CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986

(PROPOSITION 65)

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MEETING OF THE SCIENCE ADVISORY BOARD'S

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT (DART)

IDENTIFICATION COMMITTEE

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MONDAY, DECEMBER 17, 2001

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California Environmental Protection Agency
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Sacramento, California

Reported By: PHYLLIS MANK, CSR No. 5093

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SACRAMENTO, CALIFORNIA

MONDAY, DECEMBER 17, 2001

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DR. DENTON: Good morning. My name is Joan Denton, and I'm the Director of the Office of Environmental Health Hazard Assessment.

All of the committee who is going to be in attendance today have arrived, so I would like to introduce them.

To my right is Dr. Hillary Klonoff-Cohen, and Dr. Marion Miller, Dr. Steve Samuels, Dr. Dottie Burk, Dr. Carl Keen, Dr. Linda Roberts and Dr. Kenneth Jones. Dr. Pat Shiono is not going to be with us this morning.

I'd like to welcome everyone to this meeting. If it's December, it must be a meeting of the DART committee, right?

This is the first time we've had the opportunity to have our meeting in the building, and we've been in the building for a little over a year, but we'd like welcome you all to the new Cal EPA building.

I assume that everyone has a copy of the agenda, and you will notice that the first item on the agenda is the committee election of an acting chair.

As you all know, Dr. Hendrickx resigned this last year, and so with his departure, then the Governor

will be appointing a permanent chair, but for the purposes of this meeting, we need an acting chair and that's the activity that the committee will take up first.

So with that, what I'd like to do then is perhaps open it to committee discussion of how you would like to -- would you like to discuss the designation of an acting chair? Would you like to go ahead and nominate someone? That we need to do first.

DR. KEEN: I would like to suggest that Dr. Burk be the acting chair of this meeting.

DR. JONES: I'd like to second that.

DR. DENTON: Well, would you like to discuss that or would your like to go ahead and vote?

DR. SAMUELS: Dr. Burk would you accept the nomination?

DR. BURK: Well, I've done it before. I think I can do it this one more time.

DR. DENTON: Maybe I should say, are there any objections to Dr. Burk being the acting chair?

Hearing none, Dr. Burk you are the official acting chair.

Now, before I turn over the microphone, the second item is -- under the election of the acting chair is to affirm the agenda, and this is really an activity

that the committee chair is responsible for so we won't need a formal vote.

But there is one individual, Artie Lawyer, would like to express -- has an opinion about the agenda. So if we could entertain what he has to say and if the committee can consider it, then you can affirm the agenda and then move on.

CHAIRWOMAN BURK: Is that acceptable to the committee? All right. Please come forward.

DR. LAWYER: I will try to keep it to two minutes. It's a very simple point on the agenda. It's been a point I've wanted to bring up in several of the previous committee meetings.

Under the various items where a chemical is considered for listing under the various committees, there are four sub-bullets. There is usually presentation by OEHHA and then a separate discussion by the committee followed by any public comments, including those of people that come prepared from around the country to talk about it, and then another committee discussion.

Just over the years I've seen several of the discussions after the OEHHA one being of substance before they get to the additional points of science that sometimes come up with all the chemicals.

I'm presuming that, as in the past, the committee is going to ask questions during the presentation of OEHHA staff and, of course, any of the members of the public, but it would just seem a little more appropriate scientifically if we could have the public comments immediately following staff presentation, just make sure that comments are welcome at any time, and then get into the discussion about the consideration by the committee for listing.

CHAIRWOMAN BURK: Does anyone on the committee have an opinion on this? I personally would want to preserve the ability to follow-up with questions right after the staff presentation because sometimes we have burning questions.

I don't think we would want to get into the meat of the discussion before we heard the public comments, if that's your concern.

DR. LAWYER: That's been -- that has sometimes happened in the past, and that's what I was trying to make sure we avoid.

CHAIRWOMAN BURK: Any other comments about that? We'll try to work that way this time.

Do you have any further introductory comments, Joan?

DR. DENTON: No, I think it's just a matter of

affirming the agenda and then moving forward.

CHAIRWOMAN BURK: Let me ask one more time if there is anybody on the committee that would like to change the agenda order for any reason?

Not hearing anything, I think we will follow it as stated.

So the first order of business is consideration of a chemical as known to the State to cause reproductive toxicity, and the first one is metribuzin. We will have the staff presentation by Dr. Jim Morgan of OEHHA.

DR. DONALD: Actually, if I could very briefly introduce that, I'm Jim Donald, also of OEHHA.

Metribuzin is coming before the committee because it was a candidate for listing through an administrative mechanism but dropped out of that mechanism after notice of intent to list had been published and, as required by regulation, it has therefore been referred to this committee.

So irrespective of the mechanism how it was referred to this committee, it is up for consideration as any other chemical would be that comes before you.

Now, Dr. Jim Morgan of the Reproductive Toxicology Unit is very briefly going to present an overview of the information that was presented to the

committee.

DR. MORGAN: Good morning. My first slide has already been introduced for me by Jim Donald here, so I'll move along to the second slide.

Metribuzin is an asymmetrical triazine herbicide which is used on numerous food crops, flowers and in landscaping. It is slightly soluble in water and somewhat soluble in organic solvents.

It is fairly rapidly absorbed by the oral route, although the extent of that absorption has not been quantified. It produces numerous metabolites and distributes to all organs which have been examined.

It has especially high concentrations in the thyroid, liver and kidney and relatively low concentrations in the testes and ovaries. No data was found regarding distribution to the placenta or fetus. Metribuzin and its metabolites are excreted also fairly rapidly in urine and feces.

As far as non-DART toxicities are concerned, the acute oral LD 50 has varied by a factor of almost 10 between different species which have been tested.

Typical subchronic and chronic toxicities include reduced body weight and body weight gain and increased liver weight.

There are also complex effects on thyroid

function and circulating thyroid hormone levels and transient neurobehavioral effects.

Turning now to studies with data relevant to developmental toxicity, we were unable to find any human data. However, there are several industry-sponsored studies, mostly for pesticide registration purposes, some dating from the early 1970s.

There are two developmental studies in rats and two developmental studies in rabbits which are supplemented by two rat reproductive studies.

In the earlier rat developmental study which was conducted in FB 30 rats, there were no indications of developmental toxicity, and there was a slight reduction in maternal weight gain which was not statistically significant and occurred at the high dose.

In the later rat developmental study which was performed in Sprague-Dawley rats, reduced fetal weight was observed in the low, middle and high doses and these effects were statistically significant and dose related.

There was also delayed fetal ossification and increased wavy, curved or bulbous ribs which occurred at the high dose only. There was reduced maternal food consumption, lower body weight than controls and reduced weight gain at the low, middle and high doses.

In the earlier rabbit developmental study which was performed on New Zealand white rabbits, there were increased abortions and early resorptions, reduced fetal weight and increased incompletely ossified sternebrae, none of which were statistically significant at the high dose.

There was also slightly reduced fetal weight at the middle dose which was not statistically significant. There was actual maternal weight loss during treatment at the high dose which was statistically significant in comparison to controls.

In the later rabbit developmental study, which was performed in American Dutch rabbits, reduced fetal weight and delayed ossification was observed at the middle dose but not at the high dose, and there was reduced maternal weight gain at the high dose.

In the earlier rat reproductive study which was performed in FB 30 rats, the birth weights were generally lower than controls at all three concentrations in the F2 and F3 generations, but none of these effects were statistically significant, and there were no indications of parental toxicity.

In the later rat reproductive study performed in Sprague-Dawley rats, there were reduced implantations and litter size in the F1 and F2 litter at the middle

and high concentrations, and there was reduced maternal weight at the high concentration in the F0 group and middle and high concentrations in the F1 group.

Turning now to studies with data relevance to female reproductive toxicity, there were no human data found. We have the two rat reproductive studies, a mouse female dominant lethal study, and several subchronic and chronic studies in mouse, rat, rabbit and dog.

It should be noted these studies were not focused on female reproductive effects but were rather standard design studies which examined ovary weight and pathology among other endpoints.

I've already described the effects in the rat reproductive studies, and I won't repeat that data here. There is no additional effects relevant to female reproductive toxicity.

In the female mouse dominant lethal study, there were no dominant lethal or other adverse reproductive effects observed and mild maternal drowsiness was observed.

In the subchronic and chronic studies, most studies found no effects on ovarian weight or gross or histopathology.

There were two studies in rats which found

increased relative but not absolute ovary weight in the presence of reduced body weight.

There was a chronic study in dogs which found reduced absolute and relative ovary weight at severely systemically toxic concentrations.

Turning to studies with data relevance to male reproductive toxicity, again, no human data were found.

There were the two rat reproductive studies, there were two male mouse dominant lethal studies and several subchronic and chronic studies in mice, rats, rabbits or dogs.

Again, these studies were not focused on male reproductive effects but were standard design studies which examined testes weight and pathology among other endpoints.

I've already described the effects in the two rat reproductive studies. No other additional male reproductive type effects were observed.

In the male mouse dominant lethal studies, there were no consistent dominant lethal type effects or other adverse reproductive effects observed. Mild maternal drowsiness was observed.

In the subchronic and chronic studies, most studies found no effects on testicular weight or gross or histopathology.

Two studies in rats found increased relative but not absolute testes weight in the presence of reduced body weight, and the chronic study in dogs found reduced absolute but not relative testes weight in, quote, immature, end quote, testes at severely systemically toxic concentrations.

To briefly summarize the possible indications of developmental toxicity, in the Sprague-Dawley rat developmental study, there was reduced fetal weight, delayed ossifications and rib anomalies at the high dose and reduced maternal food consumption, lower body weight and reduced weight gain at all doses.

In the Sprague-Dawley rat reproductive study, there were reduced implantations and litter size in the F1/F2 generations at the middle and high concentrations, and there was reduced maternal weight in the F0 generation at the high concentration and the F1 generation at the middle and high concentrations.

In the New Zealand White rabbit developmental study, there were increased abortions, absorptions, incompletely ossified sternebrae and reduced fetal weight at the high dose and there was maternal weight loss at the high dose.

To briefly summarize the possible indications of female reproductive toxicity, in Sprague-Dawley rat

reproductive study, there were reduced implantations in litter size in the F1/F2 generations at the middle and high concentrations, but no other indications of female reproductive toxicity.

There was reduced maternal weight in the F0 generation at the high concentration and F1 at the middle and high concentrations.

There were also two rat subchronic studies which found increased relative but not absolute ovary weight in the presence of reduced body weight, and the dog chronic study with reduced absolute and relative ovary weight in the presence of severe systemic toxicity.

To briefly summarize the possible indications of male reproductive toxicity, in the Sprague-Dawley rat reproductive study, there were reduced implantations and litter size in the F1/F2 generations at the middle and high concentrations, but no other indications of male reproductive toxicity.

It should be pointed out that both males and female were exposed and reduced maternal weight in the F0 at high concentrations and F1 at middle and high concentrations were observed.

In the two rat subchronic studies, there was increased relative but not absolute testes weight in the presence of reduced body weight, and in the dog chronic

study there was reduced absolute testes weight and, quote, immature, unquote, testes in the presence of severe systemic toxicity.

That concludes this presentation. I will be glad to respond to questions at this time.

CHAIRWOMAN BURK: Thank you very much, Jim, for your excellent report. We really appreciate getting these very detailed reports to study.

Does anyone on the committee have a question for Jim at this time?

I guess we will go to the public comments. Do we have any? Thank you.

We have Ghona Sangha from the Bayer Corporation who would like to speak.

DR. SANGHA: Thank you very much for giving me this opportunity to make some comments. I'm Ghona Sangha from Bayer Corporation. The next slide, please.

I think Dr. Donald has already mentioned -- already has gone through it. I just want to point out one thing, the last one, that in 2000 OEHHA mentioned this is no longer under consideration for listing as a mechanism or technicality, therefore, to the DART committee.

What I would like to do is go over the points I think we conclude out of this last presentation that

there are four major concerns, and I would just focus on that. If I can have the next slide, please.

The first issue that was brought up or that is of concern is reduced implantation and litter sizes in the two generation reproduction study, and this was reduced implantations and litter size at the middle and high concentrations in the second generation. Next slide, please.

If you look at this table -- I think people have some handouts given to you, also -- issue one, the table shows that reduced implantation size seen in F0 and F1 generation, the only statistical significance was seen at the middle dose and not at the lower or the high dose.

Now, when one looks at this table, it shows that this is not really a dose response. It's not there. If you look at the numbers, 13 and 13.54 in the mid and high dose, they're very similar to the controls seen in the F0 generation, which sort of brings the point that F1 controlled numbers of implantation size are much higher than you normally see, but they are still within the historical control. So this effect is -- basically shows up as an anomaly because of very high numbers in the control group.

Also, one sees that these numbers are really

within the historical control, so it's not considered that it's really a compound-related effect, but due to high controls -- the number in the high controls. If I can have the next slide, please.

This one, basically what I mentioned, is mentioning that in the text and from the records.

Now, the next slide shows the effect on the litter size. The effect on the litter size is really related to the implantation size. We have reduced implantation size, so it's going to reflect the same way in the litter size.

So looking at the table here, one sees that in the middle dose, again, the same F1 generation, the middle dose, shows up as statistical significance, which is again related to its high dose response.

It's again showing up as the control being higher than the control in the F0 generation, and the numbers in the mid and high dose and the reduced litter sizes are really due to that the control is high, but they're very similar to the control in the first generation.

