MEETING

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OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

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Mr. Stan Landfair, McKenna, Long and Aldridge, representing 3M

Dr. Matthew G. Marin, AstraZeneca

Dr. Timothy Pastoor, Syngenta

Dr. Laura Plunkett, AMVAC

Dr. Ashley Roberts, Cantox

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PROCEEDINGS

DIRECTOR DENTON: Good morning. Is this on?

I can't hear myself. Is it on?

My name is Joan Denton. I'm the Director of OEHHA, and it's my honor to welcome you all and to introduce the Panel. This is the meeting of the Carcinogen Identification Committee under Proposition 65. And to my immediate left -- or no to the far end I'd like to welcome the Panel members. Dr. Hopp, Dr. Hamburg, Dr. Eastmond, Dr. Mack, and then to my right Dr. Landolph and Dr. Wu.

As always just a couple of things the restrooms are out the door to the windows, either the right or the left, you'll run into the restroom. And if we have an emergency, there's an exit door here, and obviously an exit door where you came in, and we just go downstairs and out the building into the park across the street.

This actually we've scheduled for a two-day meeting. And we did that because we wanted to give the panel enough time to consider all the items on their agenda. And if the meeting needs more time than today, there is additional time scheduled for tomorrow. But we'll just see how the meeting evolves.

So I think that's it for my formal introduction. And before I turn it over to Dr. Mack to conduct the

meeting, I know that our Chief Counsel, Carol Monahan-Cummings, wanted to make a couple of remarks.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. Can you hear me?

I just wanted to, given that the Committee only meets once a year, and you have a lot of other duties that you do throughout the year, I wanted to remind you of a couple of things regarding your work here, in particular concerning the consideration of chemicals for possible listing under Prop 65. I know you get a lot of comments from interested parties, particularly over the last couple years about whether or not the standard has been met for a particular chemical. And there's often arguments that this is a legal decision that you're making. And I just wanted to clarify that, in fact, it's not.

Obviously, the decisions you make here about the listing of chemicals can have a legal effect later, if the chemical is put on the list or not put on the list. But you were appointed because you are experts in your field. Your scientific expertise is what the Governor appointed you for. And so we're asking you to apply your scientific judgment to the questions that are presented today.

A couple of specifics. You know, hopefully you noticed in your binders that in the first binder, not the one with all the studies, that we included the criteria

that the CIC Committee adopted many years ago to guide them on making these kinds of decisions. And those are the criteria that you should be looking at in terms of if you have an issue about whether a study is sufficient or, you know, the weight of the evidence as it goes one way or the other.

If you have specific questions on that, I can try and answer, or we certainly have a lot of scientific staff here that are probably better qualified to do that.

A couple of things I wanted to mention is that the identification of a chemical as showing a particular -- a hazard such as carcinogenicity can be based on either human or animal data if that data is sufficient, the issue of exposure to a chemical in California, in the California population, is not part of the question that you're asked to consider today, nor is the question about whether or not warnings will be required for particular exposures.

To some extent, you do consider exposure when you're prioritizing chemicals, which will be done later today, but that is not a concern for you this morning. So I just want to make those initial remarks and ask if you had any questions about that before you start considering continuing with your meeting agenda today?

Okay, thank you.

CHAIRPERSON MACK: Okay, I'm Dr. Mack. And I think we'll just get off to a running start if we can. So we're going to start with the evaluation of two chemicals for listing, as opposed to the prioritization of chemicals for evaluation.

So let's start with 1,3-DCP.

Martha.

(Thereupon an overhead presentation was Presented as follows.)

DR. SANDY: Thank you, Dr. Mack. And Dr. David Morry will be giving the presentation on 1,3-DCP.

David.

DR. MORRY: I'm Dr. David Morry, Staff Toxicologist with OEHHA.

Okay. I'm still high from last weekend's Monterey Jazz Festival, so this will be a spirited rendition of the hazard ID for 1,3-Dichloropropanol. It's a nice three carbon compound with chlorine on either end, and a hydroxyl group in the middle, which makes it an alcohol.

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DR. MORRY: Okay, so let's -- in discussing the exposure, there can be exposure both industrially and from food. First of all, the industrial exposure can occur because 1,3-DCP is a high production volume industrial

chemical. The industrial process involves using 1,3-DCP to make epichlorohydrin, which in turn is used to make a wide range of industrial products, including glycerin, plastics, epoxy resins elastomers.

And then the 1,3-DCP can also be used directly to make Telone II, which is a pesticide fumigant.

Next slide.

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DR. MORRY: DCP can be formed in foods during processing. It's also present in foods to which acid-hydrolyzed vegetable protein has been added, which includes soy sauces that are made with hydrolyzed vegetable protein. It's also in foods to which hydrolyzed vegetable protein has not been added, such as malt products, sausages, battered fish filets. It can enter food from packaging, and -- because it's used to make a copolymer that's a wet strength coating for paper products. And also it's used to make anti-flocculants and coagulants for water treatment, so it can show up in drinking water.

So 1,3-DCP, as we showed in the industrial processes, is used to make other products. But these other products contain amounts of 1,3-DCP, and thereby there can be exposure, either through food, beverages, drinking water, or as we said, industrial exposure.

So that's a very quick overview of the possible routes of exposure or possible ways of exposure to 1,3-DCP.

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DR. MORRY: Okay, we're going to be discussing the evidence. Let me give you a quick overview of it. First, we'll talk about the animal carcinogenicity data, which comes from one report done by Hercules published in -- or given to the EPA in 1989.

Then we'll talk about genotoxicity data. We'll go over the in vitro cell transformation assay. We'll talk about the metabolism of this chemical. We'll consider structure activity relationships. And lastly, we'll touch on some possible mechanisms by which the chemical can be carcinogenic.

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DR. MORRY: The animal studies consist of two kinds a studies. There are carcinogenicity assays. All of these came from this Hercules paper and have been reviewed in several reviews since then. There were carcinogenicity assays that were done in male and female Wistar Han KFM rats. And those were 104-week studies that were done by drinking water exposure.

Also, there were chronic toxicity assays done in the same kind of rats. And those lasted for 26, 52, or 78

weeks. And those were also done by drinking water exposure.

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DR. MORRY: Beginning with the 104-week carcinogenicity assays. These were done in Wistar Han rats. There were 50 rats for each sex and dose. The male rats were dosed with 0, 2.1, 6.3, and 19 milligrams per kilogram per day. And the female rats with 0, 3.4, 9.6 and 30 milligrams per kilogram per day. So these doses are calculated based on drinking water consumption and the body weight of animals.

Complete histopathology was done on all control and high-dose animals in these studies. And the low- and mid-dose animals that died before 104 weeks before the end of the study.

There was also limited histopathology done on the low- and mid-dose animals that survived to week 104. And those limited studies included the adrenal glands, the esophagus, the kidneys, the lungs, the thyroid, and the tongue.

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DR. MORRY: Okay. Looking at the tumor incidence in the -- to begin with the male rats. There were tumors in both male and female rats in this -- in these studies, and they appeared in four different sites and in both

genders, both sexes. So we'll begin with the male rats looking at the kidneys. There were tubular adenomas and carcinomas, which were significant both by pairwise comparison at the high-dose. So you see the tubular adenomas were significant at the high dose.

The adenomas were also significant by trend test. The P value that's under the control is for the trend test, so that was a significant trend.

When you combine the adenomas and the carcinomas for kidney, the results are significant, both by pairwise comparison at the high dose and by trend. So there's evidence for a dose response appearance of adenomas and carcinomas in the kidney of the male rats. In the livers of the male rats, again there are adenomas and carcinomas. When combined, they're statistically significant both by pairwise comparison and by trend. The carcinomas were significant by pairwise comparison.

In addition, there was one hemangiosarcoma in the liver, and that was in the high-dose animals. Note that there were no tumors in the control animals for the kidney.

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DR. MORRY: Now, looking at the thyroid in the male rats. Again, we have adenomas and carcinomas. And when they're combined, they're statistically significant,

both at the -- well, they're significant by pairwise -- excuse me, they're significant by trend. And in the high dose, they have a P value of .052. So that's not quite -- doesn't quite meet the .05.

Moving on to tongue tumors, which are very rare in this particular strain of rats. There were tongue tumors, both squamous cell papillomas. And squamous cell carcinomas. And they were significant, both the papillomas and the carcinomas. And when they're combined, they're highly significant, both by pairwise comparison, and by trend.

Also, there were two other oral cavity non-tongue tumors that appeared at the high dose in the male rats. So that covers the male rats.

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DR. MORRY: Now, the female rats, the female rat study. Again, there were adenomas and carcinomas in the liver. And the carcinomas were significant by trend and pairwise. And when combined, they are significant by -- the adenomas and carcinomas combined, they're significant buy pairwise and by trend.

The 25 percent of the adenomas and carcinomas in the liver metastasize to the lungs of these animals. Also, there was one hemangiosarcoma, which appeared at the high dose in the liver of the female rats.

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DR. MORRY: The two other sites in the female rat were the thyroid and the tongue. The thyroid follicular cells when combined were significant by trend. And the tongue tumors, which are rare, are significant when combined by pairwise and by trend. The carcinomas were not quite significant at the high dose, but the trend for the carcinomas is highly significant.

And there were other -- there was one other oral cavity tumor, non-tongue tumor, at the mid-dose in the female rats.

So we've looked at both male and female rats. In the male rats, there were tumors in four sites. In the female rats there were tumors in three sites. And all of these kinds of tumors showed dose-dependent response and were highly statistically significant, quite statistically significant.

There were also a set of studies on chronic toxicity. And we'll look at the 78-week chronic toxicity study.

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DR. MORRY: In the male rats in the kidney, there was one tumor at the high does. In the liver, there were three at the high dose -- three hepatocellular carcinomas at the high dose. And that was significant by trend.

There was one thyroid tumor, and one squamous cell carcinomas of the tongue. So what we're seeing here is that even at an earlier time, there is already beginning to be an appearance of some of the tumors.

In the female rats, it's somewhat more dramatic.

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DR. MORRY: In the liver, the hepatocellular carcinomas actually appeared even at this earlier stage. And we see that they're significant at the high dose and also by trend test. The tongue tumors, there was one tongue tumor that appeared at the high dose in the female rats.

So overall, we have tumors appearing in male and female rats in multiple sites at the 104 week time point, and a few tumors, in some cases, statistically significant, even at an earlier time point.

And all of it indicates a dose response relationship between exposure to the chemical and the appearance of the tumors.

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DR. MORRY: In vitro genotoxicity data, we've summarized this in a brief slide. There's a much longer table in the report. There's quite a lot of in vitro genotoxicity data. And in 1,3-Dichloropropanol was positive in numerous in vitro assays.

So the Salmonella reverse mutation assay, it was positive only with the presence of S9 in the two strains that indicate frame-shift mutations. It was positive with and without S9 in the two strains that are indicative of base pair mutations. There is also a salmonella forward mutation assay, which it was positive with and without S9.

There was an E. coli reverse mutation assay. It was positive with S9. And E. coli DNA repair assay, positive with S9. So in some of these tests, S9 appears to be necessary to make the chemical mutagenic.

The mammalian cell -- there were mammalian cell assays in mouse lymphoma, thymidine kinase assay, and in a human HeLa cell DNA synthesis mutation assay. And these were positive with and without S9 activation -- S9 enzymatic activation.

Sister chromatid exchanges were positive in V79 hamster cells, and Chinese hamster ovary cells with and without S9 activation. Chromosome aberrations were seen in the Chinese hamster ovary cells, also with and without the enzymatic activation.

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DR. MORRY: In vivo genotoxicity data, there were three assays, and all of them were negative. The Drosophila somatic mutation (wing spot) assay, there was Wistar rat, bone marrow micronucleus assay and a Wistar

rate unscheduled DNA synthesis assay that was done with rat liver.

Several other -- we mentioned in our report that several -- a couple of other known carcinogens, IARC carcinogens have also been reported to be negative in every in vivo genotox test that they've been tested in. This includes -- this would be 2,3-Dibromo-1-propanol, which is an IARC carcinogen, and Telone II which is an IARC carcinogen.

There's a mistake in the executive summary of our report. Instead of Telone II, it says DBCP. We got it right in the body of the report, but it's wrong in the executive summary. But DBCP is positive in a whole strain of in vivo genetox assays, but Telone II has been negative in the in vivo genotox assays in which it's been tested.

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DR. MORRY: There was also a report of a mouse cell in vitro malignant transformation assay. This is an assay for change in the morphology of the growing cells to exhibit the piled up not contact inhibited phenotype, which is characteristic of cancer cells.

This was done with M2-fibroblasts -- mouse fibroblasts. And you'll note that from the control up to the highest dose, there's an increasing number of these transformed colonies, quite statistically significant. It

falls off at the top dose. And the probable reason for that is that the plating efficiency of the cells dropped from 22 percent down to three percent indicating that the chemical was killing off the cells at the high dose.

But at the other doses, we have quite a strong relationship between treatment with 1,3-Dichloropropanol and the appearance of this in vitro transformed phenotype.

