administration.

The developmental toxicity studies in animals are also limited, and they extend over a 50-year period. They

primarily use injection routes. Four studies reported data on pregnancy outcomes and laboratory animals. Intrauterine death and growth retardation were reported in rat studies, and altered sex ratios were seen in both the rat and rabbit study.

Malformations were evaluated by fetal exam in the rat and rabbit study, but there was no increase in malformation related to progesterone administration.

Two studies in mice followed in utero-exposed offspring to adulthood and found alterations and sex-differentiated behaviors, mating in the case of males, and postpartum aggression in females.

Because of the concern about virilization of infant girls and hypospadias in boys, studies were undertaken in laboratory animals. Primarily they used anogenital distance as a quantitative measure of genital differentiation.

The effects of the nor-testosterone progestogens were confirmed in animal studies. Two of ten studies which included administration of progesterone found anogenital distance effects in female fetuses once the progesterone was administered during pregnancy.

In the case of male hypospadias, and as reflected in anogenital distance as a measure in fetuses, six studies were available. There were increases, decreases, and no effects reported on anogenital distance. No study reported a

statistically significant change in anogenital distance in male fetuses.

So to summarize the DART effects reported for progesterone, intrauterine death and growth retardation and altered male and female sexual development have been reported in animals. These are endpoints relevant to developmental toxicity.

Suppressed spermatogenesis has been reported in humans and in animals, and also reduced fertility and altered sexual development in animals, endpoints relevant to male reproductive toxicity.

And for female reproductive toxicity, suppressed ovulation and reduced fertility have been reported in both humans and animals, and altered sexual development in animals.

And that concludes my presentation. I'd be glad to answer questions, or later in discussion to provide any details about the studies that you might be interested in.

COMMITTEE MEMBER SAMUELS: Could you -- since animal studies saw altered sex ratio, did the human studies analyze that outcome as well?

DR. GOLUB: No, there were no human studies that looked at sex ratio at birth. The animal studies with altered sex ratio, because of the issues of genital differentiation, it is important to confirm the sex. So that

could be done to a certain extent in humans, but it isn't routinely available.

COMMITTEE MEMBER SAMUELS: Thank you.

CHAIRPERSON BURK: Are there any other questions for Mari at this time? No. Thank you very much, again, for another beautiful document, and your coauthors as well.

We have one person wishing to speak, make public comment, and that is Brad Buchanan from Ementa.

MR. BUCHANAN: Emerita.

CHAIRPERSON BURK: Emerita. Sorry. Couldn't read that.

MR. BUCHANAN: My comments are brief and without the aid of Power Point. I'd like to thank the Committee members and OEHHA for the opportunity to provide comments and opposition to the listing of progesterone as a reproduction toxicant.

Understanding that our previous comments have been considered as part of the process, I would like to add comments from health care practitioners that counsel patients on their hormone options without debating the science.

I quote, and with permission, from Dr. Sue Stone, Please accept this protest from me regarding adding progesterone to the list of reproductive toxicants. Progesterone is a natural biogenical hormone with many therapeutic uses and absolutely no harmful activity, end

quote, Fresno, California.

The second and last quote that I want to read is from Gloria St. John, the Executive Director of the California Naturopathic Doctors Association. The California Naturopathic Doctors Association is opposed to the classification of progesterone as a reproductive toxin. Progesterone is a hormone integral to the reproductive process, with beneficial affects in sperm motility, fertilization, implantation, luteal support and much more, hence its use as a treatment to support fertility and maintain pregnancy, end quote.

Those are my comments. Our company also submitted comments during the review period, and they should be in the documents you have. Thank you.

CHAIRPERSON BURK: Will you take questions? Does anyone have any? My only question, what does your company make.

MR. BUCHANAN: It's Emerita. Emerita is the female of emeritus of honor and respect. Is that all?

CHAIRPERSON BURK: I understand the Latin. I just wondered what your company made.

MR. BUCHANAN: We -- Dr. Golub had listed supplements and cosmetics in one of the alternatives available, and that's what our company does. We are based out of Portland, Oregon, and distribute into California.

CHAIRPERSON BURK: Do those require prescriptions or --

MR. BUCHANAN: No, it is supplemental status.

CHAIRPERSON BURK: -- are these available over the counter?

MR. BUCHANAN: Any other questions from the Committee?

DR. DENTON: Okay. I should mention that we did receive two very late comments that are in the -- again, in the back of the binders of the Committee members. One from Judith Turgian, and another from Jeffery Kaufman.

MR. BUCHANAN: Thank you.

CHAIRPERSON BURK: Thank you. I'll give the Committee a quick chance to look at the comments, but unfortunately it is hard when it comes in late. But we did get some previously that I am sure we all looked at.

Are we ready to begin discussion of progesterone? Again, could I ask Jim again, just to clarify, this was already prioritized as progesterone. Are any of these synthetic progestogens in the database somewhere, too, or is this specifically because it does have an environmental as opposed to just therapeutic?

DR. DONALD: Well, the previous prioritization process that I mentioned was based on nominations from experts. So progesterone was nominated to us. Other

progestogens weren't at that time. So progesterone is what's progressed through the subsequent process.

I have to admit, I don't know off the top of my head if we have other progestogens in the database at this point.

CHAIRPERSON BURK: Well, it is open to anyone on the Committee who wants to start us off. Do we want to start with any particular endpoint? Are any of them clear to anyone? Do we want to take our changeover now? Your replacement is here, and we don't want to lose anything. Maybe we should just pause for a minute and think.

(Whereupon a recess was taken.)

CHAIRPERSON BURK: I guess we're back. We'll continue.

In the meantime, is anyone ready to begin the discussion?

DR. JONES: I think that the only, in any way, controversial issue would be -- would relate to hypospadias, and I -- I don't think the data is good to suggest that hypospadias is associated with progesterone exposure either, so I see no evidence of concerns relative to developmental toxicity.

CHAIRPERSON BURK: I think I agree.

On the other hand, I think male and female, I think there's something we could talk about. I mean, I think it's only just logical in some ways that a contraceptive is likely going to have some effect on male and female fertility. But we should look specifically, I guess, at the studies that were given.

Any comments from the epidemiological point of view?

DR. SAMUELS: I have a question. The gentleman who just spoke mentioned -- in one of the comments mentioned the benefits of progesterone.

In reading the articles, is there really any protective effect of progesterone in threatened pregnancies or threatened abortion or IVF support?

DR. GOLUB: Well, certainly progesterone administration is necessary to simulate the luteal phase in preparation for in vitro fertilization, and -- so this is definitely a beneficial effect, and it also makes it impossible to evaluate the possible adverse effects because you can't have a control group -- you can't have the pregnancy if you don't have the progesterone.

In terms of threatened abortion, I think that's -- that's a therapeutic use that has not been supported for many years by professional organizations.

DR. SAMUELS: Thank you.

DR. JONES: But there's no question that progesterone is being used or at least there's studies looking at the use of progesterone in premature delivery -- to suppress premature delivery --

CHAIRPERSON BURK: Yes.

DR. JONES: -- at this point now.

DR. GOLUB: I'd just like to comment that that is not progesterone. It's 17-hydroxy progesterone that was in the studies that were reported recently in, I think it was, the New England Journal of Medicine.

DR. JONES: I don't think so, but --

DR. GOLUB: We tried not to report any studies in the HID that weren't directly on progesterone even to

discuss the fact that they weren't on progesterone, but we did look very carefully at that article and the commentaries around it, and it was 17-hydroxy progesterone.