If you look at all the numbers from every other group, they're pretty much in the same range. So it's basically the control being very high in the F1 generation, both the implantation size and litter size

is reflected.

This, also, if it was really a compound effect, it would show in the reduced implantations in the litter size with the post-implantation losses. These were only the pre-implantation numbers that are being shown here.

If you go to the next table, which shows the post-implantation loss, it shows that they were not different at all in both F0/F1 generation than any of the concentrations, including control, which again reflects that these effects are due to just by chance lower implantation size more than compound effect, which would have shown in the post-implantation losses, also, if it was a developmental toxicant.

So we conclude on this basis that these effects are not really compound related and it is not a developmental toxicant, and EPA and the California toxicology group has mentioned that it's not a developmental toxicant, and we believe that it should not be consider as one.

Now, going to the next issue which was brought out, the reduced ovary weight in the dog, it was mentioned in the chronic feeding dog study there was reduced body weight at severely maternally toxic concentrations and in other studies no effects were seen.

We believe this is not a toxicologically adverse effect and not significant based on the weight of only one dog as the other three dogs died at that concentration, the concentration was so high, and this just happened to be at the high dose, one dog showing that, and it would just be a normal variation, and one cannot conclude that this would be a compound effect, and we believe that this effect is not really compound related.

Now, going to the next slide, the issue three which concerned reduced fetal weights and delayed ossification and rib anomalies in the rat teratology studies, you can say that the reduced fetal weight was seen at all dosages, which was 6, 6 and 16 percent. The lower two dosages were not statistically significant.

There was no reduction in the birth weight in any of the reproduction toxicity studies at any of these dose levels, which would have indicated that it's some kind of a compound effect.

If you go to the next slide, the other point was that there was a reduced fetal weight, delayed ossifications, and we see that these bulbous ribs at high dose, we don't consider that toxicologically adverse because they are associated with extreme

maternal toxicity, and these are also -- one can say that one can do variation on the large malformations, which a lot of times these variations exist at extremely maternally toxic dosages. And the statistic increase is only at high dose and seen when it's based on the number of pups.

However, all these studies are looked at as a litter as the unit for statistical analysis, and when one looks at the litter to be an experimental unit, there's no effect seen in dog. So it's, again, showing a variability within a large number of animals that are involved in these studies. Next slide.

Another point in this study was the delayed skeletal ossifications, and these are also not considered toxicologically adverse or significant because they are, again, associated with extreme maternal toxicity.

And the results also show that there were reduced pup weights, and it has been known in the literature that reduction in fetal weights leads to the delayed skeletal ossification in these developmental studies which, if one carries these investigations to a later time point, they show not to be effective and development is normal.

Going to the next slide, the issue of the rabbit

teratology, as was mentioned, that showed increased resorptions, reduced fetal weight and increased incomplete ossified sternebrae were observed at the high dose, and even though they were not statistically significant, there was a maternal weight loss during this treatment and abortions were also seen at this high dose. Next slide.

In response, I would like to say these are not toxicologically significant because these effects were seen at the extremely high dose of 135 milligram per kilogram.

Then we repeated that study because it was extremely high dose to bracket the dosages to go lower to establish clear no effect levels.

So in that study when the high dose was reduced from 135 to 85 milligrams per kilogram, even though it was still a maternally toxic dose, we saw a 58 percent decrease in the body weight during gestation period, no compound related embryotoxicity or teratogenicity effects were seen.

So on that basis, we can concluded that these effects were seen at extremely high dosages, and they were not the effect of the compound. They were due to maternal toxicity.

And as I mentioned, these effects are not

declared to be effects by the EPA or by the Cal EPA and not listed as a developmental or reproductive toxicant, and we propose that it should not be listed.

Thank you very much.

CHAIRWOMAN BURK: Thank you.

Are there any other public comments?

Then we will begin our discussion. As I understand this, we're looking at this as any other candidate that we're determining whether it should be listed or not, which means we should look at developmental male and female reproductive toxicity.

So, if anyone wants to start with any of those, jump in. Otherwise, I'll pick one.

Let me ask it a different way: Are there any of those endpoints that we can eliminate from discussion?

Marion.

DR. MILLER: Can we go backwards and start with male?

CHAIRWOMAN BURK: I would be thrilled. Let's start with the male.

DR. MILLER: I think there's really very little evidence to support the idea that this compound would act as a male reproductive toxicant. The lack of any pathological findings, other than the one dog, would suggest that there really is no strong evidence that

this is a male reproductive toxicant.

CHAIRWOMAN BURK: Thank you.

Does anyone else have any comments on male reproductive toxicity?

How about female reproductive toxicity?

DR. MILLER: To continue --

CHAIRWOMAN BURK: Please do.

DR. MILLER: I think the studies are similar between the male and female. Again, there looks like little evidence to support this being a female reproductive toxicant, again, based on the lack of pathology and any significant change in the ovary and pathology. And, again, that one dog study seems to be a little unusual because of the high dose levels and the mortality associated with it.

CHAIRWOMAN BURK: Any other comment on female reproductive toxicity?

All right. So that takes us to the developmental toxicity, which I think has more to discuss. We have at least three studies that we should consider closely.

Does anyone want to comment? I'm kind of looking at Steve to start with. I don't like to pick on people. I just want to make sure we cover all the bases. Any statistical issues that you see as

significant? Particularly, I'm addressing perhaps the Miles '86 Sprague-Dawley rat study that's Tables 3 and 4.

DR. SAMUELS: First of all, it's obvious in Table 3 that it appears that there was an effect on maternal weight gain which was dose related throughout the table even if the individual finding of statistical significance was only at the highest dose. So I think that was an active consideration to behold through most of the table.

It appears -- unless you can tell me why the thyroid is a reproductive organ -- it appears to be systemic rather than a particularly -- in that table a reproductive organ finding.

In Table 4, there was also -- again, without concern about statistical significance, I certainly did see dose response findings in fetal weight, high number of fetuses per litter, placental weight.

And I think I agree with the speaker, though I wasn't sure -- I lost the reference at some point during her presentation -- that the analysis with the number of fetuses doesn't mean that ribs wavy or curved was the wrong unit for analysis.

So it appears to me, and I'll leave it to my laboratory colleagues, that these findings look like

what are certainly strong dose responses, they certainly are present -- in the presence of the same dose response on the maternal body size.

So I don't see anything -- they are strong dose responses, but they may not be relevant to actual developmental toxicity, as far as I'm concerned.

DR. JONES: So, Steve, what you're suggesting is it's all maternal toxicity?

DR. SAMUELS: We'll see in the second presentation where there was a more detail of how much one could attribute to maternal toxicity, and I haven't done the calculations, but here it seems that there was certain maternal toxicity throughout the study at the lower doses.

So, yeah, it's very questionable to me whether we could -- I can't make a finding that this is independent maternal toxicity.

CHAIRWOMAN BURK: I agree with you that, in fact, we have developmental toxicity, but only in the presence of maternal toxicity.

Does anyone have any thoughts about the thyroid issue? Any further insight of what the mechanism might be?

But I agree that that seems like a plausible mechanism, but it's not necessarily an inherently

reproductive problem.

Any other comments?

DR. SAMUELS: I would just like to ask, if there are speakers after the presentations, would you please when you show us tables, refer to the tables that we have because those are the ones in which we've made our notes and it difficult to switch from study to study when there are many studies.

CHAIRWOMAN BURK: I appreciate that. I tried to prepare in that way, so I wrote down each study and what table it was on so I could cross-reference. That's how I knew we were talking about Tables 3 and 4, 6 and 11 and 12.

So if we want to make one quick perusal, Table 6 was the New Zealand white rabbit study with what was considered to be -- actually, that goes with Table 5 as well -- fairly -- let me make sure I have this correct.

DR. SAMUELS: Fairly consistent maternal weight gain effects.

DR. JONES: And nothing statistically significant.

DR. SAMUELS: There's nothing statistically significant reported in Table 6.

CHAIRWOMAN BURK: Right, and even though we did have some maternal toxicity at the high dose.

Linda, maybe you could just comment, nothing to do with this in specific, but I'm curious about the statement that it's a known fact that the wavy ribs and so forth are considered just variations.

DR. ROBERTS: I don't automatically discount substantial maternal toxicity in the rabbit study in Tables 5 and 6. What I wanted to point out is --

DR. DENTON: I'm sorry, Linda, they can't hear you.

DR. ROBERTS: In Table 5, if you look under weight gain gestation day 6 to 18, which covers the dosing period, the animals at the top dose actually lost 300 grams. That's a substantial amount of weight loss, and that would normally be quite a bit higher than you would want to have in a study because it can impact the interpretation.

In the rat study, in the absence of other findings -- other skeletal findings, I am less inclined to see wavy ribs as a clear indication of developmental toxicity on its own.

Does that make sense to everyone?

CHAIRWOMAN BURK: Yes, it makes sense to me.

DR. MILLER: I seem to remember in a previous DART committee meeting, when Andy Hendrickx was asked exactly this question, he also indicated that these were

variations and could be associated with the malaise in the mother.

DR. ROBERTS: One other thing about the rat study, again, if you look at the period of dosing and the weight gain that the animals had, the control group gained about 49 grams, which is fairly typical. And the 25 and 7 milligram per kilogram group gained about 30 each. So the high dose gained approximately 40 percent of the weight gain that the control group was having.

CHAIRWOMAN BURK: Are there any other comments on developmental toxicity?

Are we ready to vote? Okay. I have an official, I guess, voting statement here that I will read through for each of the possible endpoints.

So please indicate by a show of hands if, in your opinion, metribuzin has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity.

I see no hands. Okay. Then the record should reflect zero votes to add metribuzin to the Proposition 65 list as causing developmental toxicity.

Okay. Second, please indicate by a show of hands if, in your opinion, metribuzin has been clearly shown through scientifically valid testing according to generally accepted principles to cause female

reproductive toxicity.

Again, I see no hands. So the record should reflect zero votes were cast to add metribuzin to the Proposition 65 list as causing female reproductive toxicity.

And, finally, please indicate by a show of hands if, in your opinion, metribuzin has been clearly shown through scientifically valid testing according to generally accepted principles to cause male reproductive toxicity.

Again, the record should reflect zero votes were cast to add metribuzin to the Proposition 65 list as causing male reproductive toxicity.

I didn't mention this, but a majority of five of the eight appointed members is required to add a chemical to the list. So, therefore, accordingly, metribuzin is not added to the Proposition 65 list.

All right. Are we ready to move on to the next agenda item? Agenda item IV, consideration of chemicals listed via the authoritative bodies mechanism for possible removal from the list.

The first one is cyclohexanol.

DR. DONALD: After you actually affirmed the order of the agenda, we'd like to ask if we can change it.

Dr. Campbell, who is going to make the presentation, apparently has been delayed. So with your permission, we'd like to change the order and have the presentation of 2,4-DP first.

Prior to that, our Chief Counsel, Colleen Heck, is going to make a few comments.

CHAIRWOMAN BURK: Okay. Colleen.

MS. HECK: This is the first time this committee will be reconsidering -- or considering chemicals for possible removal from the list of Proposition 65 chemicals known to the State to cause reproductive toxicity.

I should briefly note that your counterpart committee, the CIC, has done so on one occasion, considering five chemicals for possible removal from the list, and, in fact, voting in a manner that did remove four of those five.

But I wanted to briefly put your decision in procedural context in case there's any confusion about whether you're voting to put it on, keep it on, take it off, et cetera. So let's see if we can try to prevent any confusion before we actually get to any discussion and voting.

I think the best way to look at this decision you'll be making and the way your votes are cast and

counted is as follows.

The sole reasons cyclohexanol and 2,4-DP are on the Proposition 65 list is because they were formally identified by an authoritative body as causing reproductive toxicity.

Those same authoritative bodies no longer formally identify the chemicals as causing reproductive toxicity. Therefore, unless this committee independently concludes that the chemical should remain on the list, it will, in fact, be removed from the list.

So under the regulation, the chemical is required to be referred to this committee. I think it's a policy statement that the regulation drafters made that before we take something on and then perhaps have this committee separately decided, well, we would have kept it on, to keep the list from being on again, off again, you have the pass over on a chemical before any action is being taken.

Jim has reminded me that, in fact, there are two provisions under the regulation that call for a chemicals removal. There's the authoritative body no longer considers, and there is a related provision in the same subdivision that says there is no substantial evidence that the chemical actually causes.

We're into another procedural subnuance where a court of appeals decision limited the evidence that we could take into account in determining whether or not there was, in fact, substantial evidence. Limiting ourselves to what the court told us we can look at, we have now concluded that there is no substantial evidence. So I'm sorry for the confusion.

The bottom line kind of rule that applies is the same unless this committee would vote to keep the chemical on based on the evidence that you'll hear, a kind of de novo presentation, it will, in fact, come off.

So you will be voting just as you do on independent initial listings whether or not the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity.

Just as with your last vote, and Dr. Burk's observation, unless there are five votes for that proposition, the chemicals will come off the list.

Thank you. Thank you for that clarification, Jim.

DR. DONALD: Dr. Mari Golub is going to make the presentation on 2,4-DP.

Just another minor introductory note. As

Colleen has already pointed out, there is a current listing for 2,4-DP, that's for dichloroprop, the racemic mixture of 2,4-DP, which has a CAS number of 50-29-3.

The committee today will vote on whether or not that listing will continue. The current listing is based entirely on developmental toxicity, but the committee has the option to continue the listing on the basis of any form of reproductive toxicity or any combination of forms.