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DR. MORRY: Now, we move on to the complicated issue of metabolism. So 1,3-Dichloropropanol is the chemical that's shown in the green box. And there are two major pathways. All of this slide is based on studies in live rats, and also with rat liver extracts. So 1,3-Dichloropropanol, there are two main pathways for metabolism of it.

It can be metabolized directly to 1,3-Dichloroacetone. And this chemical has not been evaluated by IARC, but it is a mutagen, and it is a skin tumor initiator in mice. The other pathway is to Epichlorohydrin, the same as the industrial change. Epichlorohydrin is, of course, an epoxide, which is an IARC carcinogen, highly mutagenic chemical.

And epichlorohydrin is combined with glutathione, and then produces this mercapturic acid, which is excreted in the urine.

Epichlorohydrin, in turn, can be metabolized to this compound, which is the one we'll be talking about later this morning. So everything from here on down is the same for this compound that I'm talking about and the compound that Dr. Tomar will be discussing.

So the 3-MCPD can be converted to glycidol, another epoxide, similar to epichlorohydrin, also an IARC carcinogen, also highly mutagenic.

Glycidol can be converted to glycerol, and then carbon dioxide or it can be combined with glutathione and go through this pathway down to another mercapturic acid, which is excreted in the urine.

The other pathway is from 3-MCPD over to a beta-chloroacetaldehyde, which then can be metabolized to beta-chlorolactic acid and oxalic acid or over this way to 1,2-propanediol. So many of the chemicals on this slide we'll be discussing shortly with regard to structure activity relationships.

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DR. MORRY: So structure activity considerations. We're going to discuss 10 structurally related halogenated compounds. And 7 of the compounds we'll discuss are IARC and Prop 65 carcinogens.

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DR. MORRY: We've grouped them into groups. And

the first group are halogenated propanols. And in this group are the compound I'm talking about right now, the one that Dr. Tomar will talk about later, and then there's one more that's a halogenated propanol, and this is 2,3-Dibromo-1-propanol which is an IARC 2B carcinogen, and a Prop 65 carcinogen.

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DR. MORRY: Two other structurally-related compounds that I highlighted on the metabolism slide are epichlorohydrin and glycidol. These are the two epoxides, and they're both IARC carcinogens and Prop 65 carcinogens. And they're both metabolites of the chemical that we're talking about today, 1,3-Dichloropropanol.

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DR. MORRY: Here are some other three-carbon halogenated compounds. 1,3-Dichloroacetone is the compound that can be made directly from 1,3-Dichloropropanol. It's not been evaluated by IARC. 1,2,3-Trichloropropane is an IARC carcinogen.

Telone II, which in industry is made from 1,3-Dichloropropanol, is an IARC carcinogen and Prop 65 listed. And DBCP, Dibromochloropropanol is an IARC carcinogen.

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DR. MORRY: Lastly, there is two phosphate

triesters. The TDCPP, the one with the chlorine. This one we call chlorinated tris. And it's not been evaluated by IARC. If you break this compound here and convert this add a hydroxyl group to this oxygen here, or make this oxygen to a hydroxyl group, this compound is 1,3-Dichloropropanol. So this TDCPP can be metabolized to 1,3-Dichloropropanol. It's not been evaluated by IARC.

The other one is the so-called brominated tris, TDPP. This structure, by the way, is wrong in the -- in our text I put 1 -- I accidentally put one extra carbon in here, but it's correct on this slide.

And if you -- just as I said for this compound, if you break this compound here, then you get 1,3-Dibromopropanol, and that's an IARC carcinogen.

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DR. MORRY: All right. Tumor site concordance. What I've done on this slide is, if you remember from the animal evidence that 1,3-Dichloropropanol is positive in three sites, liver, kidney, thyroid and tongue. So I've only taken those sites for this table. And the top line is 1,3-Dichloropropanol, which shows that it was only tested in rats. It hasn't been tested in mice.

In rats, it was positive in all four of these in the males. And it was positive in the liver, thyroid, and tongue in females.

3-MCPD is the next compound that's going to be discussed. And it was positive in rats in males and females in the kidney. Remember, I'm only listing the sites that are 1,3-DCP, so you'll hear more about 3-MCPD later.

Glycidol, which was that epoxide, was positive in mice, in the liver, male mice, and in the thyroid in male mice and rats, in the tongue, in the case of female rats.

2,3-Dibromo-1-propanol is the metabolite of brominated tris, is positive in the liver, and in the tongue and oral cavity. 1,2,3-Trichloropropane is positive in the liver in male and female mice, in male rats, female mice and male and female rats in the tongue.

Telone II, the propene compound, was positive in male rats in the liver. DBCP causes kidney tumors in male and female rats and male -- and tongue and oral cavity tumors in male and female rats.

The two trisses. First of all, the chlorinated tris was positive in male and female rats in the liver, in male and female rats in the kidney. And the brominated tris was positive in female mice in the liver, in male and female mice and rats in the kidney, and in male and female rats in the tongue and oral cavity.

So what we're showing here is that all these other compounds that are related to the one we're talking

about today have produced positive carcinogenicity data in the same organs that this chemical -- where this chemical produced them in rodents, mice and rats. Remember, our chemical was tested only in rats.

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DR. MORRY: So possible mechanisms. First thing to emphasize is that we don't know the mechanism by which this chemical causes tumors in rats. There's a lot of possibilities that you can discuss. One would be that it might be a genotoxic chemical and cause cancer that way. It was positive in a string of in vitro assays, negative in the in vivo assays.

Another possibility is that it's hepatotoxic in the liver, causing fatty liver, which can lead to liver cancer, to hepatocarcinogenesis. There might also be a toxic -- it might be secondary to toxicity in the kidney. So you can think up different mechanisms for different organs, but you've got a chemical here that causes cancer in four different organs. So that kind of suggests a more general mechanism, such as genotoxicity or some other general mechanism, maybe epigenetic mechanism, or it could be some combination of general and specific -- and organ specific mechanisms. We just don't know.

Direct contact carcinogenicity is probable in the case of the tongue and oral cavity tumors, which are rare

in the animals -- in the rats that were tested, so there's a combination of different possible mechanisms. There can be lots of hypotheses about whether it's one of these or a combination of them. There isn't much data -- or there isn't enough data to make a choice between the different possibilities and say, well, this is the mechanism or this is not the mechanism by which this chemical works.

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DR. MORRY: Finally, to summarize the evidence. We've talked about animal evidence, consisting of rat studies and two sexes. Only rats were tested. Only one species, only one strain. Tumors appeared at multiple sites in both male and female rats, including the rare tongue tumors. And there was definitely a treatment related phenomenon in the appearance of the tumors in the rats.

Genotoxicity appeared in multiple in vitro assays, without and without S9. When it appears without -- with S9, but not without S9 it indicates that it may require some metabolism before it can be active as a mutagen.

There was an in vitro malignant transformation assay in mouse cells. There's metabolism to two epoxide carcinogens that are IARC carcinogens. And finally, we talked about some structure activity considerations, where

we showed that it's structurally similar to seven IARC carcinogens.

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DR. MORRY: And I believe that's the last slide.

CHAIRPERSON MACK: Thank you, David.

Before we sound off on the Committee, and before the public makes any comments, let me just make one reminder. And that is that we're here to discuss the carcinogenicity of this compound, and of the other compound we're going to discuss shortly, and not the distribution, even though David has described the distribution and we can see that this is a slippery stealth chemical that can go back and forth between multiple moieties under certain circumstances.

But we're interested in the carcinogenicity of this compound not where it is, and not whether it turns up in one food or another at any given time. Just whether or not there's evidence that it's a carcinogen.

So having said that, who is the lead person on this compound?

Is it David?

COMMITTEE MEMBER EASTMOND: It's Joe.

CHAIRPERSON MACK: Go ahead, Joe.

COMMITTEE MEMBER LANDOLPH: So I want to thank Dave and his co-authors for writing a very clear and very

detailed document that was extremely helpful. Good authors and great reviewers as well.

I started out by testing a hypothesis that it was not a carcinogen. And eventually I threw that hypothesis away, because, as Dave pointed out, you've got kidney tubular adenomas and carcinomas. The adenomas are statistically significant. You add them together, they're statistically significant. The hepatocellular carcinomas in the males, which is an important tumor are statistically significant. They're dose dependent. And the trend is statistically significant. And the same is true for the combined adenomas and carcinomas.

Then you also have thyroid tumors. And all these three -- all four sets in the male have a very low background. Most of them are zero, except for an adenoma or so in the liver.

The thyroid, as Dave pointed out, is dose dependent. And the trend is statistically significant for adenomas, and adenomas and carcinomas combined. Carcinomas is a little bit weak, but there is one against the background of zero.

And the tongue, which is an unusual tumor, is statistically significant for the trend, and dose dependent for squamous cell papillomas, and also for carcinomas. Although, they only appear at the high dose.

And the combined is dose dependent and statistically significant. So that's pretty strong data in that male Wistar rats.

And in the female Wistar rats, you've got three tumors, liver, thyroid and tongue. And the data is similar. I was particularly impressed by the hepatocellular carcinomas in the females that goes in control 0, 0, 1, and 36. I mean, that's a lot of tumors at the high dose, and the trend is statistically significant.

And the combined goes 0, 1, 2 and 41. And that trend is statistically significant. So that's very strong data.

You've got additional data, combined adenomas and carcinomas in the thyroid. And the tongue you again have a dose dependent induction of squamous cell carcinomas, and the trend is statistically significant.

So you've got both sexes, three tumor sites in the females, four tumor sites in the males, and most of these are statistically significant for the trend, and they show a nice dose response. And Dave pointed out, you've got a little bit more data in the 78-week study, which is positive. A little bit weaker than the longer study. And the same thing for the females. So that data is pretty strong.

The genotoxicity data, there really is a plethora of data here compared to what you often see in other chemicals. And I'm looking on page 14, the TA98 and TA100, the frame shift mutation is positive when you add S9. And there are a lot of positives for TA100, TA1535, and both of them together. So that's a pretty strong database for bacterial cell mutagenicity. And it's positive in the forward mutation and bacterial cell mutagenicity.

And in the reverse mutation, for bacteria in E. coli. And this compound induces DNA repair in E. coli. So I just see a lot of positive. And then it goes up to mammalian cells. The mouse lymphoma, TK plus/minus assay is positive with and without S9. The lymphomas, again in another assay, it's positive. And in HeLa cells, it induces DNA synthesis. This compound also induces SCEs, chromosomal aberrations. So all the in vitro data is positive.

I don't know about the in vivo data. That seems to be negative. And I don't know why that is, but that does sometime happen.

The morphological transformation study out of Hanz Marquardt's lab is positive. It's dose dependent. The trend is statistically significant. And, Dave, you convinced me completely with your elegant slide that there

are a number of genotoxic metabolites, the 1,3-Dichloroacetone, the epichlorohydrin, the glycidol, two of which are epoxides. And many of these are carcinogenic and their structural isomers are carcinogenic analogs.

So I was -- in general, I didn't see anything I didn't find to contra -- to go against the hypothesis that this is a carcinogen. So my recommendation is that it be voted as a carcinogen.

And thank you for your nice and thorough presentation.

CHAIRPERSON MACK: Thank you, Joe.

David? Who would you like to speak next?

Does anybody have anything to add to what Joe has said?

David.

COMMITTEE MEMBER EASTMOND: This is a question really for Dave Morry. Can you comment about the actual cancer bioassays themselves. I understand there was a fair amount of mortality in those bioassays, and some -- unless I'm mixing up my chemicals, but...

DR. MORRY: Yeah, there was -- I think there was some mortality that 1,3-Dichloropropanol is toxic to the liver has caused liver toxicity, both, in rats and in humans, and in industrial situations. So there can be a

fair amount of mortality among the rats. But there were enough rats surviving to make a valid carcinogenicity assay and statistically significant result.

DR. SANDY: David, if I can pipe up on page five --

COMMITTEE MEMBER EASTMOND: Yeah, I've got it.

DR. SANDY: Martha Sandy.

What we have is we have a document from Hercules, and then we have reviews by other groups, secondary reviews. So we've read all of those. And the information we have on survival in these studies is that at 104 weeks -- let's see, there's no treatment related differences in survival in low- or mid-dose rats as compared to controls. In the higher dose animals, you do see some reduced survival.

So in the male study, you had 36 percent survival at 104 weeks in controls versus -- or sorry, in the high dose versus 64 in controls, so 36 survived in high dose versus 64. In the female study, 46 surviving at 104 weeks versus 74 in the controls, but -- 74 percent. But we also have statements in these documents telling us that at 74 and 78 weeks survival -- sorry, that's on body weight gain.

COMMITTEE MEMBER EASTMOND: Reduced body weight gain.

DR. SANDY: Yeah. So we're just reporting everything we could find on this. We don't have the full, you know, however many volume study write up with individual animal data. We have to rely on the information we can get.

COMMITTEE MEMBER EASTMOND: Do you know if the cause of death -- any insights into what the cause of death was in the animals that died earlier? You think liver toxicity or no --

DR. MORRY: I don't think the report tells us that -- answers that question. Liver toxicity would be the most likely possibility, but I don't think they told us.