CHAIRPERSON BURK: Is that something that you would need to see to make a decision?

DR. JONES: No, absolutely not.

CHAIRPERSON BURK: Because I know I just read something in the popular press about pre-term delivery and the use of progesterone, but you're not sure when you read it there what it actually is. That's just sort of a generic term. So we'll take your word for it there.

Any other comments? I sense almost that this is going a little quicker than the other, but I was accused of rushing before, so I'm going to go real slow. If anyone wants to say something -- are we ready to --

DR. SAMUELS: Dr. Burk, you mentioned there's more evidence for female reproductive toxicity? Or maybe I misunderstood you.

CHAIRPERSON BURK: No. Tell me there isn't. I --

DR. SAMUELS: I mean, I didn't see strong --

CHAIRPERSON BURK: I don't see it -- I don't

see it strongly. I mean, we've had a few cases, but let me review.

DR. SAMUELS: No, I just -- I just may have misunderstood your comment.

CHAIRPERSON BURK: Well, I tend to get into mechanisms more than I should, I suppose, and certain things just seem sort of logical, but we're basing it on the studies that we have. We're basing our decision on what we have to look at.

So let me find my -- pardon? Is there any other discussion of male or female? We have a male expert still if there's anything that we don't feel comfortable with.

DR. GOLUB: I might comment that Dr. Li did read these studies and contribute to the HID in the male reproductive section.

CHAIRPERSON BURK: All right. I will go through unless -- last chance. Okay.

And this time we'll do it by the book and vote separately on each endpoint for progesterone.

Go ahead.

DR. SAMUELS: May I interrupt?

I know this has happened before. I mean, the only evidence -- strong evidence is for male reproductive toxicity. On the other hand, progesterone

is marketed for -- to women, and I'm sure these creams are -- for example, are intended to women.

And the listing process, you know, doesn't make a distinction, and so there's concern by the physicians that women will be discouraged from using progesterone if -- if there's a warning.

And I know at least one time in the past the committee used its discretion to ask that the warning be specific to the susceptible subgroup. I don't know whether we have any options there, but I'm asking.

DR. DENTON: Why don't you give us just a minute. Do you remember what chemical that was?

DR. SAMUELS: I think it was aspirin, which was --

CHAIRPERSON BURK: I remember that one well, and it was just third trimester exposure, I believe. And we put something on Vitamin A, I think, or something like that at the time, you know, that -- I think it depends how the thousand-fold safety factor would be applied. Would it result in --

DR. SAMUELS: That might affect the listing, but it could -- might -- it would not affect production. Again, that I don't know.

CHAIRPERSON BURK: Yeah, and I don't know. And part of the problem is I know historically we do the

hazard identification phase, and then it goes beyond that if it's listed.

But if we know something ahead of time and you want to add some kind of a footnote to it -- I think it's been done.

MS. MONAHAN: If you want an example, in the context of aspirin, there's a note along with the listing that says:

"It's especially important not to use aspirin during the lasts three months of pregnancy unless specifically directed to do so by a physician because it may cause problems in the unborn child or complications during delivery."

So that was a fairly long comment. But, of course, when -- if you did the listing for male, then it would -- I mean, that would be the notation in the list, is that it was male, not female or developmental. So it would also be limited in that regard.

DR. GOLUB: Could I say a word in connection with sensitive populations? While it's true that the HID presents evidence that progesterone suppresses testosterone and sperm production, it also presents evidence that testosterone suppresses ovulation and fertility in women.

So it's a different effect. Certainly the

same -- you know, the same endpoint wouldn't apply across, but women as a sensitive population should also be considered.

DR. SAMUELS: So it sounds like, even though that's the recommended use, our problem is that progesterone is present in products not intended for the medical use for which it's indicated and -- and those -- and so its use conceivably could have an influence on women.

And, of course, we haven't talked about tests on children at all, so that -- that's also open as to what -- as to effects on both male and female children.

So you're saying that there's also evidence for female reproductive toxicity as well as male?

DR. GOLUB: Well, for effectiveness as a contraceptive.

DR. JONES: Well, it seems to me this is an important issue that we need to discuss here before we vote.

So there's absolutely no question that progesterone affects ovulation and a variety of issues like that and it's used in that way and -- are we then suggesting that that's a female reproductive toxicological effect? I mean, that would be a --

CHAIRPERSON BURK: Well, I think --

DR. JONES: -- fairly --

CHAIRPERSON BURK: I think it is.

DR. JONES: -- thing to say.

CHAIRPERSON BURK: I don't know how you could say that that isn't an effect.

And I can sort of read to you from our criteria that -- this was a number of years ago that we put together what we considered possible adverse female endpoints.

And for female reproductive toxicity, you know, there's one section, genetic damage, but then a second, alterations in ovulation, menstrual cycle, so forth. A third one, impaired or altered endocrine function and complication of pregnancy. But I mean, it is -- it is on the list as an endpoint.

Now, I know we tend to think more specifically toward fertility, but even then that could certainly have an effect on fertility, so that's why I'm kind of -- I see it a little differently.

But I understand the concern that we don't want to list something with a lot of therapeutic use and benefits that would confuse people --

DR. JONES: Right.

CHAIRPERSON BURK: -- as to what the hazard is for them.

DR. JONES: Right.

CHAIRPERSON BURK: So that's why -- I mean, it's possible that we could put some little statement after it if we did choose to list it.

DR. ROBERTS: If I recall, also, Vitamin A, which, like progesterone, you need some of it at least for successful reproduction and too much of it is -- is harmful, it looks like progesterone is in sort of the same boat.

MS. MONAHAN: Do you want to know what -- what's on that listing?

DR. ROBERTS: Yes. I'm wondering if that could be a precedent that could be followed.

MS. MONAHAN: The listing actually says retinol -- retinyl esters when in daily doses -- dosages in excess of 10,000 Iu or 3,000 retinol equivalents. So it's -- that's the limitation.

And then there's a note that says: "Retinol" -- "Retinyl esters are required and essential for maintenance of normal reproductive function. The recommended daily level during pregnancy is 8,000 Iu."

DR. ROBERTS: Do you know if that latter part was specifying the level at which it is considered to be harmful was something done by the committee or something done by OEHHA.

MS. MONAHAN: I'm told that it was by the committee. I wasn't present at that meeting.

CHAIRPERSON BURK: I actually remember that, and the concern was, of course, that if you applied a thousand-fold safety factor to the NOEL you'd be in a nutritional deficiency state or whatever you want to call it. In other words, you would be deficient.

MS. MONAHAN: The other thing that I could point out, also, is that under our regulations, the warning requirement wouldn't even be triggered for any -- for this chemical if it was used as a prescription since we exclude those and say that the warnings that are already required with the prescription are sufficient under our regulation. So we'd really only be dealing only with over-the-counter products.

DR. DENTON: Carol, if we can have just a little chat here. Now, the listings, the examples of Vitamin A and aspirin, the parentheticals behind those listings were more dose related or the trimester.

Now, the committee to make a recommendation on the appropriateness or inappropriateness of a warning, that gets into another whole new -- that's a different ball of wax.

That's not a scientific limitation on a

warning. That's more of a getting into the regulatory enforcement, you know, implementation portion of the -- of Prop 65, which I'm reticent to think that's a good idea.