As another point of clarification, in the hazard identification document that was provided to the committee, there are data on the (+) enantiomer of 2,4-DP, and those data are in there because we consider them relevant as a potential of the racemic mixture to cause developmental and reproductive toxicity.

But just to clarify for everyone's benefit, the committee will not vote today on whether or not to list the (+) enantiomer, but it is an option for the committee to request that information on the (+) enantiomer be brought back to them for consideration at a future meeting after appropriate notice and comment periods on the (+) enantiomer have taken place.

Mari.

DR. GOLUB: Thank you.

My name is Mari Golub, and I'm with OEHHA. I'm

going to be presenting an overview of the HID on 2,4-DP.

2,4-DP, or 2,4-dichlorophenoxypropionic acid, is a member of the widely-used chlorophenoxy acid herbicide family which includes the acetic acid, the butyric acid, the propionic acids, their salts and esters and structural derivatives.

The chlorophenoxy acid herbicides are structural analogs of the plant hormone auxin. This is thought to be the basis of their herbicidal action. They are broad-leafed herbicides. They're not effective against grasses. So they're most widely used for lawns and landscaping. There is little agricultural use. Several 2,4-DP salts and esters are registered for use in California.

2,4-DP is a stable molecule that shows minimal soil absorption and bacterial breakdown in soil. It has a long half-life in ground water.

Some information on pharmacokinetics. The chlorophenoxy acid herbicides show a high gastrointestinal absorption, high protein binding and a high volume of distribution. They're excreted largely unchanged by the kidneys. 2,4-DP has been determined to have a serum half-life of ten hours in rats.

This pharmacokinetic information and all of the

rest of the toxicity information I'll be presenting is from animal studies. We weren't able to identify any relevant human studies.

2,4-DP has a characteristic pattern of chronic toxicity which includes hepatotoxicity, kidney toxicity and anemia. Interestingly, although it is not metabolized by the liver, it induces P450 enzymes and it has been identified as a peroxisome proliferator.

Due to its effects on lipid metabolism, there are typically changes in circulating cholesterol and tryglyceride in chronic and subchronic studies.

There are a number of animal developmental toxicity studies for 2,4-DP, that is, studies in which 2,4-DP was administered during organogenesis, and the fetuses were examined at term. All the studies used an oral route of administration.

As Jim mentioned, 2,4-DP is a racemic mixture, it's an optically active molecule, and here that's represented as 2,4-DP.

There are also toxicity studies on 2,4-DP(+), there was a dextrorotatory enantiomer, because both of these agents are used commercially and must have been tested for their toxicity.

A mouse study appeared in the peer reviewed literature in 1983 using a broad range of doses of

2,4-DP and 2,4-DP(+).

In addition, there are a number of studies that were performed for pesticide registration purposes in rats and rabbits: a pair of rat and rabbit studies of 2,4-DP in 1979 and '80, and a pair for 2,4-DP(+) in 1993. I'm going to go through the effects that were seen in these studies.

At the highest dose in the mouse study for 2,4-DP, there was a spectrum of developmental toxicity including intrauterine growth retardation, intrauterine lethality and fused ribs and cleft palate. This study reported a decrease in pregnancy weight gain of 18 percent in terms of maternal toxicity.

At the next highest dose, decreased fetal weight and fused ribs were seen. At 300 milligrams per kilogram, only the decreased fetal weight. And 200 milligrams per kilogram was the NOEL for this study, no effects on maternal or fetal toxicity.

In the 2,4-DP(+) study, the NOEL was also 200 milligrams per kilogram. The developmental toxicity showed a slightly more severe profile at higher doses.

Moving on to the rat studies, there are three rat studies.The first two, using doses of 100 and 125 milligrams per kilogram, found no effects on maternal or fetal toxicity as reported in the study. You'll note

that these doses are lower than the NOEL identified in the mouse study.

The third study using 2,4-DP(+) at 160 milligrams per kilogram identified decreased fetal weight and skeletal ossification, increase in extra ribs and hydroureter, and maternal toxicity in this study was reported as a 13 percent lower pregnancy weight gain. The NOEL for this rat study then was 80 milligrams per kilogram.

Now finally we have the two rabbit studies. The first rabbit study performed in Dutch-belted rabbits, the high dose of 75 milligrams per kilogram, there was a report of decreased fetal weight and of three multiply-malformed fetuses in the high dose group.

This study is difficult to interpret because of a high maternal mortality rate throughout the study. In all of the dose groups there was a high maternal mortality rate.

In addition, the litter size in the control group was unusually small and analysis indicated that the reduced fetal weight may have been associated with this problem with the concurrent controls.

The second rabbit study with 2,4-DP(+) found, using Himalayan rabbits, an increase in extra ribs, decreased skeletal ossification, and maternal toxicity

here was a decrease in maternal weight gain very early in dosing only.

So, in summary, the dose-dependent effects on developmental toxicity was seen in the mouse study, and there's support for this in the rat and rabbit studies in a similar dose range.

Now I'm going to talk about female reproductive toxicity a little bit. The most relevant studies are two rat multigeneration studies. I'm going to be presenting information only from the second study. The first study was in agreement with the second study.

There were no effects on fertility -- on the female fertility indices in the study.

The perinatal effects were seen at the high dose, and they were the most striking effects in the study. There was prolonged gestation and dystocia in the dams.In the fetuses, increased still birth, lower litter size and a lower birth weight.

In addition, in the observational data, a greater incidence of insufficient maternal care was reported and a failure to cut the umbilical cord and consume the placenta.

The parental toxicity, the genotoxicity in the study followed the characteristic 2,4-DP pattern with liver and kidney effects and serum cholesterol

changes.

In terms of weight gain during the premating period, there was about a 20 percent lower weight gain in the breeders that were treated at the high dose with 2,4-DP.

As is the case for most of our chemicals, there are a number of chronic and subchronic studies that we looked at to try to get what information we could on reproductive organs, and we did not find consistent effects on ovarian weight or pathology in the studies that were available.

The same two rat multigeneration studies are relevant for male reproductive toxicity. No effects were found on the male fertility indices in these studies.

There was a report of decreased absolute testes weight in the breeder males in the F0 and F1 generation. One dominant lethal study in rats was available and no effects were found.

And then in the chronic and subchronic studies, in a 13-week rat study, a decrease in absolute and relative testes weights was reported. A longer study using the same doses did not find these effects. At the end of the study, however, there was a report of an increased incidence of prostatitis.

So to summarize, developmental effects have been reported in mice, rabbits and rats. Female reproductive toxicity was seen as paripartum effects in rats in multigeneration studies. And for male reproductive toxicity, effects on testicular weight in rats.

At this point, I would be glad to answer any questions about this data set.

CHAIRWOMAN BURK: Are there any questions for Mari?

I want to thank you very much for a beautiful report.

Linda.

DR. ROBERTS: Mari, in rabbits you referenced a paper that looked at food restriction in rabbits as well?

DR. GOLUB: Yes, in the HID I tried to find papers that were relevant in an empirical way to the relationship between maternal and developmental toxicity, so that was the paper that I presented in terms of changes in maternal food restriction, effects on weight gain and consequent fetal toxicity.

DR. ROBERTS: In those papers, did they look at effects upon weight gain or weight loss early in organogenesis similar to --

DR. GOLUB: You're talking about the rabbit food

restriction study?

DR. ROBERTS: Yes, did that paper provide that data?

DR. GOLUB: I don't think I'm going to remember that. If I didn't report it in the study, I doubt that that was the case. I think they just gave it over the period of treatment as the most -- as the finest level of analysis.

DR. ROBERTS: In the mouse study, two questions on it. One, for fetal weight, that is on the basis of mean fetal weight per litter and then the analysis?

DR. GOLUB: The analysis doesn't state that. The section on statistical analysis only says that they used P test and chi-squared. It doesn't say what the basis was.I believe the study was from the early 1980s. So we don't know for sure because it doesn't say it was a report in the open literature.

I would imagine that the litter -- based on other studies done during that time, that the litter was used for the fetal weight, but that the pool fetuses were used for the variations and malformations.

DR. ROBERTS: Was there any other data reported in that for maternal effects other than the pregnancy weight gain?

DR. GOLUB: No, the only information was a table

on pregnancy weight gain.

CHAIRWOMAN BURK: Any other questions for Mari? Did we have any public comments?

DR. ROBERTS: Mari, can I ask you one more question?

The subchronic study that was referenced earlier for rats, it had adverse effects reported at 94 milligrams per kilogram per day. Was that a 13-week study?

DR. GOLUB: The study that showed the testicular effects was a 13-week study. It was done in preparation for the chronic study.

CHAIRWOMAN BURK: We have John Pearson of JP Registration and Regulatory Services. No? I guess we don't.

Any other public comments? No.

Okay, let's continue the discussion. As I understand this, we're open to look at all endpoints, although the initial listing was for developmental toxicity.

Does anyone want to say anything about the male or female reproductive toxicity?

Well, Marion you have to say something.

DR. MILLER: Again, similarly to the last chemical, there isn't anything -- I don't think there's

data to clearly indicate that there is an adverse effect on male reproductive capabilities.

There is inconsistency in some of the studies in terms of the testes weight, but on the basis of lack of changes in fertility or any defined changes in testes pathology, I don't really think this has been clearly shown to have any effect on the male reproductive capabilities.

CHAIRWOMAN BURK: Okay. Any comment on the female?

DR. MILLER: To continue, my perception of the female, I think there is a little bit more room for discussion, in that, again, there really could be something going on in terms of gestation time, and I would appreciate some feedback from the committee.

Again, these effects tends to be happening at high doses, so the dose level where maternal effects could be coming in may be important in terms of defining whether or not there's female reproductive toxicity, or whether we really just have a toxicity to the female in terms of systemically.

CHAIRWOMAN BURK: That's correct. I think Table 10 maybe is what we're looking at here now.

DR. GOLUB: I think I have that slide here, too.

DR. MILLER: My note to myself on that table is the effects we were seeing were at 226 milligrams per kilogram, which was a very high dose level.

CHAIRWOMAN BURK: I wish I knew more about the female system as far as whether you would expect to see these type of things in the very high dose such as this. Does anyone have -- like the prolonged gestation and so forth.

Linda.

DR. ROBERTS: I don't know. That's why I asked the question about the subchronic study because the usual 13-week study is, in essence, the same as the prenatal exposure period plus the gestation, and we were seeing effects at 94 which is less than half.

DR. GOLUB: I can go over the toxicity in the study. There were no deaths. The weight gain, as I said, was about 20 percent lower. During gestation, it was about 12 percent lower.

There were changes in lower serum cholesterol and circulating triglycerides, a lower statistically significant MCB in hemoglobin, although not in the anemia range, and some urinary crystals indicating a little bit of a kidney problem and enlarged livers.

CHAIRWOMAN BURK: Any other comments on this issue?

DR. KEEN: Mari, do you remember what the food intake was in that study at the high end?

DR. GOLUB: In the multigeneration studies they do food intake every week, so it's a little bit difficult to summarize.

But as I recall, there was reduced food intake early in the premating segment of the study, and I think there may have been at odd weeks during gestation.

Now, during lactation, because of the serious postnatal mortality -- some of the litter -- I think the average litter size was one and two and perhaps four in some of the generations, so they were nursing a much smaller litter, and the food intake was lower, also, during that time.

DR. ROBERTS: Mari, there is a comment underneath Table 8 in the text that says parental effects were almost entirely confined to 2000 ppm. Was there anything significant at the 400 ppm group?

DR. GOLUB: Not statistically significant as reported in the study.

DR. ROBERTS: Were there any other behavioral measurements noted?

DR. GOLUB: No, there were no neurobehavioral measurements.This was from cage-side observation.

CHAIRWOMAN BURK: Well, I don't know where we

should go with this at the moment. This is very intriguing, but whether it's sufficient, I don't know.

DR. MILLER: There is obviously a lot going on with those animals at the 226 milligrams per kilogram per day systemically in terms of their cholesterol, hematocrit, urine crystals, et cetera.

I don't think in any of the other studies -- even if they were done at a similarly high dose, they never developed that level of maternal toxicity.

DR. GOLUB: That's very typical of the toxicity of 2,4-DP.The chronic and subchronic studies, of course, are done in different rats, different periods of time, different durations of dosing, but the pattern is very similar with the anemia, enlarged liver, enzyme reduction and the signs of kidney toxicity.

DR. MILLER: As would be typical of a peroxisomal proliferator.

DR. GOLUB: Right. It's not an unexpected pattern from what we know about the biological activity of the peroxisomal proliferators.

DR. MILLER: It seemed that that group of rats responded more severely than any other group. Am I right?

DR. GOLUB: It's difficult to compare the chronic and subchronic studies with the animals that are

mated and go through pregnancy and lactation. So I would find it difficult to compare the quantities of the severity except to say that the pattern is very similar to that type of toxicity. It looks like the -- a pattern that's not unusual for that agent and that classification of agent.

DR. MILLER: I think there is a possibility that there is some relationship that's more direct than the consequence of maternal effects.

But at the same time, there are so many maternal events going on, that I find it a little difficult to tease out that these changes in gestation, duration, et cetera, may be more associated with the systemic event going on in the whole animal, which ultimately may translate into a female reproductive effect, but I can't quite see that as a direct link.

DR. KEEN: I guess I'd like to agree with you, Marion. I'm underwhelmed with the firmness of the data. They're intriguing, they're provocative, but is there definitive evidence? It doesn't pass that test for me.

DR. MILLER: I would tend to agree.