DR. SANDY: There's another possibility that it's liver tumors. The female rats in the high dose had quite a high level of liver tumors. It's possible animals are dying of tumors, if not toxicity, but we don't know that.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Just a quick question too. So Hercules, that was an independent research and consulting company, I gather from the citation?

DR. MORRY: Yes, it was, hired by the Hercules Company. Then they submitted that report to the EPA. And the report we have is called part one, but we never were able to get ahold of any other parts. So it's like a --

part one is like a not -- doesn't have like data on the individual animals and all that. It's like a summary of the results.

COMMITTEE MEMBER LANDOLPH: So it's a company report. It's not in the peer-reviewed literature --

DR. MORRY: That's correct.

COMMITTEE MEMBER LANDOLPH: -- as we understand it.

And what was the context in which they decided to test this compound? Does anybody know why did they test it?

DR. MORRY: They were probably told to do so by EPA.

COMMITTEE MEMBER LANDOLPH: And you don't know why EPA told them?

DR. MORRY: It's been part of a regulatory consideration for a long time.

COMMITTEE MEMBER LANDOLPH: Thank you.

DR. SANDY: It's a high production volume chemical. We don't know if or why someone might have requested it being tested, but yeah.

DR. MORRY: But also it's not only high production, but also as part of food, it's very widespread and probably will never go away.

CHAIRPERSON MACK: Yeah, the structure probably

has something to do with that too.

DR. MORRY: Yeah. It's related to a lot of other carcinogens.

CHAIRPERSON MACK: Okay. Let's go down the list and see if anybody has any comments.

Marty, do you have anything to add?

COMMITTEE MEMBER HOPP: What concerned me about these studies were the multiple different sites that were carcinogenic -- that appeared to be carcinogenic. That was most striking.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: I want to comment on the excellent review of Dr. Murray or is Morry, I'm sorry I can't see that far?

DR. MORRY: Morry.

COMMITTEE MEMBER HAMBURG: Thank you.

I don't see any question about this at all. I think it's very clear.

CHAIRPERSON MACK: David, anything?

COMMITTEE MEMBER HUNTER: No additional comment.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: No.

CHAIRPERSON MACK: And I don't have any addition either.

So let's go to the public.

Do we have any comments to be made by the public. And remember, we'd really appreciate it if it was strictly confined to the issue of carcinogenicity, not the distributional issues.

So Lois Haighton.

MS. HAIGHTON: That's me. I have a presentation now.

(Thereupon an overhead presentation was Presented as follows.)

DIRECTOR DENTON: Lois, there's the podium there.

MS. HAIGHTON: I work for Can -- I don't know if you can bring up the presentation.

The green button is on. I'm just not talking close enough.

CHAIRPERSON MACK: I couldn't hear you.

MS. HAIGHTON: I'm just waiting for him to put up -- there it is.

I work for -- my name is Lois Haighton. I work for Cantox Health Sciences. Cantox was requested by the International Hydrolyzed Protein Council to look at the data available for this compound, and to make a determination of the tumors seen, whether they're likely due to the sustained high dose in rats, or any kind of species-specific sensitivity, such that when you question these relevance to humans, do you have the same sort of

support for a known human carcinogen as a known rat carcinogen.

If you could find the slides that start DCP

--o0o--

MS. HAIGHTON: I had started with MCPD.

There. The next slide, please.

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MS. HAIGHTON: So we have, as our animal data, an unpublished oral drinking water study in Wistar rats. And the tumors noted were benign, malignant, and/or combined benign and malignant tumors of the liver, kidney, tongue, and thyroid, predominantly significant at the high dose.

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MS. HAIGHTON: Now I'm not a statistician, but I would like to bring to your attention the table that was presented in the OEHHA document. It concerns the squamous cell carcinomas of the tongue. And you have an incidence of zero out of 50, zero out of 50, zero out 49, and six out of 50. And with that, it was still significant with the trend method. So I'd just like to bring the attention that if you look at the actual raw data and the incidence data, you have to also consider do you have a statistical significance and biological significance or just a statistical significance.

Next slide, please.

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MS. HAIGHTON: So when we look at the liver tumors, they were at the highest dose noted. There was hepatotoxicity, as indicated by increased liver relative weights, non-neoplastic liver lesions, including fatty liver, and Kupffer cells, sinusoidal peliosis and a few other findings all at the high dose.

It did not increase the incidence of unscheduled DNA synthesis in liver cells of Wistar rats. That's an in vivo assay. And apart from OEHHA's mention of liver tumors, we were unable to find mention of that in the other groups that have reviewed this compound.

Furthermore, hepatic tumors are known to arise secondary to metabolite disturbances, specifically the 1,3-Dichloroacetone is a known glutathione depleter. And glutathione, as you know, is essential for detoxifying epoxide metabolites.

Next slide, please.

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MS. HAIGHTON: We talk about kidney tumors now. The kidney tumors were not observed in the females, even at the high dose, which was quite a bit higher at 30 on a per body weight basis. The 19 which is the male rats.

Also, males are known to be -- male rats are known to be sensitive to chronic progressive nephropathy,

noted both with MCPD, as well as with the DCP. And that is a secondary response to sustained cell proliferation. Again, statistical findings were at the high dose.

If you could move to the next slide, please.

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MS. HAIGHTON: We now have the tongue tumors, which are, as I agree, a very odd finding. And one of the hypothesis put forward for the high concentration was that this may be a direct sustained irritation effect, that with the daily exposure through drinking water could have resulted from the chronic irritation, hence I'm not sure if you would have seen this tumor type by gavage or diet, if there were those such studies available.

Next report, please -- or next slide.

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MS. HAIGHTON: You have the thyroid tumors now. And that was barely statistically significant. It was a very low response, and it was dismissed by JECFA and other authoritative bodies who have reviewed this has probably not been reliable enough for consideration of known carcinogens of humans.

Next slide, please.

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MS. HAIGHTON: Therefore, this review that we've obtained by looking at the tumor-specific and narrowing in

on each tumor type specifically to determine if there likely to have been a result of the high dose in male rats or female rats, which weren't -- did have the findings, but not to the same extent.

Liver, which we discussed -- and I think I might have jumped over that one -- is also likely to be due to the hyperplasia, which is secondary response.

So no studies, other than this one unpublished study, were available to look at whether this substance does cause sustained, and is likely to be carcinogenic in other species. And the malignancies were not significant usually unless combined with the benign.

No studies -- the findings were statistically significant at the high dose. I've already pointed out the comment about the trend data with the 0006 showing positive. So I question the methodology there.

Also, in vivo is the whole animal. And although you have S9 in a petri dish, you don't have glutathione. The whole animal itself would not have the flaw of in vitro work that it would actually have the metabolism necessary to determine whether you have a mutagen that would last long enough to be -- to cause tumorigenic findings in humans.

And given the likely rapid conjugation toxification of any mutagenic metabolites of 1,3-DCP in

vivo, there is no conclusive evidence at the present for a genotoxic mechanism of action.

Next slide, please.

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MS. HAIGHTON: Kidney tumors may be secondary to sustained cell proliferation resulting from chronic progressive nephropathy. The small increase in thyroid tumors may be due to sustained cell proliferation, if not just chance. Tongue tumors may be the result of chronic irritation. And liver tumors may be due to metabolic disturbances. Glutathione depletion, in particular, by the metabolite 1,3-Dichloroacetone. And I note that the higher response in females, there was actually quite -- you had 19 milligrams per kilogram on the body weight in males, and 30 in females. So you don't really have a direct comparison, but you had greater liver response, and also you would have a higher dose, which is more likely to deplete glutathione leading to a greater response in females.

Last slide, please.

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MS. HAIGHTON: Therefore, the potential carcinogenicity of 1,3-DCP has been evaluated under conditions of only one single two-year rat study, and no additional studies in other animal species or other

strains of rat are available to corroborate the results of this study. In combination with the fact the mechanisms of action responsible for the tumors may be non-genotoxic, raises doubts about the relevance to humans.

If your weight of evidence has the guidance I reviewed is to show clearing showing of tumorigenic and cancer risk to humans. I don't believe this compound meets that requirement. And a lot of the surrogates that were mentioned are either probable or possible human by IARC's evaluation and not known human carcinogens.

Last slide, please.

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I believe that was it. I thank you for your time.

CHAIRPERSON MACK: Thank you, Ms. Haighton.

Joe, do you have any response?

COMMITTEE MEMBER LANDOLPH: Well, I want to thank the scientist for the nice presentation. And certainly there are holes. We have to act on the data which we get. If we think the data is sufficiently weak, then we pass and we don't call them.

And I certainly would love to see more carcinogenicity data. I'd love to see some mouse data, some hamster data, some data by other people. And you're right about that, but unfortunately we don't have this

data. And I find it difficult just myself to throw away four positive tumor sites in male rats, and three in female, which are dose dependent, and where the trends are statistically significant.

And the question of mechanism is always a tough one. That's going to take another 15 years to figure out. People are going to have to start looking at oncogenes and whether there are mutations there and tumor suppressor genes. But this is an impressive list of in vitro gene toxicity data. There's not much negative there. It's overwhelmingly positive to me as a genetic toxicologist.

So I would politely and respectfully indicate that I would still vote this a carcinogen by my thinking.

CHAIRPERSON MACK: Anybody else want to comment?

Marty.

COMMITTEE MEMBER HOPP: I also think our presentation was really very well done. Thank you, Dr. Morry.

What bothers me about these studies is, as I said before, the wide range of them, but the dose response curve that occurs too often in multiple of these studies at very -- you'll see nothing at zero, but as you progress through the dose responses, its linear. And in linear sites, particularly in the tongue, that I think is not irritative, it doesn't appear to be an irritative effect.

But dose response curves like this I think are instructive for us to evaluate. Very convincing.

CHAIRPERSON MACK: Anybody else?

I make one comment, and that is, for better or worse, our mandate is not to decide whether or not it's a human carcinogen. Our mandate is to decide whether it causes cancer. And we have to leave it at that. Obviously, we know what the intent is, but that's what the words in the initiative said.

You want to say something.

DR. ROBERTS: Can I just make one comment.

My name is Ashley Roberts and I work for Cantox also.

I just wanted to make one comment, and that was related to the mechanism of action here. And we heard from Dr. Morry who said that he -- that there wasn't enough data to determine what the actual mechanism was. And therefore, with the, I think, plethora of in vitro data, which wasn't substantiated by the in vivo data, and looking specifically at the UDS data, which was primarily related to the liver, which showed no effects, I think that really brings into question the mechanism of action here. And therefore, it could potentially be a non-genotoxic mechanism.

I think we have to bear that in mind. With that,

in relationship to the single study that we have here, that's been unpublished and not peer reviewed, and we've also heard about the deficiencies in this study related to the details of the individual animal data, and how that relates to -- how each individual animal responded in this study. We heard about a significant number of descendants within the study, and how these weren't evaluated for -- or we don't have the data to determine what the root cause of death of these animals was.

I think this just raises some doubts about the whole validity of this single study. And therefore, you know, I would call into question whether, you know, this is, you know, by weight of evidence approach, you know, can be considered a carcinogen.

Thank you.

CHAIRPERSON MACK: Thank you.

DR. SANDY: Dr. Mack, if I could speak to the statement made just now, that this study by Hercules, the report was not fully reporting everything. We have the summary of a multi-volume industry study, that we have read. And we've also read summary reviews by the World Health Organization and the International Life Sciences Report, and there's a Committee on Carcinogenicity and a Committee on Mutagenicity. There's many reports all cited in the HID.

It looks like WHO's report from 2007 had access to the entire study. And we took the incidence data from the World Health Organization 2007 reference and we cite that in our tables as that's the source. So we're citing a source -- a report that actually had the individual tumor data. And they compiled the incidence data. They haven't written in their report what the individual survival data were, so I can't answer Dr. Eastmond's question about what was the survival and the different dose groups at different time points. We only can give you what we have available to us.

But I wanted to emphasize that there are these other studies or reviews that actually had access to the full Hercules report.

CHAIRPERSON MACK: Thank you, Martha. I think we're ready to call the question.

Joe.

COMMITTEE MEMBER LANDOLPH: Just an attempt to make a constructive comment to the gentleman from Cantox.

In situations like this, one thing you might consider doing is perhaps write to the NTP and ask them to retest it, because I see them testing a lot of chemicals, which to me are not that high priority. So if there are doubts, that's probably a fair way to proceed, in terms of getting more information with modern -- the most modern

testing.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: If I can weigh in. Certainly, you can appeal to the NTP to do some bioassays. The company itself can sponsor bioassays on this compound and produce the data. One of the things that seems to be a gaping hole for me is there's no DNA adduct data at all. And that's a very, relatively easy to get and a big hole.

With 1,2,3-Trichloropropane, one of the key pieces of evidence behind why it was determined to be a mutagenic mode of action was the fact that there were DNA adducts formed in vivo, even though it was negative in almost all the other genotoxicity tests in vivo.