MS. MONAHAN: Really, our own regulations on warnings are only recommendations. They aren't mandatory. The individuals, when they decide whether or not to put a warning on, still have the option not to use the warnings that we recommend.

So I'm not sure that -- I mean, I think that it would be much better for you to stay more focused on whether or not this has been clearly shown to cause and put whatever caveats you believe would be appropriate to that and not worry about whether or not a warning is actually going to be required because it would be so specific to, you know, is it a prescription, is it not, what level's present, you know, those kinds of things that aren't really within the authority of this group and, to some extent, even the enforcement under the law isn't even within our control so --

DR. DENTON: I agree.

CHAIRPERSON BURK: So what I'm hearing is we should focus on the science and the hazard identification and not -- not worry about what's going to happen.

DR. DENTON: Again, the charge of the committee is to -- is to make a judgment on the scientific evidence whether or not -- as Carol says, whether or not something's been clearly shown or not. In your scientific evaluation, has this chemical been clearly shown or has it not been clearly shown.

If it has been clearly shown in one instance rather than in another, which is the parentheticals associated with aspirin and Vitamin A, then that -- that is appropriately added into the -- into the listing.

But it's -- you know, this -- I think this implication sort of discussion goes beyond the actual scientific basis of the listing.

DR. KEEN: Just a quick observation because we've kind of treaded in this water once before besides for Vitamin A when we were discussing, well, for some of the essential minerals or, for that matter, any essential nutrient, we're effectively saying, well, almost by definition that they all are reproductive toxicants at high enough levels, they're all reproductive insults if they're at low levels, and really -- this is exactly the same category.

And when we last had the discussion, in part what we agreed to is to try to steer away from it so we didn't hopelessly confuse the individual out in society,

which I have great fears of.

Because of using this logic, particularly if there is a huge area of -- apparent window of safety, then you could have individuals wind up -- now, if we go back to nutrients, say, well, I should stay away from all these things, or I should label them if they're full of the very same nutrients that another branch of the government, such as the FDA, is saying we should consume. And it's a real problem of mixed messages, so I'm uncomfortable.

I mean, on one hand, by definition, with progesterone, I don't think there's any real debate that, if you have high enough concentrations, does it affect the reproductive process? The answer is yes, and it is unequivocal.

But it's a message which I think is very confused if people -- we start telling people and they perceive it as a risk suddenly.

CHAIRPERSON BURK: I agree, but it's hard for me because I'm still in this mode that we look at the data and we make our decision, and then things happen after that that hopefully give the right warnings, the right -- I know. Maybe -- maybe we feel we need to have more control over that, and I remember many years back talking about that all the time. What's going to happen

if we list this?

But I would hope that somehow some reason would prevail in the way that it was -- maybe George can comment on that since he's waving his hand.

DR. ALEXEEFF: Well, I have -- George Alexeeff -- two comments.

One is, progesterone is listed as a carcinogen since 1988, so that's one point.

The other thing is if -- as we note in the other parentheticals, they're fairly specific. We have dosages, trimesters and things like that.

One possibility could be that you could ask staff if they could come back at a future meeting with some specificity for a proposed parenthetical.

If that -- I'm not sure if we could, you know, come up with something as clear as this; but if that was something you felt that somehow there's this dividing line you wanted to clarify, that could be something we could investigate to see if that would be helpful.

CHAIRPERSON BURK: So would we like that idea? I'm seeing some nodding heads.

DR. KEEN: I think that's an excellent idea. It will probably be a lot more difficult than it was with Vitamin A because there, there was actually a pretty rich body of literature that was developing at

around the same time that this committee was asked to look at it, and some pretty clear-cut papers that one could argue, well, it was five percent or ten percent, around that number. I'm not -- I don't know if that's quite as clear here.

On the other hand, that was not the information that was provided for us to review, for good reason. I don't think it's something that normally we would have expected to see. So if that information would be provided, I'd feel a lot more comfortable at that point.

CHAIRPERSON BURK: All right. It looks like that may be unanimous. I'm seeing everyone in agreement. So does that mean you want to defer the entire -- the entire vote, am I correct, for each endpoint?

Okay. Well, that's what I'm saying. If we would like to defer it for the male and the female repro tox because that's what we're saying is our main concern, and then we'll vote on the developmental. Are you okay with that, Steve?

All right. Let's do that. At least we'll have accomplished something.

All right. So here's the question. Has progesterone been clearly shown through scientifically

valid testing, according to generally-accepted principles, to cause developmental toxicity?

All those voting yes please raise your hand.

Okay. I count zero.

All those voting no please raise your hand.

Okay. I count five. And so I'm assuming zero abstaining.

So we will -- progesterone will not be listed as a developmental toxicant, and we will defer our decision on male and female reproductive toxicity pending further elaboration of perhaps some caveat that we could put onto it or some clarification.

All right. Next on the agenda we have consideration of --

DR. KEEN: Just a quick comment since we're moving into a completely different area now.

Two or three times I've heard people up here refer to the fact that, I think, the way these two staff reports were prepared really were exceptionally good.

I'd just like to go one step farther and encourage OEHHA, if they have the opportunity, to try to get these into the public domain.

This last discussion was an excellent example of it because I could see a very good discussion of that; and if it was in the published literature, it

would be something we could deal with in a slightly different format then. So I would encourage, if at all possible, attention be given to that.

CHAIRPERSON BURK: All right. Next on the agenda, item III, consideration of the revised prioritization process, and the staff presentation will be by Dr. Lauren Zeise of OEHHA.

DR. DENTON: Before you start, Lauren, I just -- just want to give the -- a little -- and then I'm going to turn it over to George -- just a little background on this item for the committee's consideration.

We've been working on revising our 1997 prioritization process for the last several years, and we've had several lead persons from this committee, that is, Dr. Roberts and Dr. Jones, participate on -- in an ad hoc committee with OEHHA along with several members of the Carcinogen Identification Committee to try to devise a -- I guess a more efficient way of prioritizing chemicals.

This committee has not seen any chemicals that had been prioritized by using the 1997 process, but will be seeing chemicals prioritized in some form.

So we've had a -- there has been a process involved, and so I'm going to turn that over to George

who will just go over a little bit of the details of the -- of what's happened in the development of this document which you see before you today.

MS. MONAHAN: Actually, I think that's going to be me first. Sorry.

I just wanted to say very quickly that there was a question raised about the reference to the group that developed the proposed prioritization process as a subcommittee of the committees, the two, the CIC and DART, and I just wanted to clarify that that reference did not mean to imply that there was a formal subcommittee formed by either the CIC or the DART.

There were -- this was a group that was formed by OEHHA and we, at Joan's request, had asked the chairs of the DART and the CIC to identify a couple of people that would be willing to work with us on that and that's what they did.

So it was an informal group and -- so I just wanted to clarify that for the record since some of our references said subcommittee.

DR. ALEXEEFF: This is George Alexeeff.

As Dr. Denton mentioned, about two years ago at the CIC meeting it was raised that we look at the prioritization process again and try to address some of the concerns that were being raised.

And subsequent to that, we -- they suggested that a member of the committee or two, you know, also be serving as leads. We spoke with Dr. Miller at the time, and she also suggested a couple members from the DART Committee.

So last year I made a brief report that we had been preparing -- been looking at the previous process and preparing some slight adjustments to that process in hopes of making it more useful in terms of bringing the most important chemicals to the committee.