CHAIRWOMAN BURK: Let's move on to discussion of developmental toxicity. I think Table 9 summarizes this. We have a lot of studies here, which is nice, and -- but, unfortunately, in most of the cases you have

developmental toxicity at the same level as maternal toxicity except for this mouse study. So I think we should really look closely at the mouse study to start with.

Does anybody have any comments on that or any aspect of developmental toxicity?

DR. SAMUELS: Mari, the one number, looking at Table 2, I was trying to calculate total litter weight and couldn't quite do it.

DR. GOLUB: I went through that calculation, too, to try per animal the amount, considering the smaller litter size and the decrease in weight, how that compared to the maternal weight gain.

And I don't know if that's a legitimate thing to do, but I did do it, and I took some notes on it -- I don't know if I brought them with me -- but I believe that it was -- that what you would estimate from the less production of fetal tissue, it was actually more than the difference in the maternal weight gain.

But it's hard to know if that's a legitimate thing to do. There are other weights involved in the pregnancy besides the fetus. There's the placenta and the uterine weight gain and so forth.

DR. SAMUELS: Thank you.

CHAIRWOMAN BURK: We'll give people time to

mull over some of this.

DR. SAMUELS: The strongest evidence to consider is in those 300, 400 milligram per kilogram groups where there are no noted maternal effects and yet there are fetal effects.

One question I had, though, unrelated, is clearly the sensitivity in the rats and the mice were very different. Is that generally the case for this kind of comparison?

DR. GOLUB: It is difficult to make that comparison because the only rat and rabbit studies that found effects were with the 2,4-DP(+). The rat studies used lower doses. So we don't know with the 2,4-DP racemic mixture where the effect levels would have been.

It's -- we don't have a good set of LD50 values to make general statements about species differences on acute toxicity.

DR. ROBERTS: Mari, in the subchronic studies that were done in mice, were there any findings at any dose levels that we can use for comparison?

DR. GOLUB: Once again, it's hard to compare the studies because the durations and the strains of mice and so forth were different. I think there's a no effect level -- I had a no effect level in non-DART

toxicity.

In a three-month study -- I'm reading my own sentence in which I have complete confidence -- effects were seen at doses as low as 600 ppm or 60 milligrams per kilogram per day based on food intake of ten percent body weight. So that's in a mouse study.

Here again, they're looking at clin chems and CBCs and so forth, and I think that would probably be the most sensitive endpoints in those studies, although I don't have a record of it here.

DR. SAMUELS: Perhaps this has been asked, but are the effects on cleft palate, fused ribs using, again, the individual fetus as the unit of analysis?

DR. GOLUB: Don't know for sure; but from the presentation in the table, it looks like it was the pooled fetal evaluations.

DR. SAMUELS: Which is, unfortunately, the wrong unit, I think.

DR. GOLUB: Yes, it's not on a per litter basis.

DR. ROBERTS: Mari, one other question. On page 11, looking at the same paragraph on subchronics, there was a three-week pilot in mice, and the 600 ppm comes out to about 60 milligrams per kilogram per day. Would it be approximately correct to assume that 2700 ppm

would be about 270 milligrams per kilogram per day?

DR. GOLUB: That's an assumption that's often used in risk assessment is the ten percent. It's kind of a metric.It helps us compare studies. We don't know for sure.

DR. JONES: I don't know whether you can answer this question or whether anyone can shed any light on it.

I must admit I'm rather intrigued by quite a bit of the data here, and I'm also intrigued by the fact that 2,4-DP is a peroxisome proliferator. So from the standpoint of both biologic plausibility and biologic action of this agent, can you comment on that relative to --

DR. GOLUB: It's always something that's interesting to think about, and I could present some information if people would like to hear it. I've prepared a couple slides.

CHAIRWOMAN BURK: Please do.

DR. GOLUB: The chlorophenoxy acid herbicides are really very well-known peroxisome proliferators, and many of them have been studied. There's been several different nuclear receptors, and they seem to have different functions in different life stages.

So it's -- particularly the gamma and the delta

that are found in embryos. The alpha -- PKR alpha is more the classic liver or hepatic peroxisome proliferator.

But we do know a little bit about peroxisome proliferators in steroid metabolism. We know that consistent with the hypocholonemic effects, that some of the cholesterol synthesis do occur in peroxisomes.

We know that 17 beta estradiol dehydrogenase, HSD-4 it's sometimes called, is up regulated in connection with PPAR activation, and we know that the mouse specific CYP2C11 is down regulated.

There hasn't been a lot of study of 2,4-DP directly and not as much as you'd like to see on steroid hormone production, but in terms of the possible consequences, you can imagine that there would be increased estrogen activity in males because of the failure of the CYP2C11 to deactivate the estrogen and perhaps a decreased estrogen activity in females because of the more rapid conversion and more thorough conversion of the estradiol to the less effective estrogen estrone.

Those are some possible considerations. As always, we'd like to have a five- or ten-year mechanism study to help us along, but we can at least think about it, I guess.

DR. JONES: So you would see this far more from the standpoint of male and female reproductive toxicity than developmental toxicity; is that what you're saying?

DR. GOLUB: It's hard to know. Certainly the male steroids are important during pregnancy and parturition.There's changes in the balance of estrogen and progesterone and so forth.

We don't have any data on those circulating levels to know whether there were even changes in those hormones and to what extent you can use those changes to make a functional conclusion.

CHAIRWOMAN BURK: Very interesting. Also, perhaps we should have a discussion about the effects of maternal toxicity in this case since we have a number of studies that have a co-occurrence of developmental and maternal toxicity. And Mari provided us with some information that was -- perhaps I'll put it into context. Let me make sure I understand.

Your conclusion, Mari, was that food intake reduction would not be expected to be the cause of the developmental toxicity?

DR. GOLUB: Well, you wouldn't know that without testing that hypothesis, but just to try to line up studies with food restriction with this study and

compare the consequences of food restriction alone without the other effects of the toxic agent, that's what I tried to do. But, of course, it's a project in itself to come up with a definitive conclusion.

CHAIRWOMAN BURK: In this particular case, I think it would be more interesting to get at the mechanism of the peroxisomal proliferators and so forth. Because I have a feeling that, if one could understand that, it would make a lot more sense.

Are there any more comments, discussion on any aspects of developmental toxicity?

DR. MILLER: Can I make one more comment?

In the previous discussion of the metribuzin, we saw maternal toxicity and decreased maternal weight gain associated with lower fetal weight.

In some ways we're looking at a not dissimilar situation here.Except it seems to me, particularly in the mouse study, you have no effects on the mother, no maternal effects, and a pattern of effects that is much broader than what we saw with metribuzin.

Again, I would ask Linda if she would like to comment, and it seems that the developmental endpoints cover a wider range of toxicities that may be less nonspecific than skeletal variations. These may be a little more substantive. Can you comment on that?

DR. ROBERTS: I would still tend to put them towards the sorts of things that can be associated with maternal toxicity: the reduction in fetal weight, the increase in resorptions and cleft palate. The malformed vertebrae and the fused ribs could be. I'm not sure.

The amount of body weight gain/reduction that is recorded is not particularly extreme. We're looking at, I think, 16 grams versus 20 or 21. So about 80 percent, 75 percent, or so.

That's one of the reasons I asked about the subchronic studies as well because we're seeing this at dose levels of 300 to 500 over about a ten-day period of exposure and a couple days to recover. The closest we can get is a subchronic study done for three weeks and at 270 we had findings.

I guess part of it -- I'm not certain if what findings that are there are possible -- are plausible for maternal toxicity. I think they're plausible for not being maternal toxicity.

I'd like to pass the question back to Steven as to how well he believes that what he sees as statistically significant, the fetal body weight and resorptions, is accurate.

DR. SAMUELS: Well, resorptions would have been done on a per dam basis, so I believe they're probably

accurate, but I can't tell without looking at the original document.

Mari has obviously taken a good look at it to see if there is any indication they did a correct analysis.

DR. GOLUB: There is no more information in this table as far as the statistical analysis. And as I said, the methods section just said they used chi-squared.

DR. SAMUELS: Well, chi-square is usually a red flag because it implies that they're simply doing counts. And if they're counts of cleft palate, for example, then it's the wrong unit, and the P value is too extreme.And with these dam sizes, I believe that the P values are probably not as significant as reported, but then that's not based on good evidence.

DR. ROBERTS: Mari, one other question on this study. I noticed with the group sizes that there's a lot of variation in the number of animals.

Is there any indication from the methods that all of these animals were done at the same time or the reason why the highest dose would have just ten?

DR. GOLUB: It's difficult to know. The study also included several other chlorophenoxy acid herbicides.I don't know if they were able to estimate

different group sizes, you know, if they did successive studies, or quite what the reasoning was for the difference in group sizes.

But that's true for the other agents, too. They have different group sizes. I don't know if they did pilot studies. There's no indication.

DR. ROBERTS: Did the data suggest that they might have used a single control group other than the multiple studies, which would be okay if you're doing the studies at the same time?

DR. GOLUB: That's a good question. I don't have the study here, so I'm afraid I can't answer it for you. I don't recall that I had that impression. That information is in the report, but I don't have it here.

DR. ROBERTS: It does surprise me, looking at that, that the high dose and low dose has only ten animals as opposed to the others being at least double.

DR. KEEN: Fifty-nine.

DR. ROBERTS: That suggests to me that there are multiple control groups pooled together.

As I said, if they're doing two studies in the same room and there are really only two control groups on paper, then it's okay to have the data from all those animals used at the same time. If they're not doing it that way, they're doing it sequentially, then it should

be reported separately.

DR. GOLUB: The control groups were different sizes for the 2,4-DP and 2,4-DP(+). They used the same vehicle. It's hard to speculate because we just don't have that information.

DR. ROBERTS: Was there a description of the malformed vertebrae?

DR. GOLUB: Most of the information was in tabular form. I think it was a general category that they used in the skeletal examination.

DR. MILLER: Can I make one more comment?

CHAIRWOMAN BURK: Please.

DR. MILLER: It's interesting that there's more in developmental effects after the (+) isomer in that this may suggest that maybe there is a receptor type mechanism involved with the developmental changes, and that would fit with the PPAR or some sort of receptor that was isomer specific, and maybe that would support that there is something going on specific to development rather than nonspecific with the -- nonmaternal with the mother.

DR. GOLUB: I got that information on the control group size for the MCPA and MCPP, which are two of the peroxisome proliferator sites. They have the same control group size for the mixture of 24 and for

the dextrorotatory of 59. So it looks like possibly the mixtures were done at a different time than the isomers -- than the (+) isomers and the enantiomers and they used pool controls.

CHAIRWOMAN BURK: To get back to the mechanism for just one second, Mari, the -- you discussed that there's a classic peroxisomal proliferator, clofibrate, and also there's some resemblance to valproic acid in terms of -- can you comment more? Have there been studies on clofibrate as to developmental toxicity?

DR. GOLUB: Just a few small studies. Of course, DEHP would be sort of the most studied peroxisome proliferator for developmental toxicity.

Again, we don't know the specific binding patterns of all the agents, the specific binding patterns, and whether we can make -- you know, generalize too much.

It's good to think about it, I think, but there's no -- for some agents, like the ethylene glycols, there's been structure activity studies across the class where you have a better idea about them. That's not the case for peroxisome proliferators.

CHAIRWOMAN BURK: As you can tell, I like to have mechanisms because that's the only way I can really actually feel confident.

DR. MILLER: One of the intriguing things about peroxisome proliferators is that they are such a diverse chemical class -- not even a class -- they're a diverse group of chemical structures.

CHAIRWOMAN BURK: We cannot make any assumptions here based on any others, so we have to go with what we have.

Is there any further discussion? I'm not rushing anyone.Are we ready to -- no one is nodding yes or no.

In this particular case, I'm speaking for myself now, I know that we have a number of studies which only show developmental toxicity concurrent with maternal toxicity, but there is one that doesn't, and so for that reason I -- and there are quite a few studies, so it's not like we don't have data.

So it really seems important to me to know if the committee always intends to dismiss developmental toxicity in the presence of maternal toxicity. That's a weird way to put it, I guess, but -- in other words, we just write that off, or if there would ever be a case where we would list on that mechanism -- or on that basis. And maybe this is it. But I wish I understood more about the biological plausibility, and that would help.

DR. KEEN: If I can just comment. I would have no difficulty with some cases if maternal toxicity is going to be running parallel. In some situations we have mechanisms where we know the maternal toxicity is representing a very specific developmental insult.

I guess where I am, again, underwhelmed, what we have are two lines of data, I would argue as the weight data, particularly for the non(+) isomer, in a study that we're actually having some difficulty even knowing how they conducted it. There seems to be a lot of, not necessarily confusion, but we're kind of reading into the trial.

So I don't see it as very definitive. It's another case where you would like to see somebody go back in and do a very clean study.

That's where the hesitation is. You almost get a sense, gee, there might be something there, but I sure don't find it very definitive.

DR. ROBERTS: Dottie.

CHAIRWOMAN BURK: Yes.

DR. ROBERTS: As to the mechanism of the peroxisome, definitely ethanol sort of answers for me the question of whether or not we can list something as a developmental toxicant or not.

CHAIRWOMAN BURK: Absolutely.

DR. ROBERTS: What is problematic for me is that the only study that shows developmental effects occurring in the absence of maternal effects is the one study that doesn't seem to have been reported very thoroughly; and that's why, for me, it's not a clear threshold.

CHAIRWOMAN BURK: All right. I sense we're ready to take a vote here. Remember, in this case we are voting to remove the chemical from the list, so it's slightly different.