And interestingly, the adducts were formed through an adduct with glutathione. So it wasn't what they would predict from their in vitro studies. And since this compound is very similar, that would be certainly an avenue to look and to follow, is to look at some DNA adduct studies in vivo, as far as follow-up studies.

CHAIRPERSON MACK: So again, we're left with what we have, and we have the decision to make.

So I will pose the voting question.

Has 1,3-Dichloro-2-propanol been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer.

So all those voting yes, please raise your hands.

(Hands raised.)

CHAIRPERSON MACK: All of those voting no?

So the decision is unanimous there are 1, 2, 3, 4, 5, 6, 7, 8 votes for yes and none for no. And we therefore have decided to list this chemical under the Prop 65 mechanism.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, that's actually 7 votes, but the same result.

CHAIRPERSON MACK: I counted her.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: She didn't raise her hand.

CHAIRPERSON MACK: Seven is quite sufficient though.

So we'll move on to the next compound. Anybody else want to get counted that's sit up here?

(Laughter.)

(Thereupon an overhead presentation was Presented as follows.)

DR. SANDY: Dr. Mack, Dr. Rajpal Tomar will be presenting the evidence of 3-Monochloropropane-1,2-diol.

DR. TOMAR: Good morning, 3-Monochloropropane-1,2-diol, 3-MCPD. It's a chlorinated three carbon alcohol.

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DR. TOMAR: It is used as a dye intermediate solvent for cellulose acetate and to lower the freezing point of dynamite.

It is also registered as a restricted use rodenticide by the name of alpha-chlorohydrin, which is used as sterilant for the rats.

It is formed in the food during processing, cooking, and storage; found in a variety of foods containing acid-hydrolyzed vegetable protein, and some foods without acid-hydrolyzed vegetable protein. It has been detected in packaging material as well as drinking water.

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DR. TOMAR: Now, all together we have 10 studies, carcinogenicity studies, in animals. Four studies were conducted in mice, and six studies were conducted in rats. Out of the four studies, the third study I indicate on my slide, this study we have not reviewed in our hazard identification document, because it just came in the September issue of Archives of Toxicology.

I would be explaining this study here in detail, and I'll be happy to answer any questions for this study in particular.

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DR. TOMAR: Now, studies in mice, there's a first -- two sets of these studies by Van Durren, et al., 1974. They were conducted for 19 months in groups of 50 female Swiss mice. Mice were exposed by dermal application using 2 milligrams three times per week for 19 months. There was no treatment related skin tumors were observed in this study.

The same group of people also conducted second study by using subcutaneous injection again in 50 female Swiss mice. And the doses used were 1 milligram once per week. Again, there was no treatment related neoplastic finding in the second study.

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DR. TOMAR: In this 104 week recent study by Jeong et al., 2010, B6C3F1 mice were exposed to, in drinking, water concentrations of 0, 30, 100, 300, and 200 ppm. The highest dose 300 ppm was given for a hundred days, which was then reduced to 200 ppm, because of the toxicity.

The high-dose mice had significantly decreased body weight, food and water consumption. However, there were no treatment related neoplastic findings in the study. I might add that this study was conducted according to the carcinogenicity study guidelines. And every single step was followed in this study.

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DR. TOMAR: In rats, we have first a study by Weisburger et al., 1981, where groups of male and female Sprague-Dawley rats, 26 in number, were used. Control had only 20; animals. A dose of 30/35, 60/70 milligrams per kg was given orally twice per week for the 72-week period and observation period was additional 32 weeks. Again, there were no treatment-related neoplastic findings.

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DR. TOMAR: In the next study, the table indicates on the left-hand side organ and the lesion observed. The center of the table simply indicates the incidence data. And the last column indicates the trend test.

In males -- and this is a study by Sunahara et al., 1993 -- groups of 50 Fischer rats were exposed to 0, 20, 100, and 500 ppm for 104-weeks. There was a significant increase of Leydig cell adenoma in 100 and 500 with a positive trend.

While there were no carcinomas in 0, 20, and 100, but the three carcinomas were observed at the 500 ppm with a significant positive trend test.

Leydig cells are very common in Fischer rats. However, it's a continuum of the proliferated response from hyperplasia to adenoma to carcinoma. If you add the

adenomas and carcinomas, the combined adenomas and carcinomas is again significantly different.

While we do not know exactly whether three carcinomas were observed in the same 47 animals, or they're separate, because the authors did not indicate it. However, if you assume that three carcinomas were within the 47, it's still significantly different in a combined form.

In this study, we also had a significant increase in fibroadenoma, at the 500 ppm. Again, we also had no adenoma carcinoma at the lower doses, but at 100 and 500, we had one adenoma and one carcinoma in the study.

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DR. TOMAR: The study continued here. There was a significant increase in tubular adenoma at the 500 ppm with a strong positive trend test. As well as in female, there was a significant increase at 500 ppm with a positive trend test.

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DR. TOMAR: In the second drinking water -- third drinking water study really of Cho et al., 2008, it was conducted in Sprague-Dawley rats. We have a significant increase in Leydig cell tumor with a positive trend.

Here, the author did not indicate whether these tumors were carcinomas or adenomas. But as I indicated

earlier, the Leydig cell tumors are a continuum of proliferative response from hyperplasia to adenoma to carcinoma.

In this study, there was a significant increase in tubular carcinomas for kidney in males and tubular Adenoma in females. Also, there was a significant increase in combined adenoma and carcinoma at the highest dose, with a very strong positive trend in male as well as female.

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DR. TOMAR: Next is the proposed metabolic pathway. As we just heard from Dr. Morry, this is a metabolite of 1,3-DCP. And 3-MCPD is metabolized by two different pathway, either by oxidation to the glycidol or oxidation to the beta-chloroacetaldehyde. Glycidol can be converted into glycerol and can be exhaled through the lung as CO_2.

The glycidol is deconjugated by glutathione and then finally acetylated to form the corresponding mercapturic acid. On the other side, beta-chloroacetaldehyde can be converted to beta-chlorolactic acid, and then oxalic acid, as well as it could be converted by elimination of chlorine to 1,2-propanediol.

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DR. TOMAR: There are series of genotoxicity, in vitro tests. It has been found positive in Salmonella typhimurium reverse mutation assay in two strains, TA 1535 and 100, which shows the base-pair substitution, as well as TA 98, which indicates the frameshift mutation.

It was also positive in saccharomyces plombe yeast forward mutation assay without metabolic activation. Again, gene mutation in mouse lymphoma cells with metabolic activation, Sister Chromatid Exchange in the Chinese hamster fibroblast cells with and without metabolic activation.

It causes DNA damage in Chinese hamster ovary cell without metabolic activation. It was negative in E. coli, a number of strains with and without metabolic activation, as well as in a DNA synthesis and in HeLa cells, with and without metabolic activation.

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DR. TOMAR: Again, unlike the 1,3-DCP, it has been found negative in various in vivo assays, the same assay as was explained before; drosophila somatic mutation assay is a wing spot test; dominant lethal mutation assay in male mice; bone marrow micronucleus assay in rats and mice; unscheduled DNA synthesis in liver cells of male rats; and DNA damage in various tissues and blood cells of the male rats.

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DR. TOMAR: In a small 14-day exposure study in B6C3F1 mice, it was found, that 3-MCPD decreased the absolute and relative thymus weight. And in the subsequent study it was indicated that thymus weight was reduced because of the reduced T-cells in the thymus.

It also reduced the natural killer cell activity of the cells, as well as reduced the antibody production to sheep red blood cell. What it basically means is it has reduced the capacity for cell lysis as well as recognition of the tumor cells.

In vitro 3-MCPD has been demonstrated to decrease the proliferative response of con A and anti-CD3 antibody, which reduced the proliferative response of the T-cells, as well as lipopolysaccharide, which would reduce the proliferative response of the B-cells. It decreases the spleen cell production of interferon-gamma, IL-10, and IL-4.

It reduces the macrophage production of TNF-alpha and nitric oxide. What is suggested basically, that impair the function of the T&B cells, altered the regulation of the inflammatory response, as well as the proliferated response of the T and B cells.

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DR. TOMAR: It is the same, as I said, as we have

just seen with 1,3-DCP a malignant transformation of the fibroblast. As indicated, the number of transformed foci and number of the treated foci.

As we can see at the highest dose in 1000 and 2000, it is cytotoxic to the cells and there is really no difference there. However, for the lower doses, there is a increase incidence 2/27 at 100 10/25 and 14/27. Both are highly significant.

And we know that the assay indicates the nature of the cells, how they grow their contact inhibition or whether they spread on the surface of the plastic while they grow. And contact inhibition indicate the carcinogenicity of the cells.

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DR. TOMAR: This is a slide for structure activity relationship. On the right-hand side, the bottom is the 3-MCPD. And there are eight compounds, as we have just seen with the DCP. They are structurally related three carbon chlorohydrin.

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DR. TOMAR: Six of the eight compounds are known to be carcinogenic by Prop 65 as well as by IARC. To name them 1,2,3-trichloropropane; tris, 2,3-Dibromopropylphosphate; 2,3-dibromo-1-propanol; epichlorohydrin; dibromochloropropane and glycidol.

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DR. TOMAR: Four of these eight compounds metabolize to 3-MCPD and they're carcinogenic.

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DR. TOMAR: 3-MCPD is converted to the glycidol, the first metabolite, which is a known carcinogen, as well as a mutagen compound.

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DR. TOMAR: And three of the compounds structurally metabolize to the same acetylated -- deconjugated the same way as 3-MCPD, and they're also carcinogenic.

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DR. TOMAR: Now, having gone all through that, what is the possible mechanism of this one?

We have seen the 3-MCPD causes tumor, Leydig cell tumor, and mammary tumor as well as kidney tumors. This we had have just found that it's genotoxic in the in vitro test. Why it is negative in vivo, is still unknown. There is enough genotoxicity studies which could play an important role as a genotoxic mechanism.

3-MCPD is used as a sterilant. It inhibits the glyceraldehyde-3-phosphate dehydrogenase. That's how it reduced the spermability by inhibiting the glycolysis. However, the role of this enzyme is not only in the

glycolysis, but it plays a very important role in promoting as well as inhibiting the carcinogenesis.

It also affects the regulation of the DNA repair, apoptosis, cell death, cell cycle progression, and stability of messenger RNA. And all these steps play an important role in carcinogenic process.

It causes kidney toxicity. While the mechanism again -- remember there are a number of different type of tumor cells caused. Immune effects. We have just seen that it reduces the capacity of immuno-surveillance as well as the capacity to lyse the target cell if it could recognize.

There's really not much of an emphasis on the hormonal effect in any of the carcinogenicity studies. However, short-term acute exposure one study indicated that it does reduce the LF, FSH, as well as prolactin in serum but not in their other organs it has been tested. So we really cannot say much about the hormonal activity of the 3-MCPD.

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DR. TOMAR: To summarize it all, animal evidence for carcinogenicity, tumors in both sexes of two strains of rats. Tumors at multiple sites in two strains of male rats.

It causes kidney tumors in Sprague-Dawley rats,

combined adenoma and carcinoma in male and female. By the way, it is a rare tumor in S-D rat. They're usually of less than one percent is what we consider rare tumors. In Fischer rats increased adenoma in male and female.

It causes mammary tumors in male and female Fischer rats, increased fibroadenoma, adenoma, and adenocarcinoma observed in mid- and high-dose. It is an uncommon tumor in males.

It causes Leydig cell tumors in Fischer rats, increased combined adenoma and carcinoma. In the Sprague-Dawley rats, it increases Leydig cell tumors.

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DR. TOMAR: It is, as indicated, genotoxic in vitro. It causes malignant transformation of cells, like 1,3-DCP. In fact, that if you look at the data, it is parallel to the 1,3-DCP. It's a metabolite to the glycidol, a genotoxic carcinogen and is structurally similar to the six known carcinogens.

Thank you.

CHAIRPERSON MACK: Thank you, Rajpal. Again, very concise, and a nice summary.

David.

COMMITTEE MEMBER EASTMOND: I'd like to thank Rajpal for his presentation as well.

As I think was described in the presentation,

from my point of view, there are really kind of four studies that I would consider to be substantial studies have been conducted on this compound.

Two in rats and two in mice. The two in mice one was -- well, both studies in mice did not show an increase in tumors. The first study, the doses were relatively low, so that one is less -- you can't put as much weight on that. The one that was published more recently appeared to be a properly done study and really saw no increase in tumors in that study in the mice.

With regards to the rat studies, the compound has been shown to be tumorigenic in multiple organs, testes, kidney of males and females, mammary gland of males, and probably the preputial gland. I don't know if you came across that. But in the IARC -- in the JECFA study, there were very high increases, but they didn't have tumor data for all the animals, so they couldn't really evaluate. But it appeared to be of pretty substantial increase in -- so they left it in this. We can't really judge, but it looked like it was in that category. I don't know if you want to comment.

DR. TOMAR: With respect, we really did not have the original study, and it was a review of review. So we could not present it here, because we didn't have anything to back it up, but that's true.