And in May of this -- of early this year, we released a draft document for public comment. We had a public workshop in June. Then we looked at the public comments, and then we've released them again and then given another opportunity for the public to comment on it prior to this committee and also for them to give you comments as well.

So I just want to mention that we've had this process ongoing, and Dr. Zeise will briefly go over what -- what our proposal is.

DR. ZEISE: Hi. What I'll do is I'll go through the flow chart that you see on your computer screens and that basically lays out the prioritization process.

So the process starts with a tracking database.

That's the first box on the flow chart. And OEHHA has maintained for some time a tracking database of chemicals suggested for carcinogenicity review and chemicals suggested for DART review.

These suggestions come to OEHHA either through its own literature searches, the committees might make suggestions, other state organizations may suggest chemicals for review, the scientific community and the general public.

So the next step in the process is to look at the chemicals in the tracking database and screen them to see whether or not those chemicals have a potential for exposure in California.

Some time ago we didn't put the chemicals through this screening process and resulted in moving ahead some laboratory curiosities and things that really just aren't worth our while to review in terms of public health.

In addition to the exposure screen, we also looked to see whether or not there are data, in this case for reproductive toxicity, in order to initiate some kind of a review to see if they can be prioritized.

So the chemicals passing that very preliminary toxicity review and the exposure screen go into the next

box, the candidate chemicals.

So we have this large group of candidate chemicals, and the next kind of review we do is different from what we have done in the previous process in terms of -- in terms of the way it will work.

In this case, what we're going to do is -- the proposal is to do a very focused literature review, one that is suggested by this work group, and that focus screen will change over time.

Now, the initial screen that the work group has suggested is that we review the chemicals for epidemiology, so for the presence of epidemiological data. And, of course, in the review, analytic epidemiological studies, individual level epidemiological studies will carry much more weight, of course, than case reports and so forth.

So the initial screen would be to see whether or not there are epidemiological data available. Then if it passes through that screen, we will then look at other toxicity data, such as data from animal studies, on those same chemicals for which there are epidemiological data.

So in addition to the epi data, we will look at animal data and also other relevant data like mechanistic data and pharmacokinetics.

On the basis of that review, we will then propose chemicals for committee consideration and provide some rationale in writing for the proposal and release that list of chemicals with the rationale to the public and also to the committee. The public can then provide written comments on those chemicals.

The next stage of the review will then be to consult with the committee in an open public meeting of the committee on that list of chemicals.

At that meeting, the public can also provide oral comment and the committee will also have the written comments provided earlier on the proposal -- the public comments provided earlier.

So the committee will discuss the chemicals we are proposing and advise us on which ones to initiate hazard identification materials. OEHHA will then consider the committee's advice and make a selection of chemicals for hazard identification.

So that all is above that dotted line, and everything that I've just talked about is really part of the prioritization process.

Just to quickly go over the following steps, and those are the steps that we're following now, we'll go to the next slide.

So once we have this selection of chemicals for

review, as we do now, we will then initiate a data call-in. This is a request for information from the public occurring over a 60-day period. The public sometimes sends us data submissions. We actually would like to encourage more of that.

Then we would begin the hazard -- development of hazard identification materials. Then when the hazard identification materials are prepared, we then release them to the public for comment for 60 days.

And we then take the hazard identification materials and the public comments to the committee for their review and their listing decision. And at a meeting like this, of course, there is also the opportunity for oral public comment.

So that's the completion of the hazard identification phase of the process.

CHAIRPERSON BURK: Does anyone have any questions of this? I have one. Oh, before you take it away -- it doesn't matter.

At the part where it comes to the committee for advice, you know, before the dotted line there, how much -- I know you'll have the screens. Will it just be sort of a brief abstract of what you've found?

DR. ZEISE: Yes, it will --

CHAIRPERSON BURK: How are you going to present

that --

DR. ZEISE: -- be a very short --

CHAIRPERSON BURK: -- is what I'm asking.

DR. ZEISE: -- a very short discussion of the rationale, yes.

CHAIRPERSON BURK: Okay.

DR. ZEISE: In some cases, it may make sense to also provide some material, some publications, and I think we're going to have to work with this work group to really see what -- what makes the most sense to present to the committee and the public.

CHAIRPERSON BURK: Yeah, I would say -- I'd be afraid it would get carried away and it would wind up being, you know, a whole thing and then you'd discuss it then and there instead of just saying is this something that would --

DR. ZEISE: Yes.

CHAIRPERSON BURK: I know you'd have to work that out.

Does anybody else have any questions? Well, I know Ken and Linda were part of this, and I thank them for representing us.

We have public comment, and then we can discuss it again, so do you want to say anything now or do you want to wait?

DR. ROBERTS: I was just -- very briefly just say that I think the intent is to bring forward chemicals that are worth the time for us to review that have human exposure so there's some relevancy and have sufficient data that we can actually make a decision on it without feeling that we have inadequate information about it.

And that with this first screen -- looking -- it's hard to argue that if there are positive epidemiology studies or even positive human studies of some sort that -- since that kind of indicates that you do have human exposure, that that isn't a very relevant point.

I have some concerns that we need to also put in after that step looking for the better quality animal studies, and I think that that will come with the later screens or filters as it goes.

And I guess I'd also say, at least from my part, when you all come forward with information about the list of chemicals that are being prioritized, I still figure that you probably are all in the -- it's almost an FYI and a chance for us to comment as the public does as opposed to us making the decision for you.

CHAIRPERSON BURK: I think I heard loud and

clear that OEHHA would make the decision. The committee would be advice.

DR. ZEISE: Yes.

CHAIRPERSON BURK: I'm still -- I agree with it, and I think it's -- I think it's a very promising way to get us some of the chemicals that we really want to deal with.

I'm sort of concerned that we would -- if it didn't have epidemiological data, it would just be out of the picture, is that what you foresee, or that would get a priority?

But, you know, there's some good animal studies that are very suggestive, I would say, and could be extrapolated to humans. So I wouldn't want to eliminate that as a possibility.

DR. ALEXEEFF: The whole purpose was to simply prioritize this group of somewhat close to 400 chemicals. So what -- what we thought was, well, if there's positive human data, let's start there.

We have a little better handle on the cancer issue than we do the repro issue. So we're not really sure how many chemicals will be pulled out of this screen for the reproductive. It could be a large number or it could be a small number. We're not sure.

But once we have gone through those

chemicals -- and our intent is, again, to bring the highest priority ones, not one with, you know, one epidemiologic study that, you know, doesn't appear to be very convincing to anyone. That's not the intent. The intent is to bring the higher priority ones.

So once we've finished looking at -- through the human studies, the next screen would be the animal studies. We'd have to devise how -- how we would do a cut-off for the animal studies so we're not reviewing every animal study of every chemical.

DR. ROBERTS: This is just one of my suggestions during meetings -- and I don't know if it would work or not, and there are probably other possibilities as well -- but after you get to the -- once you get to the animal studies -- it says it's on. Is that better? This button, okay.

Once you get to the animal studies, if you can search by particular words, that might help give you some quality of the data.

And one of my suggestions was maternal no effect level because usually it's a -- it's a guideline type of study or a larger study that will identify that kind of endpoint as opposed to some of the very small studies.

And that might help us aim our -- their time

and then our time towards the studies that are done in a manner that we can -- we can feel confident reviewing.

That was just one possibility, and I'm sure there are lots of other ones.