Please indicate by a show of hands if, in your opinion --

DR. DENTON: Can we wait just one minute? Jim's got a clarification.

MS. HECK: Just to revisit the notion of what you're actually voting on, depending on the outcome of the vote, it may come off the list. It is on the list, as we speak, but the call of the roll is to see whether or not it should remain on the list.

CHAIRWOMAN BURK: So we should turn it around.

MS. HECK: I think the text you have been provided by Cynthia Oshita is properly phrased in terms of what you're getting at.

But we're actually asking, just as we would in an initial listing, whether or not the evidence supports

this chemical being on the list. So you don't need to reverse anything.

CHAIRWOMAN BURK: Wonderful. All right. I'll read it as it's written.

Please indicate by a show of hands whether, in your opinion, 2,4-DP has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity and, therefore, should be maintained on the list.

The record should reflect one vote was cast to maintain 2,4-DP on the Proposition 65 list as causing developmental toxicity.

Please indicate by a show of hands if, in your opinion, 2,4-DP has been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity and, therefore, should be maintained on the list.

The record should reflect zero votes were cast to maintain 2,4-DP on the Proposition 65 list as causing female reproductive toxicity.

And finally, please indicate by a show of hands if, in your opinion, 2,4-DP has been clearly shown through scientifically valid testing according to generally accepted principles to cause male reproductive

toxicity and, therefore, should be maintained on the list.

The record should reflect zero votes were cast to maintain 2,4-DP on the Proposition 65 list as causing male reproductive toxicity.

A majority of five of the appointed members is required to maintain a chemical on the list. Accordingly, 2,4-DP does not remain on the Proposition 65 list.

Did I do that properly?

MS. HECK: Just to address the hesitancy in your statement, that's correct, since it did not garner five votes for any of the three endpoints, it will be taken off the list.

We would take the administrative step of doing that on the committee's behalf if the committee's decision is to remove the chemical.

CHAIRWOMAN BURK: Okay. Do we need to take a break? We'll take a 15-minute break, and then we'll continue with the agenda.

(Recess taken.)

CHAIRWOMAN BURK: We'll continue with the agenda, and I've been asked to remind everyone to please speak up.The microphone is your friend. That's a quote.

The next agenda item, again, agenda item IV, consideration of chemicals, listed via the authoritative bodies mechanism, for possible removal from the list, will be cyclohexanol, and we have a staff presentation by Dr. Marlissa Campbell.

First, Jim Donald.

DR. DONALD: Again, very brief introductory comments. Cyclohexanol is another chemical which is currently on the list. It was listed on the basis of male reproductive toxicity.

Here again, the committee has the opportunity, if they choose, to maintain it on the list on the basis of any form of reproductive toxicity.

Now, Dr. Campbell will do the presentation.

DR. CAMPBELL: Today's presentation will be a brief overview of the information presented in the hazard identification document, evidence on the developmental and reproductive toxicity of cyclohexanol.

Cyclohexanol is used in the production of nylon, lacquers, paints, varnishes, degreasers, plastics and plasticizers, soaps and detergents, textiles and insecticides.

Exposure to cyclohexanol may occur through ingestion of contaminated food or drinking water,

inhalation of contaminated air or dermal contact with contaminated water.

There are no toxicokinetic data in humans and no quantitative data on absorption and distribution of cyclohexanol in animals. However, there is evidence from acute and chronic studies in several animal species of toxicologically relevant absorption by the oral, inhalation and dermal routes.

Cyclohexanol is primarily oxidized by hepatic NAD-dependent alcohol dehydrogenase. Following oral or inhalation exposure of rabbits to cyclohexanol, most of the compound was excreted in the urine as cyclohexyl glucuronide, but sulfate conjugation also occurs.

The metabolic disposition of cyclohexanol is thought to be relatively rapid with a half-life of about 12 hours and without prolonged retention in the animal.

This slide just shows a comparison of lethal doses of cyclohexanol by different routes in various species. The main points to note here are that, firstly, cyclohexanol is not highly toxic. It takes very high doses.Many of those doses are in grams.

Also, to note is that in rabbits the minimum lethal dose was approximately five to ten times higher than the minimum lethal oral dose in that species. The sequence of symptoms preceding death was similar with

exposure by either of those routes.

Turning to developmental toxicity of cyclohexanol, in one study cyclohexanol was given in the diet of female mice of the TB or NMRI strains. Treatment was begun prior to mating and conception and continued throughout gestation and lactation.

Weaned young of 21 days postnatal age were continued on the treated diet. By postnatal day 21 43 persons of the NMRI pups had died as compared to 12 percent among controls. No statistical evaluation of the data was reported in this study.

For TB mice, 14 percent of cyclohexanol treated pups had died by postnatal day 21 as compared to 12 percent of the control pups.

Treatment of TB animals was continued for an additional generation, and the mortality of the second generation was increased to 53.5 percent. No data were presented for a second generation of control animals.

The pup weights between postnatal days 21 and 110 were considered to have been inhibited in the first and second generation females. The growth of male offspring was less affected. And, again, no statistical analysis was reported for these data.

In a supplementary study of the developmental toxicity of cyclohexanol, the chemical was added to

cultures of 8-cell stage zebrafish embryos. There were no deaths or morphological changes observed in untreated control embryos, and the NOEL for cyclohexanol in this study was three millimoles per liter culture media.

Effects observed at higher concentrations included edematous enlargement of the pericardial space, skeletal and muscle abnormalities and retardation of body development. Effects were seen in 100 percent of the embryos exposed to a concentration of 16 millimoles per liter.

Turning to a consideration of female reproductive toxicity, as discussed in a previous slide, the female mice of the NMRI or TB strains were exposed to cyclohexanol during mating, gestation and lactation.

TB animals were treated into the second generation.No data were presented on fertility, weights of female reproductive organs or other standard endpoints of female reproductive toxicity.

While effects on pup postnatal mortality and growth rates might have been at least partially due to effects on their dams lactational capacity, the data do not directly address this possibility. Alternatively, the pup effects may have been due to direct exposure to cyclohexanol.

Turning to male reproductive toxicity, in one

study cyclohexanol was given by the subcutaneous route to 20 adult male gerbils and 20 adult male rats.

The treatment periods were 21 days for gerbils and 37 days for rats with evaluations conducted at 24 hours following the final dose.

Exposure was stated to have had no effect on body weight in either species, but these weight data were not presented.

Significant weight reductions were reported for testes, epididymides and ventral prostate in both species. Seminiferous vesicle weights were also reduced in both species, but the difference was reported to be statistically significant only in the rat.

At the histological level, degenerative changes in the seminiferous tubules were reported for both species. The paper reports loss of type-A spermatogonia, spermatocytes, spermatids and spermatozoa, as well as vacuolation of sertoli cell cytoplasm.

The chemical changes reported for the male reproductive organs included decreased protein, RNA, sialic acid and glycogen, as well as increased testicular cholesterol and alkaline phosphatase activity.

In another study, cyclohexanol diluted with

olive oil was given orally to male rabbits at a dose of 25 milligram per kilogram for 40 days. The final mean body weights and relative adrenal weights did not differ among the groups of rabbits.

For five animals which were evaluated at 24 hours following the final dose of cyclohexanol, significant reductions were found in relative testes and epididymal weights of the treated rabbits.

Histopathological examination of the testes revealed loss of type-A spermatogonia, spermatocytes, spermatids and spermatozoa. The epididymal luminal epithelium was reported to be reduced in diameter as were the diameters of seminiferous tubules and Leydig cell nuclei.

Chemical changes included reduced testicular and epididymal protein, RNA, sialic acid, glycogen and acid phosphatase.

For five treated animals which were evaluated following a 70-day recovery period, spermatogenesis, organ weights and seminiferous tubule and Leydig cell dimensions were returned to normal. Biochemical parameters had either returned to control or near control values.

In a third study, cyclohexanol was given to 12 30-day old Sprague-Dawley rats. This was at a dose of

450 milligrams per kilogram per day by the gavage route for seven days. Control animals were given corn oil, and evaluations were performed at 24 hours following the last dose.

Relative liver weights of cyclohexanol treated animals were significantly increased as were the specific activities of hepatic biphenyl 4-hydroxylase, 7-ethoxycoumarin o-deethylase and aniline 4-hydroxylase, as well as cytochrome P-450 content. Cyclohexanol had no effect on relative kidney or testes weights.

There was no mention in the study of a histological evaluation of testicular tissue from the cyclohexanol treated animals in this study.

Then just to summarize the data on developmental and female reproductive toxicity, there were no data from human studies relevant to the potential developmental or female reproductive toxicity of cyclohexanol.

In the developmental study conducted in mice, cyclohexanol was given continuously from prior to conception throughout pregnancy and lactation into the postweaning period and in some cases into a subsequent generation. Data on growth and mortality were collected only after postnatal day 21.

In a supplementary study of zebrafish embryos,

cyclohexanol exposure was associated with morphological abnormalities.

The only animal study involving treatment of females during reproduction was the mouse study described above for developmental toxicity.

In that study, the observed postnatal pup mortality and growth deficits might have been at least partially due to effects on the maternal reproductive system such as lactational insufficiency, but the data do not directly address that possibility, and the findings could alternatively have been due to direct effects on the growing pups.

The last slide is a summary of information on male reproductive toxicity. As for the other endpoints, there were no human data relevant to the potential male reproductive toxicity of cyclohexanol.

The findings of two animal studies on the male reproductive system were substantially in agreement despite the use of different species and routes of exposure.

In both studies, the observations included adverse effects on epididymal weights and histological appearance of male reproductive tissues as well as biochemical alterations. In a rabbit oral study, a 70-day recovery period allowed for significant reversal

of effects.

In a third study, cyclohexanol was given to 30-day old male rats at a higher dose for a shorter period of time.

This treatment had no effect on relative kidney or testes weights, although exposure was reported to be associated with liver enlargement and induction of some hepatic drug metabolizing enzymes. There were no histological findings reported for testicular tissue in that study.

That concludes the presentation, and I would be happy to entertain any questions.

CHAIRWOMAN BURK: Thank you very much for your report.

I see no blue cards. Is there anyone from the audience that wishes to speak?

I guess we can begin our discussion. Maybe I can simplify it.

Is there anyone that wants to say anything about developmental or female reproductive toxicity?

We have some data, but it's just not sufficient, in my opinion. I like the zebrafish thing. It would be great if it was supporting something.

So that brings us to the male reproductive toxicity, which is the basis for the listing at this

time.

Any comments on that?

DR. MILLER: I must admit I am quite surprised that such different dose levels produced such different responses in that the study by Tyagi et al., which was in gerbils and rats, was producing an effect at 15 milligrams per kilograms; whereas the study by Lake et al. produced no testicular damage -- no overt testicular damage at 455 milligrams per kilogram.

There's clear differences in the studies in that the Tyagi study treated for 37 days in rats, and the Lake study treated the animals for seven days. The 37-day treated animals were for the adults. The Lake et al. animals were 30 days old. So there are definitely some major differences in the study.

I should note that the gerbil and rat Tyagi study and the rabbit study by Dixit et al. are essentially coming from the same laboratory, same group of people. Such diverse response in terms of -- in 15-plus fold differences in responding to toxicity.

It's very unclear to me whether another additional study carried out in the adult animal with the same starting material or some verified -- some verification that we really are working with cyclohexanol would be appreciated in these studies.

I thought the Tyagi et al. and Dixit et al. took the cyclohexanol and distilled it in order to assert purity. I wonder if something chemically might have happened in that step. I think there's a real need to verify the chemical starting material when you see such diversity.

CHAIRWOMAN BURK: So you have a real concern that they're not really testing cyclohexanol?

DR. MILLER: Well, the Lake et al. group probably really had cyclohexanol. Either there is a huge difference in terms of adult versus 30-day old animals or the starting material is under question.

CHAIRWOMAN BURK: I don't know how we're going to deal with that. Say, assuming that the Tyagi and the Dixit, I know it's the same lab, but they essentially agree at least in finding the pathologic effects.

DR. MILLER: They are seeing testicular damage.

CHAIRWOMAN BURK: Yes. Assuming that it was cyclohexanol, what would you make of it then? To me, it's quite clear, but I'm worried.

DR. MILLER: If it is cyclohexanol, then there is that study reporting male reproductive damage. I just find the disparity between the two studies so marked.

DR. ROBERTS: Marion, is it possible that the

seven-day period is just too short?

DR. MILLER: The seven-day period is just too short. The half-life of the compound was 12 hours, yes?

DR. ROBERTS: Yes.

DR. MILLER: So if you think of the half-life of the compound in terms of 12 hours, the seven-day period could well be too short in the accumulation that ultimately can build up over the longer time.

With a 12 hour half-life, you're only going to lose 75 percent of the dose in 24 hours, so that would keep building so that the exposure level is increased.

So, yes, the duration of exposure and potential for accumulation makes that relatively long -- 12 hours isn't that long -- relatively long within a 24-hour time period half-life, but that could provide an explanation.

CHAIRWOMAN BURK: You may know more about this, but what is considered a good study in terms of male reproductive toxicity. Seven days doesn't seem long enough to me to make sure you've got the entire kind of cycle of spermatocytes and so forth.

DR. MILLER: Well, within the testes, there are different stages of development in terms of stages of spermatogenesis.

But 30-day old animals are just getting past --

you're beginning to see ram spermatids, maybe a couple of them may be beginning to elongate. That's all. So you really don't have the full spectrum of the spermatogenesis reflected. So there's multiple questions.