COMMITTEE MEMBER EASTMOND: I agree, but it certainly maybe suggestive there. There were two studies done in rats. The results are quite similar for the two studies, which is also an important point. And there were increases in cancer seen in the Cho study, certainly in the kidney, which, as Rajpal indicated, was an uncommon tumor type.

With regards to -- it's kind of an interesting compound. It's quite positive in the in vitro genotoxicity test, but consistently negative in the in vivo test. I count up something like nine assays or endpoints.

However, most of those were not conducted in target organs, so there's also a target organ issue that comes up. However, the last study, which was done, did use a common assay in a number of the target organs and did not see any increase in DNA strand breakage.

As I indicated -- well, I didn't indicate, but similarly what is lacking for this is DNA adduct data, which would be actually quite informative, particularly since one of these other halogenated propanes does cause DNA adducts through an unusual mechanism involving glutathione conjugation. So the adduct actually has a glutathione conjugate, so it would be interesting to know about, but we don't have any information in that area.

As Rajpal indicated, it could metabolized through the epoxide intermediate. That is mutagenic and carcinogenic. However, it appears the predominant pathway looks like it goes through the aldehyde to form the acid. Maybe you can clarify that.

DR. TOMAR: Yes. I noted that comment many times. However, there are no data in rats and mice are labeled which indicate that one pathway is preferred over the other. And I would like to add that formation of the glycidol is an obligatory metabolite. You cannot have 3-MCPD directly conjugated to the glutathione and form acetylation.

And there are no data to indicate that only one pathway or another, because if you look at all the data, I indicate they found almost the same amount of metabolites both ways.

COMMITTEE MEMBER EASTMOND: Okay, thanks.

As indicated, these other halogenated propanes and similar compounds exhibit somewhat similar mutagenicity and carcinogenicity profiles. It's not a perfect correlation, but there's enough stuff going on there that certainly is supportive.

I should mention that apparently in reading some of the background material, this has been reviewed by a number of regulatory bodies, including JECFA, the World

Health Organization, bodies from the United Kingdom, European Commission, U.S. EPA, Office of Pesticide Programs. And they've pretty much concluded it's a carcinogen. They believe it works through a -- it's a non-genotoxic carcinogen based on the in vivo -- the negative in vivo genotoxicity results.

And they propose a couple of mechanisms, which Rajpal had indicated, one being the sustained -- chronic sustained toxicity may be responsible for the kidney tumors. They believe the testicular and mammary tumors are due to hormonal imbalances, with those in the testes being the primary effect, and apparently those in the mammary gland being a secondary effect.

However, the amount of data really to support this is pretty limited. This is kind of speculation that's been generated in the absence of really firm studies.

So anyway as I've looked coming back to the overview, it seems to me that we have clear evidence for an increase in tumors in well conducted animal studies, two different rat studies, and increases not only in benign but also malignant tumors in some cases. So it seems to me to fit the criteria for listing.

CHAIRPERSON MACK: Thank you, David.

Joe, do you have any comment?

COMMITTEE MEMBER LANDOLPH: Yeah. I'd also like to thank Rajpal for a very nice presentation. I pretty much agree with Dave. The Sunahara study, I note was sent to WHO. It was not published in the peer-reviewed literature, but it's got a lot of data. It shows tumors in three sites for the males. The testes data is a little bit iffy, because of the high background for adenomas, but the carcinomas are positive. So that's three tumors for three different sites in males, one site in females for adenomas.

And the fibroadenomas in males was very high, 10 out of 49. And that was statistically significant by the trend test.

So we've got two different studies here by two different authors, which gives me more credibility for this whole thing. And the study by Cho et al. has some very interesting data. The tubular hyperplasia is dose dependent and the trend is statistically significant. The same thing for the adenomas and the carcinomas and the combined. So that's strong male kidney data, and also strong female kidney data. It's dose dependent and statistically significant. So that's two.

And I was impressed by the fact that you've got beta-chloroacetone and glycidol, which are likely two of the carcinogenic metabolites.

I'm also, like Dave, a little bit puzzled by again you've got a lot of in vitro genotoxicity data, but no in vivo and I don't know why. And again, it's probably going to take another 15 years to figure out the mechanism by which this acts.

But for me, that's a preponderance of data that I can make my mind up on.

CHAIRPERSON MACK: Thank you, Joe.

You've got another comment?

COMMITTEE MEMBER EASTMOND: Can I just make one other comment. Maybe I'm not clear, but in the metabolic -- in Figure 2 which shows the metabolic pathways, it appears that you can go through the acetaldehyde directly in the parent compound and don't have to go through glycidol. And that's what's kind of the argument, that it wasn't obligatory to go through --

DR. TOMAR: You mean deconjugated without going through the glycidol?

COMMITTEE MEMBER EASTMOND: I mean that's certainly what's shown in the figure.

DR. SANDY: Yeah. I think Raj is misunderstanding you. You're correct, David. Two main pathways are going either from 3-MCPD to the beta-chlorolactaldehyde or to the glycidol. And so there's two pathways there.

And what Raj is saying is that to get from -- that the glycidol isn't intermediate and necessary to get one of the mercapturic acids. But you're right, there's --

DR. TOMAR: And you're right, but there is no evidence that it will just take one pathway and forget completely the second one.

CHAIRPERSON MACK: Marty.

COMMITTEE MEMBER HOPP: What bothers me about this analysis is understanding how it's carcinogenic.

The mechanism of action clearly is not direct from what I summarized. This is not genotoxic. It's a secondary effect of the material not a primary factor.

DR. TOMAR: I'm sorry. I didn't hear it very clearly.

COMMITTEE MEMBER HOPP: I said what bothers me is I don't see a direct -- can you hear this?

DR. TOMAR: Yes.

COMMITTEE MEMBER HOPP: -- a direct effect of the carcinogen, a lack of in vitro -- or in vivo genotoxicity is suggesting to me that it's a second -- that the carcinogenicity is a secondary effect, an effect of the metabolite in someway or another rather than the chemical itself. And the lack of real mechanism of carcinogenicity bothers me. Although, I'm sure we don't know all the

mechanisms of carcinogenicity. And that clearly I don't think this fits any of the ones that we're familiar with.

However, its effect is fairly clear. We just don't know how. And I don't know everything, but --

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: I know less than he does.

(Laughter.)

COMMITTEE MEMBER HOPP: I do want to say -- excuse me one second. I do appreciate your comprehensive presentation. I thought it was wonderful and very helpful understanding it.

DR. TOMAR: Thank you.

CHAIRPERSON MACK: David?

Pass.

Anna?

Pass.

CHAIRPERSON MACK: All right. Do we have any number comments?

No public comments.

COMMITTEE MEMBER EASTMOND: The same ones.

MS. HAIGHTON: Me again.

CHAIRPERSON MACK: Sorry about that.

MS. HAIGHTON: I might as well seeing that I flew all this way.

CHAIRPERSON MACK: Oh, you should have really started with it last time.

(Thereupon an overhead presentation was Presented as follows.)

MS. HAIGHTON: If you could bring up the presentation.

Again, our review was at the request of the International Hydrolyzed Protein Council.

Next slide, please.

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MS. HAIGHTON: Next slide, please.

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MS. HAIGHTON: We've already had the listing of studies. We just reiterated them here, and noted that there is the MOE study, which was by dermal and subcutaneous, the rat study. The Charles River one was not a standard full-term. It was, I believe, 72 weeks and it was by oral gavage twice a week, though it showed no tumor increase, which may be significant, in that you had a break in the dosing. It wasn't daily, so it may have required a daily sustained dosing to see the tumor effects.

Next slide, please.

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MS. HAIGHTON: Then you have the two rat studies.

I guess Sunahara was unpublished. That one showed Leydig cell adenomas, mammary gland fibroadenoma, adenoma, and tubular adenoma. None of those are carcinomas.

And Cho showed some tubular carcinoma in males, as well as adenomas and Leydig cell and the mammary tumors. That one was -- the last one which I think wasn't discussed in great detail in the OEHHA presentation. But just to note that that again was in mice, drinking water, a GLP study, no significant increase in tumor incidence, and sort of completes the circle that you have no tumors in mice. So your tumors are restricted to one species, which are the rats.

Before I proceed, I'd also like to point out again the comment I made with DCP, that you have two instances. I draw your attention to male testes Leydig cell carcinomas, where you have 0/50, 0/50, 0/50, 3/50, yet a positive trend study. That was the Sunahara study.

And also in Cho, I direct your attention to tubular carcinoma, which is the only carcinoma finding that was statistically significant, the high dose. And again you have 0/50, 0/50, 0/50 and 5/50, yet you still has a positive trend test. So I question possibly the statistical analysis that, in my mind, would result in a positive trend test, when you have no tumors in the control and the two doses and then a relatively low

instance in the high dose.

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MS. HAIGHTON: So we speak first of the kidney tumors. And the actual malignant tumors or combined malignant and benign kidney tumors reported only in the Sprague-Dawley rat in a single study. No malignancies of the kidneys were in the Fischer 344 rats of comparable doses. You had benign tumors there.

Also, these rats are sensitive to nephropathy again. And there's a clear correlation between the severity of the nephropathy and the incidence degree of renal tubular hyperplasia and the presence of the adenomas.

Next slide, please.

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MS. HAIGHTON: In females, the incidence of malignant lesions did not differ from controls. The incidence of renal -- sorry, I'm still on kidney.

The only increases in mammary gland hyperplasia at the mid- and high-dose and fibroadenoma at the high-dose level were reached -- were reported to reach statistical significance, and then only in the Fischer rats.

Only a single instance of adenomas was reported

in each of the mid- and high-dose versus none of the controls. Those were not statistical. And a single instance of adenoma was reported in each of the mid- and high-dose versus none in the control.

Neither the occurrence of the single adenoma nor adenocarcinoma at the mid- and high-dose was statistically different from controls. There is an absence of mammary grand lesions in the Sprague-Dawley rats, the Charles River rat. And the occurrence of the lesions in the Fischer rat may have been a result of the hormonal basis with the Leydig cell mammary gland tumors in the male rat in the species. It was also in the presence of Leydig cell tumors, potentially indicative of a secondary to hormonal disturbance response.

Next slide, please.

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MS. HAIGHTON: In Fischer rats, the only increase of Leydig cell adenomas -- sorry. In Fischer rats, the incidence of Leydig cell carcinoma was only significant when you combined the carcinomas and adenomas.

In Sprague-Dawley rats, the authors only reported an incidence of Leydig cell tumors, but they did not distinguish between adenomas or carcinoma, with the carcinomas being the more indicative of a carcinogen response.

Leydig cell tumors in rats. Rats are sensitive to this type of tumor, and also to -- it may be secondary to mediated hormonal variations in rats. Has chemically induced increases in Leydig cell tumors are not -- are in rats are considered to be of a dose -- sorry, a tumor that rats are sensitive to. It is not necessarily relevant to assessment of carcinogenic potential to humans. Again, from before, I gather the decision is whether it causes cancer, not necessarily causes cancer in humans, but I point that out.

Next slide, please.

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MS. HAIGHTON: This is just an overview of all of the oral studies. You have the mice, which is the recent one, where you have no tumor types. You have Charles River, which was the abbreviated chronic study, and then when you look at adenomas versus carcinomas, you see tubular carcinomas down in the kidneys, which may have been due to chronic nephropathy, to which it has been demonstrated in the literature that rats are susceptible with this compound or they're from combined.

Next slide, please.

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MS. HAIGHTON: To support a clear human carcinogen, it is my understanding that you either have to

have clear evidence in humans or clear evidence of a malignancy in animals. 3-MP -- monochloropropanediol was not tumorigenic in mice via dermal, subcutaneous, or oral exposure. The malignant kidney tumors observed in rats was only in 1 of 3 studies at the high dose. Again, that's malignant. And this is likely a response secondary to chronic progressive nephropathy and renal tubular hyperplasia which was also seen.

The mammary tumor was benign only in a single rat strain and not observed in females or other rat strains. And Leydig cell tumors in rats are not well predictive of carcinogenic potential to humans.

Next slide, please.

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MS. HAIGHTON: You have your genotoxic response observed within in vitro assays, not confirmed in vivo. Again, in vivo being the whole animal, which would have metabolic processes that your in vitro would not -- could not -- has adequately compensate for.

Also, in the in vitro test system, particularly the bacterial cells, it's metabolized to genotoxic intermediates, the glycidol.

In vivo, it's excreted in the urine primarily, as beta-chlorolactic acid, resulting from a different pathway than that involved in the production of glycidol

or is conjugated with glutathione forming mercapturic acid derivative.

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MS. HAIGHTON: A chemical would be identified for listing if the weight of evidence shows that it causes invasive cancer in animals, but not if the cancer is a result from a mechanism of action that is not related to humans. The information on invasive cancer comes from the guidance document, 2001. Tumors observed in rats occurring via mechanism of action that are -- or may be specific to the rat and bear little relevance to the assessment of human risk would not indicate that that substance would necessarily be a known human carcinogen has -- is the list.

Furthermore, not all tumor types were identified consistently among the studies or among the different strains of rats.