CHAIRPERSON BURK: We have one public comment, Dr. James Coughlin, consultant for CHPA, GMA and NFPA. He can explain that.

DR. COUGHLIN: Thank you, Dr. Burk.

I'm Dr. Jim Coughlin. I'm a consultant. And I want to thank the committee and OEHHA for this opportunity to address you today on this issue.

I'll be speaking on behalf of the three organizations that you mentioned. I want to tell you a bit about each. They're keenly involved in and interested in Prop 65 activities and the proper implementation of Prop 65.

The Consumer Healthcare Products Association, CHPA, represents the leading manufacturers and distributors of nonprescription OTC drugs and nutritional supplements.

The Grocery Manufacturers of America, GMA, and its member food and beverage and consumer product companies employ more than 2.5 million workers in all 50 states and make just about everything you see in a grocery store.

The National Food Processors Association, NFPA, is the voice of the food processing industry on scientific and public policy issues that involve food safety, food security, nutrition on technical and regulatory kinds of matters.

Combined, these three trade organizations represent companies that account for probably more than $500 billion sales a year in -- just in the U.S.

Next slide, please, Jim.

I want to touch on four issues today listed here. Comments I'd like to make on the revised and proposed prioritization procedure are summarized here.

We think the new process closes the door to new information, it does not evaluate key issues, it reduces important communication and information transfer, and also we think it treats authoritative bodies inconsistently.

I'll go through each one of these slide by slide. Jim.

What you'll see on the next series of slides is a comparison, left and right, of the current procedure and the proposed revisions.

In the aspect that I first mentioned there, the no review of new information, in our current procedure, and this is a quote, assigned priorities may change as

new scientifically valid tox information becomes available.

And what we see with the proposed revisions is that, once the prioritization decision is made, it's kind of closed to new information and there can't be a change in the prioritization evaluation.

This makes -- we think this kind of makes no sense because it makes no allowance for changing prioritization evaluation based upon new information that becomes available. Again, the prioritization decision would be final, and we don't believe this is a very scientific process.

As you saw in Lauren's chart, a decision will come to you -- not a decision -- but it will come to you in a committee to see how you feel about it, but then we have these meetings once a year, and it will be a year later we'll be developing the HID and making comments. So things could change, but this doesn't give the opportunity for a change in the prioritization with new information.

Next slide, please.

Second issue is that we don't believe key issues will be examined as closely as they have been in the past during the prioritization process.

In the current procedure, the level of analysis

employed during the course of assigning final priorities varies according to the complexity -- and that's the important word I want to point out there -- varies according to the complexity of the toxicological issues to be addressed.

While we agree that, you know, the easy chemicals -- many of you have, from these very microphones, said the easy ones have been done before. It's the complicated ones that we're going to be struggling with.

The -- but in the proposed revisions, the complicated -- that's a quote from page three -- the complicated scientific issues concerning chemicals to be considered are not addressed in the prioritization process. The complicated stuff waits until the HID and your committee decisions.

So we think that with this procedure -- the revised procedure, OEHHA looks like it kind of intends to close their eyes to some really tough kind of scientific issues that we used to be able to address earlier in the process and do a quicker run through and bring something to you only looking at the periphery of what's happening in the chemical database.

I want to thank Dr. Keen for mentioning something near and dear to my heart, I'm basically a

nutritional toxicologist, and Carl mentioned, you know, the nutrients and other beneficial things perhaps like polyphenyls and other things that you work on, I know, for sure.

The idea that -- that's getting complicated; and if we wait until final decision making time to even bring up those issues -- in the past we brought up complicated issues during the course of the prioritization procedure, and we see this opportunity kind of being lost.

Next slide, please.

Continuing on the key issues not examined arena, in the current procedure, it very much specifies that maternal toxicity, which you discussed this morning, will be discussed in detail.

It appears in the proposed revisions that these kinds of issues like maternal toxicity, systemic toxicity that are more complicated look like they may be ignored.

Currently during the process of prioritization interspecies differences and toxicokinetics, pharmacokinetics, toxicity get discussed and we get to comment on them, and it appears in the new revised proposal that some of these more difficult issues will probably -- and more complicated issues will probably be

ignored.

On the next slide, in the arena of less communication and information, the current procedure requires a preliminary assessment of all the key scientific issues that appear in the data that has been gathered, and it looks to us, however, in the proposed revisions like, again, these complicated issues are going to be sidetracked and be put off for a later time.

We also, with the current procedures, have the opportunity for a public workshop to discuss and define and refine and talk more about some of the more complicated issues.

If things aren't complicated, there haven't been workshops that have been set up, but we've had a lot of good interchange of ideas between the interested parties and the agency in these public workshops, and we see no opportunity here or not much opportunity for a public workshop to occur in the proposed revisions.

There's also a discussion of -- with these two limitations, we believe that if we don't do it in this stage, that the quality of the hazard identification documents, the ones -- you've reviewed two of them in getting ready for this meeting -- we think the quality would probably decline if you don't start struggling

with some of these issues earlier on in the process.

Finally, in the -- no, I'm sorry, Jim, right back -- I've got a last point to be made on our authoritative body.

The current procedure requires consideration of authoritative body analyses. You've got several authoritative bodies in the DART arena; and in the proposed revisions, it appears to us that the authoritative body analyses will be treated inconsistently.

Going a little further -- on the next slide -- on the authoritative body treatment, the two procedures, the current and the proposed, are pretty consistent when it comes to an authoritative body decision where a causal link has been shown and it's considered authoritative.

But -- on the bottom lines there -- we don't feel that we do have in the current procedure, if there's a pretty firm determination by an authoritative body, that there is no evidence for causality, it doesn't appear to us that such findings would carry much weight in this prioritization process that's being proposed.

On the next slide, a new area. I -- we've re-used the same less communication and information

exchange in describing the whole process.

This is the chart that Lauren showed you. Anything in -- on -- in black in the boxes and on the right side Lauren has already described to you. I'll briefly go through some of the key problems we're having with the revised procedure.

This whole issue of the epi screen as the first screen, which you've just talked about, it's very undefined. It looks like to us kind of a -- a mysterious black box approach.

In the current procedures, it goes on for a very, very long paragraph about what a good epi study should have in it, and they were listed in somebody's slides earlier today, the postulates of epidemiology.

But we -- it's not very clear to us what is really going to be going on in this epidemiological screen. It seems a little mysterious to us to just be focusing on epi results as the gate keeper to what winds up going through.

I made the point earlier that the complicated issues will be -- will be left -- the complicated scientific discussions will be left to later in the process. There seems like there'll be only a partial preliminary tox review rather than the more full one we get in the process that began in 1997.

Another point -- and you can see that dotted line there is the one that Lauren told us about where the prioritization process ends and hazard ID process begins. There have been chemicals that have moved forward to both the DART and CIC committees. They got there because there was -- they did not meet the criteria for listing by the authoritative body, or an authoritative body, and we've got some -- some issues around that.

The two final comments in red there are the complicated scientific issues and in-depth tox review. I've talked about them, but we put them there to show you how much later in the process after prioritization is over that these things appear to be -- begin to be struggled with.

We would really like to see, like we have currently, the opportunity to look at the complicated scientific issues earlier on, the example being -- a nutrient would be a very good example of that.

We think this is really late in the process to be doing the important stuff. The stuff will wind up in the HID document, but we're going to miss opportunities that we had in the past early on to really come forward to the agency in workshops or in more detailed comments.