CHAIRWOMAN BURK: There are, but I'm still curious why -- I know you feel the Lake study is good because they're a reputable group. But seven-day and 30-day olds, I don't understand what the reasoning was for doing --

DR. MILLER: I think they were doing studies where there's a difference in sensitivity.

DR. ROBERTS: Were 30-day old rats a sensitive subgroup of rats?

DR. MILLER: Yes, there's juvenile sensitivity.

DR. ROBERTS: I notice in here that they did get reproductive effects with one of the materials that they were testing during that seven-day period.

DR. MILLER: Yes.

DR. SAMUELS: Excuse me, Marion.

Again, I'll ask my colleagues, this study puzzled me and I'm glad we had the original document to look at because cyclohexanol was a metabolite of the main compound of interest in the Lake study. So that the effects that they found from the other compound they

do not attribute to the -- by inference they do not attribute to the cyclohexanol metabolite?

DR. MILLER: Yes, that would be the design of the study to identify the more active metabolite.

So I think there are possibly multiple causes for the disparity in the two data sets. One, the age of the animal; two, the half-life, the duration of exposure, so that they allowed -- accumulation would have occurred in the longer durations; or three, the purity and the nature of the chemicals that were administered.

CHAIRWOMAN BURK: So is that enough to -- the two Tyagi and Dixit studies that seem to support each other, to me, appear to be sufficient unless -- I guess I need more compelling evidence to say they weren't really using cyclohexanol. If they were, to me, it seems pretty straightforward.

DR. KEEN: Marion, since I think we are at a dilemma here, in the absence of the Lake paper, would you have been as concerned about potential purity of the compound being tested? Are there other experimental issues you would find in these papers?

DR. MILLER: In the absence of the Lake paper, I would not have been so concerned, even though in any good study you would have checked, and I don't think

that was done here.

Also, the rats were not identified by strain. They were house rats. So did they catch them?

DR. KEEN: Actually, that's an easy thing to almost laugh over, but it's not a trivial issue because it would be next to impossible to go back and ask the question whether or not there was something unusual about the models that were used here.

I was just curious as to whether there were other issues as to experimental design.

DR. MILLER: There are multiple issues potentially with the experimental design. I have no issue with the pathology that they saw.

DR. ROBERTS: One other possible question about it, I guess, is the usual models that we look at -- I don't know what kind of rabbits these were, but they're about half the size of the typical rabbits used in developmental studies.

They must have been full grown because I think they were about one-and-a-half grams at the start of the study, and 130 days later recovering animals were still about one-and-a-half kilograms at the end of that study. So they're approximately half the size of rabbits we normally see.

DR. SAMUELS: I had -- a question arose with the

Tyagi study. I was puzzled by the statement that the house rat was more potent -- the effects on the house rat were more potent than on the gerbils, which appeared to be because of the weight of the seminal vesicle.

So I went back and calculated the P value, and it appears, at least for the seminal vesicles and for the ventral prostate, that they are not statistically significant, at least according to the standards that we have here. They are not significant at .05.

I'm also always amused that in this paper and the Lake paper the word randomized is used. I guess it's just understood by toxicologists.

CHAIRWOMAN BURK: Any other comments? I understand some of criticisms with the study. It's hard to deny the pathology that they saw, in my opinion.

DR. KLONOFF-COHEN: I just want to discuss a metabolic issue that Marion brought up. I can understand what she is saying, that the rat strains would be very critical.

In terms of age, I guess I'm having the same problem in that I saw those two studies and was kind of taken by them.If you're not sure about the rat strain, then that certainly makes sense to me.

In terms of the purity and nature of the actual substance, that's worrisome. I don't know how to

address that. I guess I took it at face value that that was pure.

Are there any other issues that we should be aware of in terms of those particular studies that would be limitations?

Because of the fact that the Lake study you feel is -- or that lab is such a good lab, are there other studies or other things that I'm missing?

DR. MILLER: I think one of the more important issues is the duration of the study, which is, if the half-life is 12 hours, so that within a 24-hour time period is an opportunity for 75 percent of the material to be excreted, then with multiple daily dosing there is a potential for accumulation over that time period, so ultimately a toxic dose level could be reached.

I think that's a very plausible reason for the differences in response based on the kinetics and the actual dosing actually accumulating over the seven days versus and 70.Then the juvenile or the young animals sensitivity may also be another issue. And the third thing is the nature and the purity of the starting material.

So three unknowns, but the pathology is real.

CHAIRWOMAN BURK: Are the unknowns enough in your mind to discredit the studies or make them

invalid?

DR. MILLER: I really would like to have seen something else, some other -- maybe a developmental study for the female.

DR. KEEN: Marion, if I could just reask that slightly differently, rather than say it invalidates the study, what I'm hearing you suggest is there's enough confusion that it's not clear? That's different than saying it is a discredited study.

DR. MILLER: Well, it's not a discredited study, but it is -- Prop 65 is meant to list based on scientifically acceptable testing and principles -- I'm not quite sure of the wording -- and I'm not quite sure this would be scientifically acceptable.

CHAIRWOMAN BURK: That's sort of what I'm asking here. If it's determined to be shown through scientifically valid testing, to me, it's clear. But if the studies aren't valid, then that part is questionable.

DR. SAMUELS: Let me ask: What was the source of the cyclohexanol? Do you know that?

DR. MILLER: I can't remember. Anybody?

DR. SAMUELS: Would distillation itself change the compound in a way that would make what would be analyzed not cyclohexanol?

DR. MILLER: It would depend on a lot of circumstances.How they distilled it -- I really can't --

DR. SAMUELS: I understand. I mean, that's the question you brought up.

DR. ROBERTS: Marlissa, going back to the Lake study, cyclohexanol didn't have the testicular atrophy, but the MCHP did.

One of the questions, of course, is the half-life of the material. You wouldn't happen to know the half-life of the other metabolite?

DR. CAMPBELL: No. I'd have to check that.

CHAIRWOMAN BURK: I guess we have two options. One, we could defer this longer; or the other, we can take our poll.

The thing we have to remember, too, at least if I understand this correctly, is that this chemical is already listed. I don't know if that makes any difference. It really shouldn't. We're really basically asking the same question.

DR. KEEN: Again, I'm underwhelmed. It's been that sort of day, I guess.

In looking at this, we have conflicting data. In one of the data sets, it appears that there is a positive male reproductive toxicity. There is

information within the papers that are not clearly defined.

And, thus, it would seem as though it is not clear using the standards of science that typically we're asked to evaluate the papers from. At the end of it, it seems to be not enough.

CHAIRWOMAN BURK: Are there any other comments? It's a difficult decision.

DR. MILLER: I suppose we could look at the data we have and look at it at face value and not trying to read in too many possibilities, but I find that a little difficult.

The data sets from the Tyagi and Dixit groups do make me a little unsure about what really went into the animal.But it's only speculation.

CHAIRWOMAN BURK: Does anyone else want to say anything? One more chance to make the case one way or the other.

As I suggested before, the other possibility is to defer the decision. The question is: What further information could we actually get that would aid in this decision?

DR. MILLER: Some chemical stability information.

DR. SAMUELS: My concern is that it's a compound

closely related to chemicals that are known to have a very strong effect, and it was exonerated in the study of the juvenile rats over a shorter period of time. So could it have been transformed something like the chemical that it's related to?

DR. MILLER: The chemical you think it's related to, I assume, is toxiethanol?

DR. SAMUELS: Would the distillation itself have changed the compound, the stability question.

DR. ROBERTS: I think that might also be dependent on what they distilled it out of and what they ended up distilling it into as well.

Is there any other tox information out there? Is this the one that had information that you were told not to use?

DR. CAMPBELL: No, this is everything.

DR. ROBERTS: Okay.

CHAIRWOMAN BURK: Well, I need to know, do you want to vote? Do you want to defer? But I would have to have a good reason for doing that, I suppose.

DR. ROBERTS: I guess my problem is, I don't know if we're going to get anything else better. It doesn't sound like there is any other tox data.

I'm sure I could ask chemists what could happen in the distillation process. Their answers are probably

going to be ambiguous.

CHAIRWOMAN BURK: I think the problem now is that's pure speculation. My feeling -- this is personal -- but I think maybe we have to take this at face value. This is the information we're given. If you really think the studies are not valid, then that can make your decision.

I guess, myself, I still feel the results are fairly clear. I understand the conflict. But, to me, unless I knew something more -- I don't think the studies in and of themselves are, for the time period they were done, poor studies.

There's specific male effects and not anything else. In other words, it seems like it was a target. If it's some other chemical, then that would be nice to know, but assuming it's cyclohexanol --

DR. MILLER: And you do have a biological reason for why you see different sensitivities at the two different dose levels, which is based on the multiple durations of exposure and the half-life.

CHAIRWOMAN BURK: And the age.

DR. MILLER: So there are those two biologically clear reasons.

DR. SAMUELS: Sure.

CHAIRWOMAN BURK: We always do a weight of the

evidence type of thing. When you have conflicting data, you have to weigh them somehow and give that consideration.

Okay.I think no one has made a case for deferring, so I think we'll just have to go ahead. I'll go down the list here so we have the easy ones first.

Please indicate by a show of hands if, in your opinion, cyclohexanol has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity and, therefore, should be maintained on the list.

The record should reflect zero votes were cast to maintain cyclohexanol on the Proposition 65 list as causing developmental toxicity.

Please indicate by a show of hands if, in your opinion, cyclohexanol has been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity and, therefore, should be maintained on the list.

The record should reflect zero votes were cast to maintain cyclohexanol on the Proposition 65 list as causing female reproductive toxicity.

Please indicate by a show of hands if, in your opinion, cyclohexanol has been clearly shown through

scientifically valid testing according to generally accepted principles to cause male reproductive toxicity and, therefore, should be maintained on the list.

The record should reflect four votes were cast to maintain cyclohexanol on the Proposition 65 list as causing male reproductive toxicity.

A majority five of the appointed members is required to maintain a chemical on the list. Accordingly, cyclohexanol does not remain on the Proposition 65 list.

Next agenda item, Agenda item V, consideration of chemicals for possible removal from the Section 14000 list of chemicals that have not been adequately tested. First, "A," is a bunch of chemicals and Colleen will speak.

MS. HECK: This is a seldom noted provision of Proposition 65. Probably very few people in the room know that Proposition 65 actually mandates the creation of two lists.

One, those chemicals known to the state to cause cancer or reproductive toxicity, and another requires publication of a list, an annual revision of chemicals which are required by state or federal law to have been tested for their potential to cause cancer or reproductive toxicity but which the respective committee

finds has not been adequately tested.

That list is published in regulation in Title 22 of the California Code of Regulations at Section 14000. That's why it's indicated on your notes as a Section 14000 list.

This is an important task that has been assigned to a committee. However, in the past, this responsibility has been somewhat downplayed.

In fact, this is the first time that this committee in its currents constitution will be looking at the Section 14000 list. And, oddly enough, you're looking at it not for addition of chemicals to this list but, just like the last agenda item, for possible removal.

The reason for that is as follows. The regulation indicates that a chemical cannot simultaneously be on the list of chemicals that are not yet adequately tested and at the same time known to the state to cause for the same endpoint.

So we have gone through and compared side by side Section 14000, the not yet adequately tested chemicals and those known to cause, and under "A," the six chemicals you see do at this time simultaneously appear on both lists.

So it's somewhat of an administrative task for

you, largely a housekeeping matter, if you will. But it is the committee's responsibility, task, duty to direct us, if you are so inclined, to remove these chemicals from Section 14000 because they do, in fact, appear in the Section 12000 list of chemicals known to cause reproductive toxicity.

Just to step you briefly -- introduce you to "B," and then you can go back and take probably the proper vote on "A," Jim Donald is going to address quite a different procedural context; that is, the chemical that he'll address is not simultaneously on both lists, but we received a petition asserting that the tests that are required under federal law have, in fact, been conducted and, therefore, it should come off, which requires something more of a substantive undertaking on your part as opposed to "A," which I would characterize as almost extensively or exclusively procedural.

That's it unless there are any questions at this time.

CHAIRWOMAN BURK: Are there any questions?

Linda.

DR. ROBERTS: Colleen, as you know, I did contact you earlier to confirm that there wasn't a conflict of interest. I did not do that for these materials.Would it be the most appropriate thing to do

to recuse myself?

MS. HECK: Well, that would be the absolutely ultra-conservative abundance of caution, but I'm not going to advise you, though, that's in any way required, having no reason to believe that you have a financial conflict of interest, as that term is legally applied to your duties here, but I certainly can't tell you not to do that. Ultimately, it's your professional judgment, what you're comfortable with.

DR. ROBERTS: Okay. I can tell you, for most of these, I've never heard of them before. For N-methylpyrrolidone I have. While Chevron is not a manufacturer of it, I do believe we use it in processing, so I would like to recuse myself on that one.

MS. HECK: It's certainly your prerogative.

CHAIRWOMAN BURK: Are there any public comments? I didn't receive any.

Committee discussion?

It seems pretty much of a procedural thing. I think I understand it. It makes sense. Do you need a formal vote?

MS. HECK: I think that would be good for the record. If you can quickly do a call for a show of hands to remove those under "A" all in one lump, that

would be more than enough.

CHAIRWOMAN BURK: So the motion would be to remove all of these chemicals in "A" from the Section 14000 list that required them to be adequately tested.

All in favor, raise your hand.

DR. SAMUELS: I guess my question is: Is it the conclusion of the staff that they have been adequately tested?