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MS. HAIGHTON: Therefore, based on a collective review of the available data related to the potential carcinogenicity of MCPD and the limited relevance to humans of the underlying mechanism of action, the weight of evidence for 3-MCPD does not rise to the clear showing

that is required for -- or indicated to be required for listing decisions, and thus it should not be included on the list.

Thank you for your attention.

CHAIRPERSON MACK: Okay. Thank you, Ms. Haighton.

David, do you have any response?

COMMITTEE MEMBER EASTMOND: Well, just to say that I appreciate your comments. You know, it's true. This is not like many of the chemicals we deal with. You know, there's lots you have to -- you're missing pieces of information you'd like to have and you'd certainly like to have little better studies here.

The mouse studies appear to be negative. You have two rat studies. They're pretty similar actually in my regards. Now, some of the pathology is described a little bit differently. But when you come down to really do you have malignant?

Do you have cancer itself rather than benign tumors, there's certainly the evidence in the male Sprague-Dawley rats in the kidney appears to be -- it certainly is statistically significant and has a trend. The female rats have a similar trend, although it's not quite achieved statistical significance, but it's certainly supportive of that.

And then when you look at this, as I understand, the continuum, that these are tumors that would progress from adenoma to a carcinoma. And from the Committee's point of view, we look at those as part of a continuum. And those you also see the kidney tumors in the Fischer rats in the Sunahara study.

So those were, I think, where the evidence is -- I'm a little surprised -- well, there's a fairly high increase of these fibroadenomas and then some suggestive increases, not statistical, but increases in the treated animals in the adenomas and adenocarcinoma in the male mammary gland, which I would imagine would be quite unusual as well in these animals.

So I appreciate your comments, and certainly realize this is -- there are some points of debate, but I still consider my evaluation the way I initially termed it.

CHAIRPERSON MACK: Anybody else have anymore comments?

DR. ROBERTS: Can I make one question? Ask a question as opposed to --

CHAIRPERSON MACK: Okay.

DR. ROBERTS: I'd just like to ask the Panel a question as to why the rat is given more weight within this analysis than the mouse, in terms of carcinogenic

potential, if the mouse is clearly shown to be -- show no tumors, so why is the rat considered to be more of a specific model for assessing cancer in humans than a mouse?

Thank you.

COMMITTEE MEMBER LANDOLPH: I think I can handle your question and my comment at the same time.

The last time I looked at the database there was about a 70 percent correspondence between mouse and rat tumors for carcinogenicity. So it's not anywhere near close to a hundred percent like we'd like to say, number one.

And what's kind of classically done is one weights the positives. And I think we just don't know enough, at this point, about the mechanism of this chemical in the rat alone. And its action in the mouse to make any extrapolation to humans yet. The database is just too thin. So the data is very positive in the rats, so that's compelling data, and it's by two different authors in two different studies.

So it's very difficult for us to throw, for me in particular, to throw that data away. So I think that's what we're stuck with, and I don't think we're overweighting one versus the other. It's just there are positives in the rat. They're dual sex, multi-target by

two different authors. And so I would have to consider that and not throw it away.

Why the mouse is negative is a very interesting scientific question, and it's going to take many years to answer. And which is more relevant to humans is going to make many years to answer. We just don't have the database there.

CHAIRPERSON MACK: My answer would be that whichever is positive is more relevant to humans, even though we know nothing about mechanism.

I'd like to congratulate Dr. Haighton or Ms. Haighton on trying her very best to keep us honest, because you really did go through everything with an appropriate spin on the other side.

My own concerns come to the fact that this set of moieties all seem to be carcinogenic in one way or another, but I am troubled by the fact that there are different tumors that pop up with each chemical. And yet, I can't avoid the conclusion that this particular molecular structure is doing something bad.

And again, I can come back to the fact that we're charged with deciding whether or not it causes cancer. So having said that, we'll come to the vote again.

So the question is, has 3-Monochloropropane-1,2-diol been clearly shown through

scientifically valid testing, according to generally accepted principles to cause cancer?

All those voting yes, please raise your hand?

(Hands raised.)

CHAIRPERSON MACK: We have 6 out of 7.

On those voting no?

(Hand raised.)

CHAIRPERSON MACK: One

So 6 yes, 1 no.

The judgment is that the compound will be listed under Prop 65 mechanism.

Let's take a 10-minute break.

What do people feel, do you want to go to lunch?

Is everybody hungry?

All right, now when -- can we cut it to the shortest possible lunch period or is there a State mandate on how long it takes to have lunch?

(Laughter.)

CHAIRPERSON MACK: 12:30. Okay, we'll commence again at 12:30.

Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just the usual reminder that as you're having lunch, please don't discuss the issues that are coming before you this afternoon.

You can talk about anything you did this morning,

but not this afternoon.

Thank you.

CHAIRPERSON MACK: Believe me, we wouldn't want to anyway.

(Laughter.)

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON MACK: I'd like to compliment the audience on being here before the Committee.

With that, we're going forge ahead. So Martha, you want to give us a prelim?

(Thereupon an overhead presentation was Presented as follows.)

DR. SANDY: Sure. So as we turn our attention now to prioritization --

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DR. SANDY: -- I wanted to remind everyone the purpose of the prioritization is to identify chemicals for evaluation by your committee, the Carcinogen Identification Committee. And the goal of this process is to focus the efforts of the CIC on chemicals that may pose significant hazards to Californians.

I do want to reiterate the prioritization is a preliminary appraisal of the evidence of hazard. By necessity, it's preliminary, because we can't devote all the resources you see we've devoted for writing hazard identification documents.

So here's a little schematic of the process.

--o0o-- and

DR. SANDY: We have something we call the tracking database where we enter chemicals that have come

to our attention or been nominated by individuals from the public and elsewhere for chemicals that should be tracked for possible carcinogenicity.

We screen those chemicals to see if there's any evidence of -- suggestive that there is some carcinogenic activity associated with the chemical, and to see if there's exposure apparent exposure in California.

So those chemicals that have apparent exposure in California and some evidence of carcinogenicity are called candidate chemicals. And what we're doing is we are applying focused literature review based data screens on those candidate chemicals. And as you remember, we're doing both the human data screen and an animal data screen of all the candidate chemicals in our tracking database. And that's about, give or take, it's about 400 chemicals.

And the chemicals that pass those screens are then we look at -- we do a preliminary toxicological evaluation of all the evidence. And the ones that rise to the top we bring forward to you for consideration and consultation. So the box there is where we are today, and we're right now going to consult with you on the chemicals that we've brought to you for review.

And after that, OEHHA makes selections of chemicals for preparation of hazard identification documents, so that's the process.

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DR. SANDY: In this current screening effort, where we're applying a human data screen and an animal data screen, we brought to you last year, and we released in March of 2009 the results of what we'd screened at that point. And at that point, we'd screened about 50 percent of the chemicals, the candidate chemicals.

In July of this year, we released an update. We had, by that time, completed about 75 percent of screening of those 400 chemicals. And we predict that by early 2011 we will have completed screening the candidate chemicals.

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DR. SANDY: So at your last meeting on May 29th, 2009, you considered and ranked 38 chemicals. And today, you'll be considering and ranking 27 chemicals, and presumably at your next meeting in 2011, you'll be ranking the remainder of that screening effort.

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DR. SANDY: So just to refresh everyone's memory, here I'm showing the chemicals, the 38 chemicals, and where your prioritization rankings were for each of them. You prioritized chemicals as high or medium or low. None of those chemicals were placed in a no priority, but that does exist, if you'd like to use that category.

And what you're going to be doing today is

looking at these new 27 chemicals and placing them in one of these four categories of ranking. So we'll just add to these categories.

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DR. SANDY: So in the materials we released, we have this table, and it's a handout as well. This table just provides a quick overview of the exposure characteristics of each of the chemicals and the types of studies that exist for those chemicals that provides some evidence of carcinogenicity. It could be positive or negative evidence. So you'll -- and those are human data, animal data, and other relevant data.

So I know you can't see all of these from the screen, but there's a handout.

--o0o--

DR. SANDY: So now we can move -- can you put up that slide -- to discussion of each of the chemicals. And we will place it in real-time. We'll record how you've ranked them. At this meeting for each of the 27 chemicals, there are two lead discussants that will be proposing a ranking and then the Committee can discuss that further.

So I'll hand it to you, Dr. Mack.

COMMITTEE MEMBER MACK: Okay, thank you Martha. The way I would like to proceed is by the categories

grouped by letter. So we would begin by Group A, then Group B, then Group C. And I would propose that we take each of the chemicals in the category, and then ask each of the lead people to decide how they group them, and in a sentence or two why? And then the person -- the group that's the highest of the two, that is to say the most high priority of the two will then make a vote on the Committee to see whether we accept that grouping.

If that vote fails, then we go to the alternative, if there is an alternative, and see what happens with that.

Is that fair?

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, when you say vote, are you referring to just kind of a advisory vote?

CHAIRPERSON MACK: This is a straw vote.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right, or an advisory opinion.

CHAIRPERSON MACK: Yes, a vote on the advisory opinion.

CHIEF COUNSEL MONAHAN-CUMMINGS: All right.

CHAIRPERSON MACK: I'll give you an example. So we take a particular chemical. Let's say that Dr. Landolph and I both have looked at that chemical. I judge it to be medium priority. He judges it to be low

priority. We'll then take medium priority and ask how the others -- whether the others agree with that.

If the others don't agree with that, then it will be low priority, and see if the others agree with that, which means, of course, that if the others all happen to wish it to be high, then we'll have to discuss it in more detail.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. And then the follow-up question would be also, of course, there will be public comments and then you can rerank it.

CHAIRPERSON MACK: Yes, this is a tentative first shot. And then after the public comment, we'll make a judgment as to whether or not we accept all of them as they have been ranked to date. Does that sound good?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, that's find. I just wanted to point out it was advisory.

CHAIRPERSON MACK: There's a gentleman from the back who wishes to make a comment.

MR. LANDFAIR: Thank you, Dr. Mack. I'm Stan Landfair from McKenna, Long & Aldridge.

DIRECTOR DENTON: You need to use the microphone

CHAIRPERSON MACK: You have to get the mic.

MR. LANDFAIR: I'd like to ask for a clarification. Dr. Mack, I'm Stan Landfair from McKenna, Long & Aldridge. And I'm here in the capacity of

representing 3M today. But my point of order or question addresses the totality of the chemicals. Do you proceed and tend to proceed sort of bunch by bunch or do you want to hear the recommendations on all of the chemicals to see where they lie relative to each other before you take your action?

CHAIRPERSON MACK: We're going to go chemical by chemical beginning with the four in Group A, 1, 2, 3, and 4. Then the four in Group B. Then having gone through all the chemicals and having a collective decision on how we do it, we get the public comments for each of the chemicals that they're concerned about. And then we resolve any and we discuss that and resolve any inconsistencies.

MR. LANDFAIR: And I'm not trying to be a pest here, but then you'd anticipate some reordering at the end when you've got the whole group in context, because it seems like prioritization implies that one is relative to another. And we can't set priorities just looking on four at a time.

CHAIRPERSON MACK: No, no. One at a time.

MR. LANDFAIR: Nor can we do it one at time, but that we need to look at all of the chemicals as a group.

CHAIRPERSON MACK: I'm sorry. You're misunderstanding me.

MR. LANDFAIR: Perhaps I am.

CHAIRPERSON MACK: The letter grade only is the order in which we take each one.

MR. LANDFAIR: Yes.

CHAIRPERSON MACK: So the first thing we will take is methylphenidate and its salts. We will decide what we think about that here. Then we'll go to the next one and then go through all of them. And then after having gone through all of them, we'll look at the comments that have been suggested, for which there are really only three compounds that the public wishes to comment on.

We'll hear those three comments, and we'll then rediscuss those three comments -- those three compounds okay. And having done all of that, we'll file a final categorization of each of the 27.

MR. LANDFAIR: That's what I was waiting to hear. At the end, after you've heard all the comments to all the preliminary votes, then you'll look at the group in toto and decide relative to each other whether they fall.

CHAIRPERSON MACK: Yeah. We'll be deciding relative to each other as we through. But you're right, we'll summarize it at the end.

MR. LANDFAIR: There's a little wiggle room --

CHAIRPERSON MACK: Well, we'll put each one in a

high, medium, and low category.

MR. LANDFAIR: Yes.

CHAIRPERSON MACK: And this is based not on comparison with the other 26, but based on what we think is the public's best interest.

MR. LANDFAIR: Right.

CHAIRPERSON MACK: Okay.

MR. LANDFAIR: And then at the end, when you've looked --

CHAIRPERSON MACK: At the end, we'll recategorize each of them.

MR. LANDFAIR: Yes. Then there could be a little reshuffling at the end depending on how you've looked at everything.

Yeah, okay, thanks. Thank you for explaining it. I think we're clear now.

CHAIRPERSON MACK: I'm sure I explained it very clearly.

(Laughter.)

MR. LANDFAIR: I'm sure you explained it perfectly and it was my failure to comprehend the first time, but I do understand now.

(Laughter.)

CHAIRPERSON MACK: It's not a simple process.

MR. LANDFAIR: Thank you.