If we don't know what the agency is struggling

with in the early going, under the new procedure, we won't be making comments about it, and then it's all going to be left until the -- until the end.

And in the last slide I'm just summarizing the four points, and our three associations urge the committee members not to adopt the revised -- revisions of the prioritization process as they're currently constituted.

Instead, we believe that OEHHA should maintain the 1997 process that has been in place. It took three years, from '94 to '97, and a lot of open public comment to get those in place, and we think they've been working, so we urge, you know, no action at this point on adopting the current -- or changing the current and adopting the revised.

Thanks much.

CHAIRPERSON BURK: Thank you.

Would any of the staff like to make a comment?

George.

DR. ALEXEEFF: First of all, I want to really thank Dr. Coughlin for being here and making his comments.

And I would like to say that, you know, we've looked over the comments submitted by the associations he's representing, and our -- our general feeling is

that we feel that -- well, we disagree with his understanding of the current prioritization document, and we feel that we can clarify that in a number of different points.

It was not our intent to do a number of the things that -- that are being suggested, so I could just go through a few of the points, for example, the concern about not being open to new information. So our concern is that at each point new information could be provided.

I think one of the confusions is previously -- you know, in the previous system, which was -- which we've been doing a lot of the carcinogens, the lottery system where we randomly select chemicals regardless of whether they have a level of toxicity or not.

So in this case -- and we have previously by lottery picked some chemicals and then we try to bin them, high, medium, low. So we'd have these priorities; and then if something was high, they might say, no, here's some evidence saying it's lower than high. So we had to reorganize them over time.

So in this case, if -- as we look at the chemicals along the very specific screen, epi data, if a substance has no epi data during the first screen, we won't consider it anymore. We're not -- I mean, not

during this round.

At a subsequent round we'll consider it, but during the first round we will not look into its mechanistic data or anything else if it doesn't have the the epi data.

So that's a little bit -- that streamlines our resources not to look at the chemicals that we're not going to proceed on at that time.

So I think that's -- that's part of the -- so I think we can change some of the wording just to clarify that we are being open to new information. It's just that the way process is working, it's not similarly.

In terms of the complicated issues, that's also something we're also open to. I think, as Dr. Zeise mentioned, that we're -- we're going to consider essentially the same information that we've considered in the previous procedure; but, again, with the caveat that if we're doing an epi screen and there's no epi data, that chemical will not be considered at that time.

Then on the third point, we think also that this -- this -- there is -- there -- as far as we can tell, there's the same opportunities for public input as in the current version, the current procedure, and we think that having a very specific screen -- in other

words, right now we're saying we plan to go and look at the chemicals in the grouping to see if any of them may have epidemiologic data.

That just is a lot more transparent than to say, well, there's the 400 chemicals, next week we're having the lottery and we're going to pick randomly some chemicals. So we think in the end it will be transparent, and we think -- if we just add some additional language just to clarify.

For example, there reference was made to a larger discussion of the epidemiologic evidence that we would consider. Well, we'll put that paragraph back in. That was just an oversight. We left it out. We were thinking along the same lines we had previously. So we can just add that kind of information back in.

The last point was the inconsistent use of authoritative bodies, and our impression is that, again, we haven't changed any opinion of the authoritative bodies or how we would use the authoritative body information. We looked at -- and we thought we were using exactly verbatim the same language as before.

So what we will propose to do, we will meet with the representatives just to come up with language to make sure that it's clear what it is, that we're not really changing those aspects of the procedure that we

had in the previous procedure.

CHAIRPERSON BURK: Okay. Thank you.

Are there any further questions from the committee? I'm waiting for Joan. Oh, Sam -- oh, Steve, sorry.

DR. SAMUELS: Well, just --

CHAIRPERSON BURK: About the prioritization process.

Oh, another speaker? Okay. Another speaker will be Michael Schmitz of CLEEN, C-L-E-E-N.

MR. SCHMITZ: I'll make it very brief. Thank you for your -- giving me the opportunity to speak.

My name is Michael Schmitz. I'm the executive director of CLEEN. It's a statewide environmental and public health alliance.

We've submitted comments jointly with the Natural Resources Defense Council in support of the prioritization process proposed.

I just want to make two brief comments. First is that we think the proposal is a great improvement over the existing system. We think it's rational. We think it's based on the concept of looking for those chemicals which potentially cause the most -- the greatest concern to -- to California. We think that makes a lot of sense and, frankly, we strongly support

it for that.

The -- most of the particular issues we are actually pleased with the initial responses we're getting from the agency, and we look forward to continuing to work with the agency in this.

And we just wanted to emphasize in particular the issue of being able to pull -- petition to pull a high priority chemical like perchlorate if there is -- if the need arises out of the process even within this, and that something be -- a mechanism be put in place to do that.

With that, I won't take any more of your time except to say that we do think that this would be a significant step forward.

CHAIRPERSON BURK: George.

DR. ALEXEEFF: Along similar lines, we were not planning of changing that aspect of the guidance, so we can talk to Mr. Schmitz and make sure that, you know, we have -- or use the previous language or some -- some version so that it's clear that for a certain concern a chemical could be taken out of order.

MR. SCHMITZ: Thank you.

CHAIRPERSON BURK: Is there any further committee discussion on this? I see here it says discussion and decision. Are we expecting a vote or

can --

DR. DENTON: No, I think we would just like your advice, and -- that's what we need.

CHAIRPERSON BURK: Well, I know we had two members participate, and I just want to say, from my perspective, I think it's excellent. And any way that we can expedite and get the more serious chemicals up here ahead of -- you know, right at the beginning of the pack, we would appreciate.

Steve.

DR. SAMUELS: Can I change the topic?

CHAIRPERSON BURK: Absolutely.

DR. SAMUELS: Since -- since we made our decision this morning on chloroform, I recalculated the one-sided p-values for the two studies I considered strong, which were the Wennborg lab study and the Infante-Rivard study of SGA in Montreal, both of which I said had -- were biased against finding an effect, and both the one-sided p-values were about .04.

So I would ask any of my other fellow committee members if they would like to reconsider their vote. It's clear we have made a decision.

CHAIRPERSON BURK: I'd ask the same. Would anyone like to reconsider their votes?

DR. KEEN: I would prefer not reconsidering

mine. I -- again, part of my concern is, if we are going to re-analyze data, my sense is we should look -- we should be a little more uniform as to when we analyze it and make sure that we have in some cases original data sets.

Oftentimes, as we all know because we all publish a lot, what is ultimately in a paper, there's a lot of missing information, and difficulty sometimes with doing post hoc analysis is we don't even know the data which is missing that some other reviewer previously had them take out.

So I'm a little bit concerned of doing that in just highly-selective cases. I think, if we're going to do it, we should do it with some level of regularity.

CHAIRPERSON BURK: This is difficult because I know that, you know, after the vote a couple of us were talking to Steve again, you know, about his analysis and how strongly he felt about it and so forth.

The main thing that came to my mind is if we had had a split vote, then we might have wanted to defer the decision until we had a larger committee constituted to look at it.

Whether that would make any difference in the decision, I don't know. It would -- it would essentially just defer it and have more people look at

it, but I don't think the data would change, so your comment is well-taken.

The more I think about it, I'm -- I'm still comfortable with the way I voted so -- even though I respect what you've done with your calculations, I do think there's something there. It just wasn't strong enough for me. I don't know.