MS. HECK: We did not weigh in on that. That will be the issue, if you want to put it to staff, as to "B." "A" is that a chemical cannot, as a matter of law, if you will, co-exist on both lists at the same time. There's no need to delve into the merits of adequately tested or not.

CHAIRWOMAN BURK: Are there any of these that you think we should consider? I mean, they're already listed by whatever mechanism.

Okay.Well, back to the motion. A show of hands to approve the motion. It's six in favor and one abstaining.So that passes.

Okay, part "B," could you remind us again --

MS. HECK: I'll let Dr. Donald take it from here.

CHAIRWOMAN BURK: Jim.

DR. DONALD: As Colleen mentioned, we received a

petition to remove 1,6-Hexamethylene diisocyanate from the Section 14000 list based on the assertion that testing required under the Toxic Substances Control Act had been completed.

What you have in front of you is a slide showing a slightly abbreviated version of the relevant page from a U.S. EPA website for 1,6-Hexamethylene diisocyanate.

As you can see, it makes reference to a consent order which was published in the Federal Register in 1997. It also makes reference to the status of the chemical as being closed, all required tests have been completed.

I apologize, this slide is rather hard to read, but this is taken from the consent order. And, again, it's very much abbreviated, but it identifies the studies that were required that are relevant to reproductive and developmental toxicity under that consent order.

Basically, there was one developmental toxicity study to be conducted by inhalation in rats. One reproductive and developmental screen with functional observation, also by inhalation, to be conducted in rats and dependent on the outcome of the second test, EPA also has the option of requiring a two generation reproduction study.

With reference to the statement -- let me go back to the original slide. This is the web page notes that all required tests had been completed. I also noted the test results had been forwarded to the Risk Assessment Division for review and disposition.

A table is provided under the TSCA section of the EPA's website showing the results of the two relevant tests.

In the last couple of days we received confirmation from U.S. EPA that, in fact, all the required tests had been received, had been evaluated and had been accepted. So as far as EPA is concerned, all the required testing has been done.

So the only question that remains is -- given the wording of the statute that this is relevant to chemicals that are required by state or federal law to have been tested for potential to cause cancer or reproductive toxicity but that the state's qualified experts have not found to be adequately tested as required, the question now is: What would the committee's desire be in terms of determining that the testing that the EPA has accepted is actually adequate?

DR. ROBERTS: I had a question, Jim. I'm sorry. I'm still a little bit confused. If EPA considers it adequately tested for their purposes, are

we -- that means our purposes?

The reason I'm asking is that what they conducted was a reproduction screening, and the purpose of that screening is not to say if the material is or is not a reproductive toxicant. Its purpose is to indicate whether or not it should be a high priority for a full guideline type of study.

So it's, to me, inadequate to say it's been thoroughly evaluated for reproductive toxicity. It may be adequately tested for the purposes of this list --

MS. HECK: Let me see if I can take a stab at it.

The end of the phrase is "adequately tested as required." So you don't have to weigh in with, we know everything we need to know about the compound, but whether or not the legally required tests have been concluded.

CHAIRWOMAN BURK: We have one public comment. Ron Shiotsuka from Bayer Corporation.

DR. SHIOTSUKA: I'd just like to offer a few comments in support of removal of HDI from Section 14000(c). Next slide, please.

I'm Ron Shiotsuka, toxicologist for Bayer Corporation. I'm speaking today on behalf of the American Chemistry Council's hexamethylene diisocyanate

panel. I'll try not to reiterate what was already presented by staff.

The HDI panel made the following request that the Section 14000(c) list of chemicals for which EPA has already required testing under TSCA Section 4.

HDI was listed for, as said earlier, reproductive toxicity screening and teratology testing. Testing has been completed. No reproductive or developmental effects were identified. I'll go into a little bit more detail on that in my subsequent slides. Therefore, we request that HDI should be deleted from Section 14000(c). Next, please.

The testing. EPA proposed HDI based on an exposure finding but not a hazard finding. That was the basis for their request for testing. The panel members entered into an enforceable consent agreement in 1997.

Testing included the studies that were already mentioned.There were two studies. Testing was completed in 1999. Journal articles were published from these studies in 2000 and hard copies were submitted to the committee in the original request from ACC for de-listing.

I'll briefly go over the two studies. The reference for the publication is shown there.
The study was the standard developmental toxicity study

by inhalation exposure. It's a GLP study.

Sprague-Dawley rats were used, 30 females per group. Test concentrations are shown there. The 0 means air exposure group. Three exposure concentrations to HDI. The HDI tested was analyzed and found to be 99.7 in terms of purity.

The exposure regimen was six hours per day daily for days zero through 19 day of gestation. Day 0 in this case was the day there were found to be sperm positive. Exposures were by inhalation.

The results. Maternal toxicity was evident at the mid and high concentrations. This was based primarily on the histopathological lesions in the nasal turbinates.

The respiratory tract has been determined through a series of other studies. The subchronic, chronic inhalation toxicity studies of HDI that the respiratory tract is clearly the target organ, it's a portal entry effect. And here, too, we saw evidence of acutely irritating effects of HDI. We saw hyperplasia. Most significantly we saw degeneration of the olfactory epithelium.

In a publication in reviewing the findings of the chronic study -- and I'll show you the reference in a minute -- Foreman and others concluded that

degeneration of the olfactory epithelium is clearly an adverse effect.

It was based on the relationship between exposure concentration and incidence of that lesion and severity of that lesion, and the lesion certainly is not a reversible effect.

So that lesion, a degeneration of olfactory epithelium which we saw here, too, at the mid and high doses, was considered an adverse effect.

Also, in this study there was a statistically lower body weight at the high concentration of .3 ppm. There were no compound-related effects on reproductive parameters, embryonic endpoints including pre- and post-implantation loss and resorption, no effects on litter size, number of fetuses per implantation site, fetal or placental weights.

There were no compound-related effects on fetal external, visceral or skeletal findings. There were no compound-related effects on fetal or litter incidence or total malformation or variations.

Therefore, the conclusion is there is no evidence of developmental toxicity or teratology based on this study. Next slide, please.

This is a study where the reproductive toxicity was screened, and the reference shown there, you have a

hard copy of that reference.

The test was conducted according to OECB guideline 422. It's a GLP study. Sprague-Dawley rats were again used, 15 per sex per group, three test concentrations, including the air exposure control. Again, the same batch of HDI was used for this study as was used for the developmental toxicity study. It was analyzed to be 99.7 percent pure.

Exposure regimen is shown here. Six hours per day daily for two weeks of premating. Exposure continued during the mating phase and through gestation to day 19. Exposures were by inhalation exposure.

The findings. Maternal toxicity, again, the same lesions in the nasal turbinates were observed here at the mid and high concentrations.

In addition, statistically significant lower body weight was observed for females, and 6.5 percent is a difference between the high concentration and the control group.

Reproductive and liver parameters. There were no compound-related effects on mating, fertility or gestational indices. There were no compound-related effects on liver size, mean pup weights, gender distribution, nor on live birth.

There were no histopathologic findings in male

or female reproductive organs. In conclusion, no compound-related effects on reproduction, gestation or early neonatal development. Next, please.

There is an additional study, and this is the chronic toxicity study, again, by inhalation. The first reference is that of the final report from the study. The second reference there by Foreman et al. used the study that -- or was the manuscript that I referred to earlier where the non-neoplastic lesions from the chronic study was evaluated for any adverse effect.

I have a hard copy of that which I don't think we have forwarded to the committee, but I will leave with the committee.

In this chronic study, Fisher 344 rats were used, 60 rats per sex per group. Test concentrations, as you see there, are 0, .005, and the high concentration of .16 ppm, slightly lower than the .3 concentration used in the other studies that was mentioned earlier. Exposure regimen, six hours per day five days per week for two years. Again, inhalation exposure. Next slide, please.

Results. There was a slight weight loss of about five percent and anemia in the females. Again, the primary site of compound-related lesions was the respiratory tract. I already described those lesions,

so I won't go into that again.

Reproductive system. There were no compound-related changes in organ weights or histopathic lesions for males or females. Therefore, we conclude that this provides supportive evidence for the absence of HDI-related effects on the reproductive system even after chronic exposures. Next, please.

EPA status. This was described by the staff presentation, I think, and I will not go into the details here. It's consistent with what you heard earlier.

The last two points is that EPA's results showed no reproductive or developmental effects observed. EPA listed the status of HDI testing as closed.

Conclusion. HDI should be deleted from Section 14000(c); that is, to maintain accuracy, that EPA no longer requires testing, no further EPA action is anticipated, results indicate HDI does not pose a reproductive or developmental toxicity hazard.

Thank you.

CHAIRWOMAN BURK: Thank you.

Were there any questions for Dr. Shiotsuka?

Colleen, how do you want us to proceed?

MS. HECK: I'll let Jim weigh in as well. Again, you can have extended or limited discussion, as

you please. At some point, it is an action item to poll the committee and see if they are comfortable removing the chemical from the list. So the three options are to keep it on, take it off or decide that you don't have enough information to act one way or the other.

CHAIRWOMAN BURK: Jim, do you agree?

DR. DONALD: I don't have anything further.

CHAIRWOMAN BURK: Discussions by the committee?

DR. ROBERTS: It's not really discussion. It's just a comment. In this case, the dose levels in both studies are limited by the localized effect -- the respiratory effect. It's one of those cases where we probably could not get up to a systemic toxicity level. You see that for humane reasons in animal research.

I did want to take a slight issue with the last statement of the presenter that it's been shown not to be a developmental reproductive hazard. Because it's a repro screen, it has not been show to be a reproductive hazard.

CHAIRWOMAN BURK: I agree. We're not determining whether it is or isn't. All we're determining is whether it has been adequately tested and meets the criteria for being removed from Section 14000. If anyone wanted to put it on our list of chemicals to consider later, we certainly could.

Let's make a motion, I guess, that we remove 1,6-Hexamethylene diisocyanate from the Section 14000 list of chemicals that have not been adequately tested.

All those in favor of removing it from that list, raise your hands. It's seems to be unanimous.

All right. The next agenda item is item VI, a discussion item. This is a request by the Natural Resources Defense Council to reconsider the National Toxicology Program as an authoritative body, and Dr. Denton will speak on that first.

DR. DENTON: This item is on the committee's agenda because on November 26 I received a letter from Gina Solomon of NRDC in which -- the letter states that she would like to petition us, or me, to add this item to the agenda.

We're bringing it to you not only because it was petitioned we put this on the agenda, but because we're looking for a directive that the committee wants to take on this.

Essentially, just to remind you, in 1998, the National Toxicology Program establish the Center for Evaluation of Risks to Human Reproduction. At a July 1998 meeting, this committee reconsidered NTP along with other authoritative bodies for either retaining NTP as an authoritative body or not retaining NTP as an

authoritative body.

As you know, the authoritative body provision is another way that chemicals get on the Proposition 65 list, and it's this committee's authority, responsibility to designate which bodies are considered authoritative bodies for that purpose.

During that discussion in July, it was brought to your attention that NTP was probably designated as an authoritative body because of its expertise in cancer identification.

At that time, this committee decided to remove NTP as an authoritative body -- or de-designate NTP as an authoritative body for repro toxicity until such time as the Center for Evaluation of Risks to Human Reproduction was operational. When that Center was operational, then you would reconsider the designation of NTP as an authoritative body.

Thus, we come to this letter from Dr. Solomon requesting now that the committee consider the designation or consider re-designating NTP as an authoritative body based upon this Center.

In looking at this, OEHHA -- we have kept in close contact with where this Center is because we were directed by this committee to keep informed about the Center and to bring it back for your consideration.

The Center is up. I guess it's just the terminology of the term operational. We were, I guess, giving the Center enough time to have a body of information so we could bring it back to you so that you would be able to make a judgment whether or not the Center should be an authoritative body or whether NTP should be an authoritative body. Dr. Solomon believes it is time now to bring the Center back.

I think there are two things before the committee. First of all, whether or not you would like to consider at your next meeting, this Center or even NTP as a whole as an authoritative body.

And secondly, if you do want that put on the agenda, what kind of information would you like to be brought before you to make sure you deliberate and make sure you have enough information to make that decision.

Also, it goes without saying, but I will say it, that this decision there are many individuals, associations, people that are interested in your opinion and your designation of this or not as an authoritative body. So we would need to do a public process and solicit public input on this proposal.

So with that, I would like -- and with your approval, I would like George or Mari just to give a quick update where the Center is, perhaps to aid you in

deciding whether or not you believe it's time now to reconsider this for designation; and, if so, what information you would like to see at the next committee meeting.

DR. GOLUB: I can speak a little bit from my experience because I was on the first of the committees that met.

So the process involved was, first of all, the program had to be established within the agency and a structure was created for the program. And secondly, a contract was let to an outside vendor to support the committee meetings. A process was also established to nominate chemicals and prioritize them for consideration by the committee. So the CERHR is basically a panel of experts that's convened, a different panel for each chemical.

And so far one panel has been convened and completed its process, which was to review the information on, I believe it was, five phthalate agents, to produce review documents and to produce a conclusionary statement about the developmental and reproductive toxicity of these agents.

A second panel has been created and has met concerning methanol. The draft document has been produced but not finalized.

A third panel has been selected but has not yet met, and I don't recall what the chemical that they're going to be considering is.

So the process has been established. It has been gone through completely once, and there are two other reviews underway. I think that is the current status of the Center.

It has a website. They're trying very hard to have complete transparency and accountability. So the website does tell you exactly where they are with the process for all the chemicals. It also contains the documents that they've produced and the conclusions that they've reached.

Are there any questions that I can answer on that?