CHAIRPERSON MACK: Okay. We're are we ready to go. So let's begin with methly -- first of all, the first four are Dr. Hamburg and myself.

So the first four -- the first one on the list is methylphenidate and its salts. Sol, how do you think we should rank that chemical?

COMMITTEE MEMBER HAMBURG: I would rank methylphenidate high. I believe it is a commonly used agent throughout medicine in both children and adults. There's enough epidemiological data to support having some concern, and I would therefore recommend that we consider this in a high category.

Did you want to comment on that?

CHAIRPERSON MACK: I view it in the same way. I think it's very important to a lot of people, because it's used to treat a large number of children, as well as some adults, and there are reasons for concern, so I also would call it high.

So can I borrow the pen so I can write that down. Thank you.

So the next one is omeprazole.

COMMITTEE MEMBER HAMBURG: Omeprazole.

CHAIRPERSON MACK: Do you want to have a stab at that one.

COMMITTEE MEMBER HAMBURG: I would consider

looking at the next three together. They're all very similar agents. They're used for the inhibition of hydrochloric acid in the stomach. There is no epidemiological data to support any carcinogenicity.

However, there is some animal data that makes it of some concern. It's also a very commonly used agent. There are millions of doses prescribed annually, and I would put it, because of the lack of epidemiological data, I would put it in a medium group, simply because of the commonality. And I would put all those three drugs in the same category.

CHAIRPERSON MACK: Okay, I have a slightly different opinion.

DR. ALEXEEFF: Dr. Mack, can we just name -- excuse me. This is George Alexeeff. Can we just name the three drugs again, just to be clear.

COMMITTEE MEMBER HAMBURG: Oh, yes. Pantoprazole and rabeprazole which is in IV form, sorry.

CHIEF COUNSEL MONAHAN-CUMMINGS: And the third one.

CHAIRPERSON MACK: In my opinion, omeprazole is a very commonly used, both over the counter and in redescription form to a great many people. And there actually is some epidemiologic data. There's at least one study that you may have missed, because you were looking

at the actual molecule, the actual drug, rather than the category of drug. And maybe I could ask Anna to comment on the one study that don't know about --

COMMITTEE MEMBER WU: Okay. Well --

CHAIRPERSON MACK: -- which is written by somebody named Wu.

(Laughter.)

COMMITTEE MEMBER WU: Well, actually I'm not the only person who's been very interested in this class of drugs. There is an epidemic of esophageal adenocarcinomas worldwide, especially among white males. So there has been since the late 1980s, early 1990s, a series of case control studies done in the United States, as well as in western European countries, that have been trying to understand causes of this epidemic of esophageal adenocarcinoma. And one of the several risk factors that have emerged from this group of case control studies, namely reflux disease, high body mass index, and cigarette smoking.

In the process of evaluating or conducting these case control studies, we've been interested in looking at not only the conditions of reflux, but as well as the treatment for reflux disease. And the class of medications that we've been looking at is over prescribing antacid as well as over the counter antacids.

And there is a number of studies, including one that we conducted in Los Angeles that suggests that long duration of use of various types of antacids might be associated with the increased risk of esophageal adenocarcinoma.

As many drug studies -- as many exposures and cancer risks, you essentially need to have a population that is exposed to the agent for a long duration -- long enough duration of time before you can actually observe the findings. And I think we are essentially, at the beginning of these studies, that have accrued enough individuals who are exposed to them for a long enough period of time.

So I think there's a concerted effort certainly. We actually have an international consortium right now that's looking at both esophageal adenocarcinomas as well as Barrett's esophageal disease to try to understand really what the causes of the shift in the histology of esophageal carcinoma especially in western populations from the traditional squamous cell cancer histology to adenocarcinoma.

So I think there's certainly going to be a lot more data. And this international consortium that I am a member of, we are in the process of actually pooling the data sets from all of us who have collected extensive

information on medication use and trying to come up with comparable exposure variables across the studies, so that we can more meaningfully look at both indication of use, duration of use, specific medications, and all of those other details. So I think this information will be forthcoming.

But I certainly -- the individual case control studies, as well as pharmacy-based linkage studies have certainly suggested there is some risk associated with various types of these drugs. But I think what we really want to do is separate out both the indication of use, as well as the medications themselves.

CHAIRPERSON MACK: So that's the basis for my concern that there is some data suggesting that there might be an increase in esophageal adenocarcinoma. Although, I don't think it's by any means for sure, but I think we need to think about it as a high priority.

I would put the other two in the same category, only because it looks as though they're producing adenomas in animals of the same kind as this compound, and I think they should all be discussed at the same time.

So I would vote that all three of these get a high for slightly different reasons, if I can talk Sol into that.

COMMITTEE MEMBER HAMBURG: Yeah, I mean it's very

interesting, what Dr. Wu is describing obviously. But you've got to separate the chemical carcinogenesis from possibly the effects of inhibition of acid.

So it's not clear that what she's alluding to is going to be related to chemical carcinogenesis, but may be related to the effects of the drug -- the appropriate effects of the drug.

So for that reason, I'm okay with going to high, but I'm not convinced that what Dr. Wu is suggesting is related to chemical carcinogenesis.

CHAIRPERSON MACK: I don't think either Dr. Wu or myself would disagree with you. I think it's quite possible it will turn out to be the indications for the drug. My vote would be because of the presence of some data suggesting that there's an association. And because of the frequency with which these drugs are used, there's going to be a very high level of concern among a lot of people.

And therefore, I think it's probably good that we deal with it as soon as we can, relative to other priorities.

COMMITTEE MEMBER HAMBURG: I can certainly support that.

CHAIRPERSON MACK: So is everybody agreed that we should put this on the high list?

Okay, let's go then to the -- and we put all three of them in the same category. Then we go atrazine.

David.

COMMITTEE MEMBER EASTMOND: Well, as you know, atrazine is a widely used herbicide. It's the focus of a lot of concern and discussions. I believe the EPA is doing a series of hearings on various effects of atrazine currently. So it is a very high profile chemical.

Certainly, there are multiple reports of non-Hodgkin's lymphoma in humans. I wasn't sure if these were all separate studies that were listed or if they were essentially studies which were reporting the same thing over and over, the increased risks of non-Hodgkin's lymphoma, but there were four or five of them listed here, which would raise certainly concern for me.

And you also have the sort of a lot of mechanistic evidence for malignant mammary tumors in rodent models, which is quite a routine, regular sorts of reports.

I will say from a mechanistic point of view, I mean, the mechanisms by which atrazine is believed to work is one of the key mechanisms of interfering with aromatase enzyme which you could evoke -- understanding could be related to these mammary tumors. But apparently a number of multiple authoritative bodies have downplayed the

significance of those mammary tumors.

So I guess my take on this is simply because of widespread public concern and discussion that I would probably put it in the high category, and the multiple reports both in animals and humans. And I'm not certain it will be ultimately listed, but it would be a high priority I think.

CHAIRPERSON MACK: Thank you, David.

Anna.

COMMITTEE MEMBER WU: I would agree. I would put it in the high category. And I think the large number of human studies that have been reported. Actually, most of them are really in independent studies, so they're not reporting on the same series.

I mean, there are a number of papers from the agricultural cohort study. But I think it's also important to note that it's not just the non-Hodgkin's lymphomas and leukemias, but there are a few studies suggesting ovarian cancer risk as well. So I think it's worthy of consideration, in terms of high priority.

CHAIRPERSON MACK: Does everybody agree then that this compound goes in the high category?

Hearing no opposition.

We'll go on to the next one, clomiphene and its salts.

David.

COMMITTEE MEMBER EASTMOND: Okay. Again, this is a drug which is used to treat infertility, induce ovulation in women, and also treat oligospermia in men.

My impression this is widely used. There have been quite a few studies which report an increased risk of different types of cancers. Those tend to be cancers, certainly hormonal related cancers. But there are enough of them to raise certainly a high flag from an epidemiological point of view, including some meta-analysis.

The animal data is really not sufficient to really make much of a weight on it, but I would still, because of the large number of studies that suggest there's maybe a relationship that it would be a high priority.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: I agree. And I think the epidemiologic studies also covered various types of epi studies from following up women who were treated as well as cohorts of infertile women and the subsequent risk of cancer. So I think it's -- I would vote for high category.

CHAIRPERSON MACK: Does anybody disagree with a high category for clomiphene and its salts?

Now, we come to Malathion.

COMMITTEE MEMBER EASTMOND: Malathion has been, as you know, is a widely used organophosphate insecticide. It's been used for many years, 30 plus years. It's been the focus of quite a few studies. It would appear that there's really mixed results in epidemiological studies.

The one cohort study listed indicated there was no association of Malathion in any of the cancers they were looking at that. And that was a -- it seemed to be a large study of licensed pesticide applicators.

In the animal studies, there's some suggestion about increases in tumors in some studies, not in other studies. This has been a compound which has been, I think, widely reviewed by many different authoritative bodies. And I think most of those, based on the public comments and some of the stuff I've looked at, have not been overly concerned about the carcinogenicity or thought there was some suggestion of it. I would probably put this in a medium to low category. Just judging from this, probably put more in the low category.

CHAIRPERSON MACK: Okay. Anna.

COMMITTEE MEMBER WU: I would vote to put it in the middle category. And I understand that there's really been a large number of studies. And the human studies are very mixed. But I think one of the positive studies from

Canada, I think is actually probably one of the better done studies. And, in fact, their finding are probably stronger than some of the other studies, so I would probably put it in the middle category.

CHAIRPERSON MACK: I'm going to weigh in on this one just for a minute.

Most of the studies of occupational exposure are either in farmers or pesticide applicators, do have some consistency. But the difficulty is that the people who are exposed are exposed to a lot of different pesticides as well as animals. So the question is whether these lymphomas, which are generally the finding, are due to viral exposure or they're due to pesticides. And some of the times it's Malathion and some of the times it's other pesticides.

There are a couple of recent reports suggesting that pesticide exposure may produce consistently, even in people without the lymphomas, chromosomal translocations between chromosome 14 and chromosome 18. And this particular chromosomal translocation is very characteristic of one kind of lymphoma, namely follicular cell lymphoma. And that is the kind that's usually associated when there has been enough detail to say it. This is the kind that's often associated with farmers.

So I think there's a question about Malathion and

the other pesticides. It's not completely clear. And I suspect that more information will be coming to light relatively soon.

So I would be very much against putting it in the low category. My only inclination would be to put it high, but it seems like other people would think that medium is more appropriate. You stand with medium?

COMMITTEE MEMBER WU: Yes.

CHAIRPERSON MACK: Okay, is everybody -- can we talk you into medium?

COMMITTEE MEMBER HAMBURG: Yeah, I'd like a point of clarification. We're not suggesting when we're listing this that we're not going to review these. We're trying to get a priority list about the effect on Californians and see how to move through this. So the fact that Malathion may be carcinogenic, is it of significant effect on the population in California that we should be listing it high?

We can't overburden the staff members. So I would consider relatively low, even though there is concern.

CHAIRPERSON MACK: Well, I think that's a question. My impression is that Malathion has been used in community spraying to try and get rid of fruit flies from time to time in California.

And that means the entire population has been periodically exposed, but I have no idea of how commonly that is now or how commonly it will be. Does anybody on the staff have any information about that?

DR. SANDY: I can't predict the future use of it in communities, but it is used on crops and food so.

DR. TOMAR: Yeah, it's not only used for the crops, but sometime -- I mean to get to it -- we spray in the population in certain crops. Malathion has been used for a long time and for too much population has been exposed. So it's used usually as the organophosphate and it's also used to eradicate the pest throughout the state or half of the state when some infestation problem arises.

CHAIRPERSON MACK: Well, let's abide by my initial proposal as to how we proceed. It seems like we have a vote for medium. So the question is how many on the Committee would support a vote for a medium, raise your hands?

DR. ALEXEEFF: Dr. Mack.

CHAIRPERSON MACK: Yeah.

DR. ALEXEEFF: I know you're voting. I'm sorry I'm interrupting you. George Alexeeff. But it seemed like one of the questions has to do with the usage. That's something we can look up. And certainly we would know tomorrow, because we would look at the pesticide use

reports by tomorrow, but we can talk with DPR.

CHAIRPERSON MACK: George, there may not be a tomorrow.

(Laughter.)

DR. ALEXEEFF: I realize that. I realize there may not be a tomorrow.

So the other possibility could be is if the usage -- it's my impression the usage has gone down dramatically in California, because of the other compounds that are being used instead of it, even for things such as what you're referring to as fruit flies, because of the sterile fruit flies and things like that, and other pheromones and things.

So that's my impression, but I haven't -- I'm not fully aware of the data. We could look it up.

COMMITTEE MEMBER HUNTER: Well, we certainly know the negative ingestion usage study by B.T. Collins, et al. I think about 20 years ago, don't we. I assume everybody remembers B.T. Collins.

DR. ALEXEEFF: Is he still here?

COMMITTEE MEMBER HUNTER: Well, he drank it.

(Laughter.)

DR. ALEXEEFF: Another option is that you could wait on voting on this one, and DPR staff are in this building, and we could actually find out the information

and come back to you before you're through with prioritization, if you'd like, for us to find out about the usage.