Linda, do you want to make a comment, too?

DR. ROBERTS: I was one of the ones who -- actually, I had asked -- is this on? Okay. I had asked Steve if he could do that, and it turns out he can do it pretty easily on his machine.

Carl's point is well-taken. I hadn't been thinking about that when I asked him to -- if he could look at a one-tailed and see if there was a difference there that -- that clarified the data some.

But having -- now that he has done it, and thinking at least ahead to the future where we have these epidemiology studies, which are not my forte, I guess I would like to see if that's something that could be brought up in advance of a meeting so that we have that information both for the OEHHA staff and the presentations and the commenters as well as the committee to take a look at when there are questions about the potential different methodologies that could

be used.

DR. SAMUELS: Well, I would suggest that -- I mean, if the committee were to defer this decision -- that OEHHA contact the authors, these are two recent papers, and ask for either unpublished -- you know, data that didn't -- you know, that either was cut out of the reviews or even, in fact, for a re-analysis based along the lines we've talked about because, as I say, I think it turns out both analyses were biased against finding an effect and, nonetheless, there appears to be one there.

And in the case of genetic polymorphism, it -- there couldn't be a more specific prediction which was borne out by the data that is in the single subgroup and which, in effect, might be found. The effect was, indeed, found, and in this case it was specific to the infant and not to the mother, and there's a question whether the --

So that, as a matter of, you know, public health, I would prefer to see not a -- you know, a -- I would prefer to see this data in more detail and a clarified analysis, for example, of what would have happened under analyses that she chose -- that they chose not to publish.

There is certainly precedent in the past for

the committee considering unpublished data, and clearly the OEHHA and we have re-analyzed data based on the published papers, which is all, in fact, what I did.

I think that it's quite true, however, that -- you know, that -- I didn't -- I don't want to make any assumptions about what a re-analysis would show, only I suggest that it would be called for, and the other committee members -- you can decide whether .04 really meets your criterion, you know, in a one-sided level for effect.

But in this case, it's -- it appears these were well-conducted studies with the flaws that have been -- all the flaws that have been pointed out, and that's why -- whereas, some of the other studies, including the animal studies, I don't think I would ask for data simply to try to stretch the evidence further than it goes.

I can accept any decision the committee makes clearly, but thought I would bring it up.

CHAIRPERSON BURK: Well, does anybody else have any thoughts on this?

DR. KEEN: Well, just a clarification for my mind. There's nothing to prevent, as I understand it, OEHHA to ask for that information, get it done and then re -- bring it back up to the committee.

That's -- that's -- that seems to me perhaps a safer one than for us to put everything into abeyance and just kind of wait to see what happens.

Because it's not like it's over at this point. New evidence can be brought forth that would change the evaluation, correct? Am I off in my understanding?

CHAIRPERSON BURK: Well, I know I -- I asked that earlier today to Joan Denton, but she said it's very unusual for a chemical to come up again after it's been voted on, so it seems like --

DR. KEEN: That's because, oftentimes, we have minimalistic information. If the -- if the information significantly advances, then I would -- I would find it highly appropriate if we would suddenly re-evaluate it.

And what we're talking about is two sets of breaking data that almost, by definition, is probably going to cry out for additional -- not just analysis, but other people will try to replicate it.

So I would assume, if the tide clearly is going in a different direction because of new issues, and certainly in the genomic area and looking at SIP sort of isoforms, I'd be very surprised if there's not fairly fast replication or -- of the basic study design. Whether the results are replicated is up in the air.

But I -- to me, that's seems a highly

appropriate way to do it. I'm just a little concerned that we -- that we put too many things in the corner saying that we will return to them.

With the data that we have in front of us, it seems like it was a fairly straightforward finding to me. But show me three, four new papers --

And this reminds me when we looked at environmental tobacco -- or sidestream tobacco smoke. The data were almost overwhelming that there was nothing there, and yet I recall with some -- not chagrin, but frustration that it was a few weeks after we met a relatively definitive paper came out that would have completely -- I think would have altered the thinking of many people. But that's --

DR. DENTON: I guess the committee has a couple of options.

You could leave your vote as stands and move on.

You could re -- you could leave your vote as stands on the developmental endpoint but request us to -- to review those studies and to contact the -- I mean, and revisit -- revisit the developmental endpoint, you know, at a future meeting after we've had more time to get into more of the details and statistics of those particular studies.

You could leave your decision as stands today and wait not only for that analyses but additional new studies, as Dr. Keen has mentioned.

And the fourth -- which, I don't know, it just seems to me -- I don't know that I would necessarily recommend that -- would be just to obviate your vote today and just wait for better times.

So I think it's -- just depends upon how strongly the committee feels about the importance of revisiting these epi studies, re-looking at the data or waiting for additional data, and we can go either way -- we will go either way.

DR. JONES: I think we should leave our vote as stands today and revisit this issue again in the not-too-distant future and at the same time revisit the issue of environmental tobacco smoke, both of them, which we have not done and which is clearly something that we should be doing, and at the same time revisit this issue based on what Steve has come up with. But I think we should leave our vote as stands today.

CHAIRPERSON BURK: Go ahead, Linda.

DR. ROBERTS: I was just going to say I'd agree with that approach and second the thought about the sidestream tobacco smoke.

DR. KEEN: I would -- I would echo that. In

fact, I specifically brought up the tobacco smoke issue because I've been a wee bit surprised that we haven't been asked to re-visit it given the fact the terrain seems to have changed considerably since we did ours.

And if it turns out that there are structural problems, then suddenly -- now, I'm going to do one of these numbers. I start falling in Steve's camp because for structural reasons it's another, you know, decade before we could revisit it, even if the data comes in.

My opinion and position changes rather abruptly. My assumption is there is no real structural reason. It just hasn't happened yet for the tobacco smoke.

CHAIRPERSON BURK: George.

DR. ALEXEEFF: Couple of comments. We'd be happy to try to obtain any additional information from the authors to see if there is this information and to re-analyze those two studies and provide it at the next meeting.

Second of all, we'd be happy to bring environmental tobacco smoke as well. You may not be aware, but we are in the -- we have just -- we are just completing a study on sidestream smoke, and it's actually undergoing review by a different committee, not the CIC, but our Scientific Review Panel for Toxic Air

Contaminants, and that meeting is actually occurring at the end of this month. So we will have our -- we will get comments from them. We expect two meetings to do that.

So I think we'll have -- probably have that information, and we could provide you with the report. It summarizes all the studies by the same staff that are here, and you can just focus on the reproductive side.

We have a lot of things about asthma and other things that don't pertain to this committee, but -- all right.

CHAIRPERSON BURK: Excellent. Is that satisfactory with you, Steve?

DR. SAMUELS: Of course.

CHAIRPERSON BURK: Okay. So I'm hearing exactly what you just said, which is you would like to get more information about these epidemiological studies. We'd also like to read the -- and discuss the environmental tobacco smoke at a future meeting, preferably sooner than later.

MS. MONAHAN: Are you -- you saying that you're going to leave your vote as it stood, right?

CHAIRPERSON BURK: That's what I'm hearing.

Okay. Next agenda item, IV, updates, who's going to handle that? Oh, Cynthia is coming forward.

MS. OSHITA: Good afternoon. I'll just change speeds here a little bit.

I've been asked to report to you on the status of the chemical listings by the administrative list mechanisms under Proposition 65.