CHAIRWOMAN BURK: One question. The documents that come out, there's a conclusion, and is it in a particular format that would be consistent from one document to another?

DR. GOLUB: There's no formula that's part of the process. I don't know if that will evolve. In the panel that I was on where the phthalates were considered, we did try to frame the conclusions on each of the phthalates in a similar manner in terms of a level of concern. So it would be low concern, medium

concern or high concern.

I don't know if that has been picked up or will be picked up by later panels, but it isn't specified in the process.They don't get a script to read like you do to convey their conclusion.

But it is intended that the panel will reach a conclusion that will be helpful for public health decision making.

CHAIRWOMAN BURK: And it would be something that could translate into Prop 65 terms? Because, you know, if you just have low, medium, high, we'd have to decide.

DR. GOLUB: I think in all of the authoritative bodies a judgment has to be made whether it's suitable for Prop 65 on a case-by-case basis. So that always has to be done one chemical at a time.

DR. DONALD: Just as point of information, the other chemicals are 1-Bromopropane and 2-Bromopropane, and actually that committee has met and there is an initial draft of each of those documents available at the website.

DR. DENTON: Also, I forgot to mention that we received a letter on Friday from the Commonweal group, and they essentially support the listing of NTP as an authoritative body and would like the DART committee to act quickly so that California could benefit from the

work. They essentially sent a letter that is essentially along the same lines.

DR. JONES: Mari, what's their motivation for doing this?

DR. GOLUB: I believe that there are several public health issues where they thought that this kind of an expert review would be helpful at the federal level and that the National Toxicology Program was an appropriate place for it to come forward.

I think it has to do with concern about reproductive health in the public health community and the need for guidance at the federal level or the desire to provide it.

DR. JONES: Could you give at least me just a thumbnail sketch of the philosophy and political motivations, et cetera of the Natural Resource Defense Council?

DR. GOLUB: I'm sorry. I --

DR. DENTON: The individual who was to be here to testify is, unfortunately, not here because of illness. So there is no one who can speak for that group here.What we have before us is the letter.

DR. GOLUB: It's an advocacy group, I think, would be fair to say.

CHAIRWOMAN BURK: I think it's clear we need to

decided whether, one, we want to consider it; and then if we do, we decide what information we want to have.

So can I get a consensus whether we want to take this up -- obviously, not right now, but at a future meeting? I see nodding of yes.

So the issue would be then what sorts of information would we want to have in order to make our decision.

DR. DENTON: If I might just chime in here, too, would the committee want us to consider the re-designation of NTP or the Center within NTP? That's one element here which needs to be also laid out.

DR. KEEN: I would like to echo back to the meeting where we initially suggested they should not be considered an authoritative body until this was done because the composition of the committees were not necessarily what was appropriate.

So I'm very much in favor of considering this new particular unit as at least being considered as an authoritative body. I would suggest that the rationale for why they were not considered an authoritative body is still in place.

DR. SAMUELS: I think there was concern originally that NTP did publish reports on occasion, studies of substances which had reproductive endpoints,

but the publication of the report didn't meet our criteria for what an authoritative body was simply because their staff did research.

So I agree that -- unless NTP publishes the conclusions as their own, in other words, that that's the next step in the process, then I would like to see two things.

One is, I certainly would like to see what the reports look like and a description of the process so that we know high concern is a similar designation to what we consider clearly shown by scientific principles or close to it.

Number two, as to whether NTP or the Center itself is the designated body, we need to know, and perhaps we already do know, whether or not NTP will take the statements from these reports and list the chemicals in some fashion as IARC would or as we would. So we need that information. So I agree.

CHAIRWOMAN BURK: Any other suggestions for information that we'd like to have.

DR. ROBERTS: From an administration of programs point, I would like to have an understanding, since this is contracted out, on what that relationship is in terms of long-term and criteria guidance that any contractor would be having so that we know that the quality of what

we might see now from a first contractor is going to be something that will be consistent in the future.

DR. MILLER: I think it's important that we keep in mind what the criteria are we use for listing under Prop 65 because our criteria can be quite different from others, such as NTP.

I think their program, they're looking at -- Mari, correct me if I'm wrong -- they're looking for an evaluative] review of the different chemicals. They're looking at potential risks and deficits, deficiencies in terms of data that's available and whether or not that's clearly shown and whether they're even attempting to say whether something is clearly shown or whether they're putting together a more evaluative document.

Would you like to comment on that?

DR. GOLUB: I don't think that any of our authoritative bodies make a statement about clearly shown. It's something we have to deal with in trying to use the work that they do, and I think that's the purpose of the law is, to make sure that we're not redoing what has already been done.

I don't know if that -- they certainly will not make a statement about clearly shown. They do have a process that they follow. It's very similar to the U.S. EPA in terms of guidelines for evaluating the toxicity

studies.

The documents that they produce will review the literature, and they typically do contain -- the drafts that I've seen on the phthalate, they do typically contain critique of the study, strengths and weaknesses of the study and so forth.

The statements that they make at the end are not going to line up with our process necessarily. For example, I think exposure is more of a concern in their statements than it is here. We don't talk much about exposure, but there is an entire exposure section in their documents, and it is part of the discussion and goes probably into the final statement.

So it certainly is not the case that they're going to produce a list of categories that are parallel to Prop 65 so that we can say, yes, it's like ours, or, no, it isn't. It's not going to be that type of an output. At this point, it doesn't look like it.

The statements that they make are quite long. There's no fill in the blank type of a format. I imagine it will continue like that. Certainly I can't speak to what the plans are for the future, just what's happened so far.

DR. SAMUELS: I guess we have to see more examples. If this program actually does an evaluation

of the quality that the staff here does, even if it doesn't make the decision that we would make, it certainly would help us avoid duplication --

DR. GOLUB: In the previous use -- I think what you're saying is that we might be able to use the documents for deliberations without the decision. I don't think that's very consistent with the authoritative body process.

Maybe Colleen would like to say something about that.

MS. HECK: I think Dr. Samuels is on the right track. Any document that would come out of the Center or NTP would have to be compared side by side against our regulation to see if it meets several requirements, the formality and finality and then also scientific sufficiency.

The lead agency, OEHHA, then performs that task, and then that becomes a chemical that doesn't take up the committee's time and is not revisited de novo.

I am sympathetic to Dr. Miller's concern that what they put out actually could lead to a listing. I think the fairest thing to say at this point is nobody knows for certain what percentage of these will.

It appears from the limited information and track record that they have it's certainly well within

the realm of possibility that the documents could case by case, I don't want to prejudge, support a potential listing.

So that, of course, would be the kinds of things you would want to think about if you did, in fact, entertain re-designating NTP in toto or the Center because I can only assume the committee would not want to identify them only to lead to a null set of documents that would support listing.

DR. ROBERTS: I think one of the things that would be nice to see prior to final discussion are the final reports that come out of this program or, in lieu of that, draft reports where available.

From a practical side, is looking at this as an authoritative body going to have an impact on the chemicals we are going to review at our next meeting? Is this a resource issue with OEHHA?

DR. ALEXEEFF: No, it wouldn't have a negative impact on the chemicals you would be considering. At this point, it doesn't appear there is any overlap.

The other point that I --

DR. ROBERTS: I'm sorry. What I meant was: Are people who would normally be looking at writing up document such as we have be not looking at chemicals that are going to be brought up and instead are looking

at the Center?

DR. ALEXEEFF: Apparently, it would not be a substantial impact because we would primarily be supplying you with the reports that they have generated.

The real question in my mind is whether there are a sufficient number of reports that you can actually make a fully informed decision that the type of information they have, the type of decisions they make are applicable, at least in some general sense.

DR. ROBERTS: From that standpoint, Mari, you have been involved with one of the panels and perhaps having some idea of when we might have our next meeting, have you thought of how many of these reports might be final by our next meeting?

DR. GOLUB: I don't know for sure, but I wouldn't doubt -- the first panel did five reports, so in a way they're not all independent for your consideration -- but I wouldn't doubt by the next meeting there would have been three panels that had met and produced at least draft documents.

CHAIRWOMAN BURK: Okay. Is there anything further? We hope that will be on the agenda for the next meeting.

We're up to item VII, staff updates.

MR. ROBERTS: Gary Roberts. If this does reach the committee's agenda at the next meeting, it would be my request that the materials made available to the committee be made available at the same time that the hazard identification documents are made available so that everyone has sufficient time to look at them and possibly prepare comments. That's assuming that the undertaking would be examining the Center. I think a greater lead time would be necessary if the undertaking was examining the NTP as a whole.

It's my understanding, in response to Dr. Samuel's question, that the documentation related to the Center's process resides with the Center. There is a final transmittal document that the NTP's Center makes, but it is a transmittal document of the Center. So based on all that I've heard today, I don't see any need to re-examine the NTP as a whole.

MS. HECK: Well, that would certainly be up to the committee to --

CHAIRWOMAN BURK: I think I heard the same thing that we really weren't ready -- in fact, when we made the decision several years ago, it was we would look at it again in light of the Center. I don't think we ever said we'd look at NTP. Maybe that would come out, but it wouldn't be at the next meeting.

If I heard the committee correctly, we just want to look at the Center, we want to look at the documents and these other things that were suggested so we can get an idea of the process and the output.

As far as I'm concerned, I don't think it would take a whole meeting to do this. I think that's what Linda was trying to say. We don't want it to get in the way of staff or our time in considering chemicals.

DR. DENTON: And we would get the information at the same time to the public as we would send it to the committee.

CHAIRWOMAN BURK: Are we ready to move on? I think Cynthia Oshita has a report.

MS. OSHITA: I'd like to just take a very few moments to brief the committee members on the status of administrative listings under Proposition 65.

Since the DART committee last met in June of 2000, OEHHA has administratively added 20 chemicals to the Proposition 65 list. We have added nine as causing reproductive toxicity and ten as causing cancer. One chemical was added as causing both reproductive toxicity and cancer.

We have included a complete current list of the chemicals within your meeting binders and have highlighted the newly added chemicals for your ease of

reference.

In addition to that, we also have several other chemicals for which we have received comments, and these chemicals are still under consideration for administrative listing, and we hope to make final decisions on those in the near future.

CHAIRWOMAN BURK: Thank you.

Next we have prioritization process/random selection.Colleen Heck.

MS. HECK: Again, this is an item that is probably much more of concern to your counterpart committee, the CIC, than yourselves since we have not to date performed any prioritization of chemicals for this committee's review based on our prioritization process and procedure that we employ. We have, however, done so on three occasions for the Carcinogen Identification Committee, most recently in the fall of this year.

Very briefly, OEHHA, as the lead agency, has developed a process for prioritization of chemicals since we cannot simultaneously look at all the chemicals that we have not yet addressed. We work on them in a particular fashion, and then they ultimately, if they work through the process, come to the respective committees.

The initial component of that prioritization

consists of an actual random selection. A challenge was brought to this process by the Chemical Industry Council.

The challenge was lodged with the Office of Administrative Law, the state agency who has authority to tell virtually every other state agency that a particular practice they're engaging in is a regulation within the meaning of the law and has to be adopted as such but that it has not been. That was the nature of the challenge filed with the Office of Administrative Law in January of 2000.

The Office of Administrative Law informs us that they're about ready to make a decision on that challenge. OEHHA filed a reply indicating that we felt the prioritization process was, indeed, not a regulation and, therefore, not subject to adoption. As such, we anticipate a decision by the end of this month or the first month of next year.

The possible outcomes are that the challenge is correct and what we're doing is a regulation and the practice we have in place now, or some other alternative, would need to be adopted as a regulation.

The other possible outcome is it's not a regulation and we can continue doing it the way we are doing it or are, in fact, free to change it.

So it really hasn't affected this committee much, but there may come a time when we work through the backlog of chemicals for this committee that we actually do engage in prioritization as outlined our policy.

Jim Donald, anything to add?

DR. DONALD: No.

MS. HECK: As for the next item, I'm pleased to say I have nothing to report under Proposition 65 litigation and rulings.

We've had no final outcomes in the fairly few legal challenges that we do have pending in various parts of the state. So nothing to report under item "C."

CHAIRWOMAN BURK: Thank you.

Are there any other public comments?

Okay.Item VIII, summary of committee actions, closing remarks.

Dr. Denton.

DR. DENTON: At the committee's meeting today, the committee did not choose to list metribuzin as a chemical known to the state to cause reproductive toxicity.

The committee chose not to renew the listing -- or not to keep on the list cyclohexanol or 2,4-DP.

And for item IV, the consideration of chemicals

for possible removal from the list, Section 14000, the committee decided to remove from that list N-methylpyrrolidone -- all the ones in "A" and also in "B."

The committee has chosen to put the Center of the National Toxicology Program on their next agenda item. That we will undergo a public process and the committee has given us some direction as far as the information that they would like to see brought before them again. I understand that all of those reports are now on their website.

I guess I'm the one to turn it back to you to adjourn the committee or --

CHAIRWOMAN BURK: Okay. Do I hear a motion that we adjourn?

If there is no further business, then we are adjourned. Thank you all very much for your participation.

(Meeting concluded at 1:40 p.m.)

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REPORTER'S CERTIFICATE

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STATE OF CALIFORNIA)
) ss.
COUNTY OF SACRAMENTO)

I, PHYLLIS MANK, certify that I was the Official Court Reporter, 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 1 through 126, inclusive, constitute a complete, true and correct record of said proceedings:

In witness whereof, I have subscribed this certificate at Sacramento, California, on this 4th day of January, 2002.

PHYLLIS MANK, CSR No. 5093