And since the last DART committee meeting in October of last year, OEHHA has administratively added two chemicals, di-ethylhexylphthalate, DEHP, and 1,3-butadiene to the Proposition 65 list as known to cause reproductive toxicity. We've also listed nine chemicals for -- as known to cause cancer.

The complete current list is included in your meeting materials behind the "Staff Updates" tab of your binders.

Additionally, three public notices were published in the California Regulatory Notice Register and posted on the OEHHA website announcing, in the first case, the proposed reproductive toxicity listing of five chemicals, which include four phthalates, butyl benzyl phthalate, di-n-butyl phthalate, di-n-hexyl phthalate and di-isodecyl phthalate, and also 1-bromopropane.

In the second case, it is the proposed cancer listing of one chemical, 2,4-hexadienal, and in the third case is the proposed cancer listing of riddelliine, spelled r-i-d-d-e-l-l-i-i-n-e, which is a

plant derivative used in herbal remedies and would -- should not be confused with Ritalin, which is spelled R-i-t-a-l-i-n, a pediatric drug used to treat attention deficit disorder.

Comments were received on the four phthalates and also on 2,4-hexadienal, and those are currently under review. The comment period remains open for riddelliine until November 22nd.

And for 1-bromopropane we received no comment during the data call-in phase; therefore, it moved forward to the notice of intent to list phase and that comment period will close next week on November 8th.

Another area in which OEHHA has been busy is in developing the safe harbor levels for chemicals that are already listed on the Prop 65 list, and these levels are adopted in regulation and assist interested parties in determining whether warnings are required for the exposures to those listed chemicals and whether discharges of those chemicals to sources of drinking water are prohibited.

Since the last DART meeting, OEHHA has adopted 11 safe harbor levels, all of which have been no significant risk levels, and a copy of the June 2004 Proposition 65 status report on safe harbor levels is also included in your meeting materials with the newly

adopted levels noted in boldface for you.

Thank you.

CHAIRPERSON BURK: Thank you.

And then are we going to hear about the status of perchlorate? George Alexeeff.

DR. ALEXEEFF: George Alexeeff. Well, actually, first of all, Ms. Oshita made me remember something.

Two years ago in December there were several petitions that were discussed at the meeting, and two of them were 1-bromopropane and 2-bromopropane. And as you -- I will -- as you heard from Cynthia Oshita, 1-bromopropane has been listed.

So at that time the committee -- the DART Committee had suggested that we wait until the CERHR group and NTP complete their evaluation because, I guess, it was -- we were all aware that it was happening, and we waited for that, and we were able to list it administratively.

We're still evaluating the information for 2-bromopropane, but we're likely to make a decision in the near future on that one.

The third chemical which was discussed at that meeting was perchlorate, and at that time the -- the committee indicated that based upon the resources --

well, first of all, we indicated to you that we were in the process of developing a public health goal under our drinking water program and that we needed to complete that process first until we began and initiated a DART process on the chemical.

And the committee suggested, that after we completed that process, we should go ahead and proceed and look at it as under a DART circumstance.

So in March of 2004, so March earlier this year, we did complete that public health goal, and following the completion of that, we -- we had a -- our data call-in procedure, which then ended, and we've received information on the data call-in.

And at -- another factor that has kind of occurred in this past year, US EPA has been in the process of completing their perchlorate document as well, and that document went to the National Academy of Sciences for review.

And they -- they were able to review in their document, the US EPA document, a number of studies that were specifically sponsored by the defense industry that US EPA reviewed. So these are basically, you know, high-quality studies but are not published in the peer review literature.

So we are awaiting NAS' review of the US EPA

report which, to our understanding, will come out either this month or next month. So once we receive that information, we can add it to looking at all the other information, then proceed on perchlorate and bring it to you as soon as we can.

So that's the story.

CHAIRPERSON BURK: Well, thank you, I think. No, I -- that was very clear. Thank you very much.

So we've come to the last agenda item, summary of committee actions and closing remarks.

Dr. Denton.

DR. DENTON: This morning the committee declined to list chloroform as a developmental and reproductive toxicant under the three endpoints: developmental, male reproductive and female reproductive.

However, the committee has requested that we do additional analysis on the epidemiology data and bring those analyses back to the committee at the next meeting for consideration of -- or for re-looking at the developmental endpoint.

For progesterone, the committee did not list progesterone for the developmental endpoint. But for the male and female reproductive endpoints, the decision has been deferred pending a provisional language which

OEHHA will -- will propose to the committee, which could be potentially part of that listing. So the -- the decision to list based on male and female for progesterone endpoints has been deferred.

In the prioritization process, the committee basically endorsed and agreed with the draft prioritization proposal as -- as presented, with the idea that we need to keep an eye on animal studies and that we use selected key words as we go through these screens.

Dr. Keen suggested that we publish these excellent reports, which have been prepared by OEHHA staff, which can greatly aid in the discussion of these items.

And, finally, the committee has requested that OEHHA staff bring back for committee consideration of listing environmental tobacco smoke.

So, closing -- and then I'll turn it over to you, Dr. Burk -- I'd like to thank the committee for -- for their excellent work today.

I would like to thank my excellent staff, Jim and Mari and Farla and Lauren and Poorni and Li and George and Marlissa, and all the people who participate, Cindy, Susan, in preparing for these meetings and for your work.

And I'd also like to thank the people who attended today for their participation.

So with that, I will turn it back to you for -- I guess for closing the meeting.

CHAIRPERSON BURK: All right. I was going to thank the same people, so ditto for me, the committee, staff, anyone that attended; and with that, the meeting is adjourned.

(Proceedings concluded.)

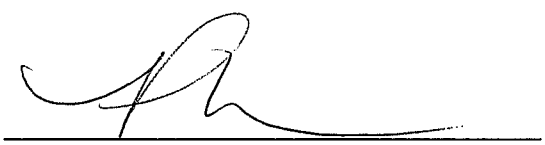
REPORTER'S CERTIFICATE

---o0o---

STATE OF CALIFORNIA)
) ss.
COUNTY OF SACRAMENTO)

I, PHYLLIS MANK, certify that I was the Official Court Reporter and that I reported in shorthand writing the foregoing proceedings to the best of my ability; that I thereafter caused my shorthand writing to be reduced to typewriting, and the pages numbered 103 through 161, inclusive, constitute a complete, true and correct record.

In witness whereof, I have subscribed this certificate at Sacramento, California, on this 25th day of November, 2004.



PHYLLIS MANK, CSR No. 5093

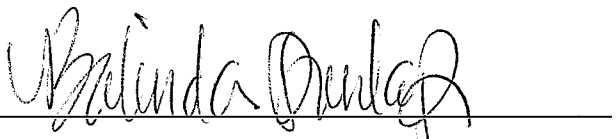
REPORTER'S CERTIFICATE

---o0o---

STATE OF CALIFORNIA)
) ss.
COUNTY OF SACRAMENTO)

I, BALINDA DUNLAP, certify that I was the official reporter and that I reported in shorthand writing the foregoing proceedings; that I thereafter caused my shorthand writing to be reduced to typewriting, and the pages included, constitute a full, true, and correct record of said proceedings:

IN WITNESS WHEREOF, I have subscribed this certificate at Sacramento, California, on this 12th day of December, 2004.



BALINDA DUNLAP, CSR NO. 10710, RPR, CRR, RMR