CHAIRPERSON MACK: Or alternatively maybe we should make a judgment based on the two alternative assumptions. In other words, if we find that -- if it turns out that usage is actually very uncommon, we'll call it low. If it is, in fact, common, we'll call it medium.

DR. ALEXEEFF: Dr. Mack, we're going to look it up right now. My guess we'll know probably within an hour, if not sooner.

CHAIRPERSON MACK: All right. So let's just put that one off.

DR. ALEXEEFF: We could probably just pick this up at the end of the list here.

CHAIRPERSON MACK: Let's therefore move to the next compound, which is PFOS.

David.

COMMITTEE MEMBER EASTMOND: PFOS is again this is another high profile chemical. It was used in a variety of manufacture of industrial and household products. And it's my understanding that the production was stopped about eight years ago, and actual exposures have been decreasing over all levels, but there's still concern about some populations of exposure.

There's some suggested evidence of potential increases of bladder cancer in study in humans. Another one showed no increase in bladder cancer risk. In the animal studies, there were a variety of different tumors which were reported to be induced by PFOS. However, these were -- increases were actually fairly modest when you looked at them.

And I guess this is one of them which there is a potential for bioaccumulation, which is another concern. So you know I would put this, I think, in the sort of medium to high category. But I think because of the public concern and discussion about it, it probably would rise into the high category.

CHAIRPERSON MACK: Anna, did you look at this?

COMMITTEE MEMBER WU: I looked at a little bit of human data. And I would put it in the medium category.

CHAIRPERSON MACK: Medium category?

COMMITTEE MEMBER WU: Yeah.

CHAIRPERSON MACK: So is there a consensus that medium will suffice for PFOS?

Anybody object?

Okay, so then we go to Group C. Let's have Martin start off with alpha-methyl styrene, which is probably on the computer right in front of you.

COMMITTEE MEMBER HOPP: Alpha-methyl styrene is

an industrial compound used in making copolymers and resins. It's essentially occupational exposure, not widely used. There have been very few reviews on this by other cancer agencies. And I think it comes up now because there are a small amount of animal studies in mice and rats, and they are conflicting. They're positive in inhalation for males in rats and positive for females in mice.

Genotoxicity is positive, but the amount of studies are limited. So I think it's an occupational chemical that has limited exposure and limited studies. I think it needs to be evaluated, but I wouldn't put it high. I marked it in the low category, low to medium. And low to medium because of the few studies that are there show some variability in carcinogenicity. And I think that for that reason those studies need to be looked at. I think there is some action there.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: Really this comes down to kind of looking at the animal studies, which were conducted by the National Toxicology Program in 2007. And in the materials we received, there's a lot of tumors listed, but they're actually, in the NTP parlance, the effects are kind of suggestive or modest.

The one that drives it is essentially the

hepatocellular adenomas and carcinomas, which was a clear increase in the females, and they consider that clear evidence. So based on the strength of that and the widespread usage, I would probably put it in the medium category. But it was kind of medium low in my ranking, but I would go medium on it.

CHAIRPERSON MACK: So of the two medium is the highest, you want to try that? Does anybody object to putting that compound in the medium category?

Marty, is that okay with you?

COMMITTEE MEMBER HOPP: That's fine.

CHAIRPERSON MACK: Okay. Now, we're to decaBDE.

Marty, you want to take that.

COMMITTEE MEMBER HOPP: DecaBDE is a very common flame retardant, and it's come up -- it's been evaluated before by IARC as well as the U.S. EPA. In IARC, it was not identified as a carcinogenic. But since that time, I think one of the biggest problems in general is its commonality and usage all over the place. And the second thing is that it's being detected now in breast milk, a very common component of breast milk.

Because of the increased awareness of this and it's, I think, sensitivity of the population, I put this in a medium to high evaluation category, because of its --

CHAIRPERSON MACK: David.

COMMITTEE MEMBER HOPP: -- increased in the findings of its commonality in the community.

COMMITTEE MEMBER EASTMOND: I generally agree. This is certainly another high profile chemical, of particular concern in California, where there's been increasing levels of these polybrominated diphenyl ethers found in individuals and breast milk, et cetera.

You know, I think what's driving this, in my opinion, is more of the concern for this -- the biggest concern I have about this group of compounds is not the deca form, per se, but it breaks down into the other derivatives that are these polybrominated derivatives, such as the octa and penta. And those apparently have other effects associated with them. So because of public concern, and this is of particular concern for California I'd put it in the medium category.

CHAIRPERSON MACK: So you're in agreement with the medium category.

Does anybody object to that?

Okay, decalin.

Marty.

COMMITTEE MEMBER HOPP: Decalin is another industrial solvent used in resins and oils. This has not been reviewed before, except in toxicological studies. And it is fairly toxic.

It's negative in genotoxicity studies. There is, again, mixed reports in both mice and rats for renal tubular adenomas. Again, variations in female and male. It seems to be fairly common here that we get different sex in female and male susceptibility between rats and mice, as we keep seeing. This alarms me a little bit, and I think it's worthy of evaluation. It's lack of public usage and widespread exposure, I think puts them in the low to medium category.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: It's my understanding that what largely is driving this is the results from the national NTP bioassays. And it's kind of an interesting compound, because there's a certain type of tumor that's induced in male rats that's caused by an accumulation of alpha 2u-globulin. And it's the impression that NTP specifically decided to test this chemical to follow the pathology of this type of agent as it went through the progression of the disease to the cancers.

And the disease -- the outcome is what was kind of predicted. They saw the kidney tumors in the male rats. They also saw the pheochromocytomas, but apparently that was highly correlated with the kidney tumors, and they thought there might be some relationship.

So this would be one of these examples where I

think it's -- the predominant mechanism appears to be one which is widely accepted as not being of great relevance to humans, so I would put this in the low category, but it does have widespread usage.

CHAIRPERSON MACK: Okay. Do you have a agreement a low. Does that make it a low category?

COMMITTEE MEMBER HOPP: Yeah, low is fine.

COMMITTEE MEMBER WU: I think Marty is right.

COMMITTEE MEMBER HOPP: I didn't hear you.

CHAIRPERSON MACK: Do you agree with low.

COMMITTEE MEMBER HOPP: I'll take low.

CHAIRPERSON MACK: The next special --

I'm sorry. I guess that's because it's not on.

Ciprofibrate is a -- I'm sorry. I'm blocking on the word.

COMMITTEE MEMBER EASTMOND: Hypolipidemia.

CHAIRPERSON MACK: Hypolipidemia lowering compound, but it's not in the PDR. I have no idea what the distribution is. In other words, I don't know whether it's on the market, and if it's widely sold or not.

COMMITTEE MEMBER HAMBURG: It's going out of -- it's going out of favor. It's not typically used. It's not very commonly used.

CHAIRPERSON MACK: That's what I thought.

COMMITTEE MEMBER HAMBURG: It's about a 20-year

old drug. Over the past decade, it's not commonly used, yes.

CHAIRPERSON MACK: Okay. Joe, go ahead.

COMMITTEE MEMBER LANDOLPH: Yeah, I had the same question about the exposure, which made it a little difficult for me to rank this. There is carcinogenicity data, but it's usually liver. And there was some argument made many years ago that because you weren't getting a lot of peroxisome proliferation in human livers, that if you believe that in rodents peroxisome proliferation is related to liver tumors, then it might not be relevant to humans. That thinking is not quite so solid these days as I understand it.

So there is carcinogenicity data. There's genetox data. And I rank it in a medium to low priority, somewhere in there.

And I'll defer to the exposure.

CHAIRPERSON MACK: Well, I put it in the low basically because I thought it was not used very often, and I didn't think the animal data was very convincing.

So do we agree on low?

COMMITTEE MEMBER LANDOLPH: Yeah, that's fine.

CHAIRPERSON MACK: Any object to low?

Okay, the next one is gentian violet.

Joe.

DR. ALEXEEFF: I can report back on Malathion.

CHAIRPERSON MACK: My God.

(Laughter.)

DR. ALEXEEFF: Computers are great.

Okay, so in terms of the use data in California, it has gone down, but it still is widely used. In 1998, there were 666,000 pounds used in that year. In 2007, there were 474,000 pounds. So it's gone down about 50 percent, but it still is 474,000 pounds used. That's still fairly widespread.

CHAIRPERSON MACK: That doesn't drop it to a low for me, but it might for everybody else.

COMMITTEE MEMBER HAMBURG: Just as a point of interest. Where do you find data like that?

DR. ALEXEEFF: Where do we find the data? From the Department of Pesticide Regulation.

COMMITTEE MEMBER HAMBURG: It shows the tonnage?

COMMITTEE MEMBER EASTMOND: Yeah, that's available.

CHAIRPERSON MACK: Okay. Joe.

COMMITTEE MEMBER LANDOLPH: Thank you. I was at a scientific meeting last week and Gloria Calaf from Chile spoke on Malathion. And it woke me up, because I was sleeping during most of the talks. And they have some data, which they think suggests that it may cause breast

cancer in rodents. So that woke me up.

And then I recall them spraying Malathion and people shooting at the helicopters and all that. So like you, I initially was at a high, but there is a lot of criticisms of that breast cancer data. So I think I could be comfortable with a medium on that.

CHAIRPERSON MACK: Can I talk you into medium, Sol?

COMMITTEE MEMBER HAMBURG: Yeah, sure.

CHAIRPERSON MACK: All right. Let's go for medium. Does anybody --

COMMITTEE MEMBER EASTMOND: I was a low, but that was fine. Medium is fine with me.

COMMITTEE MEMBER HOPP: I think medium is fine.

CHAIRPERSON MACK: So we've got down to gentian violet.

Joe.

COMMITTEE MEMBER LANDOLPH: Interesting that this is used in the Gram stain, which all the medical students and some of the physicians do all the time. There is carcinogenicity data on it. I think, in my opinion, it was used widely enough that I would be comfortable with a medium on this.

There is hepatocellular carcinoma in male and female mice, and there's lifetime feeding studies in rats,

which gives you an increase in thyroid follicular cell adenoma. And hepatocellular adenoma in males. So I could live with a medium. And there also are some structure activity considerations, with other compounds that are carcinogens. So I would go with a medium on this. I'm curious to see how it comes out, because we use the Gram stain every year when we teach the medical students how to do the Gram stain.

COMMITTEE MEMBER HOPP: This chemical is more widely used than that even exponentially more. It's used as a cancer screening agent in cancer and other areas. So I think that it's usage is much higher than you appreciate in a commonality in medicine and other areas. So if there's any suggestion that there's some carcinogenicity or concern here, I think it's our duty to -- I would put it at least medium, if not higher.

CHAIRPERSON MACK: I was going to go for low, but you've talked me into medium.

COMMITTEE MEMBER HOPP: It's usage is huge. It's huge.

CHAIRPERSON MACK: So does anybody object to medium?

COMMITTEE MEMBER HOPP: It's huge. And the other problem is that it's -- if you've ever had gentian violet or every used it, it stays in your skin for a long time.

It stains you and you've got it for a week. So I think that if there's some concern here on carcinogenicity --

CHAIRPERSON MACK: The chemical activity though in lung preceded its appearance. In other words, it probably stains the skin is no longer attractive. I have no idea. I have no idea.

CHAIRPERSON MACK: Is everybody --

COMMITTEE MEMBER EASTMOND: I would put high on this one.

COMMITTEE MEMBER HAMBURG: And I would put low on this one.

(Laughter.)

COMMITTEE MEMBER HAMBURG: So just to keep it confusing.

First of all, Joe, you're dating yourself. Medical students don't do Gram stains anymore.

COMMITTEE MEMBER LANDOLPH: Ours do, our medical students.

COMMITTEE MEMBER HAMBURG: Oh, really. Okay, well, you know, UCLA doesn't.

(Laughter.)

COMMITTEE MEMBER HAMBURG: That's number one.

Number two, again, I want to reiterate to the Committee that we're not looking at whether things are carcinogenic or not at this point. We're looking at

whether they should be prioritized for the staff to work on all these chemicals at the same time.

For that reason, I would put it on the low level. The toxicity seems relatively low as compared to some of the other agents. And again, as a priority, I do not think even though it is widespread, it is very confined to certain small populations. So I'm inclined to put it on a low end.

CHAIRPERSON MACK: All right. We have an impassioned plea for low, and a bimodal plea for medium. So let's take a vote on medium. Everybody who wants medium, raise their hand?

(Hands raised.)

COMMITTEE MEMBER EASTMOND: I was at high, but medium is good.

COMMITTEE MEMBER EASTMOND: Medium is better than low, so I'm okay.

CHAIRPERSON MACK: How many people want low?

(Hands raised)

CHAIRPERSON MACK: One, two. You lose.

COMMITTEE MEMBER HOPP: Okay.

COMMITTEE MEMBER HAMBURG: Okay, not the first time.

CHAIRPERSON MACK: Isoniazid.

Joe.

COMMITTEE MEMBER LANDOLPH: This one is really interesting, so we'll have a lot of debate on this.

There's genetox data, Salmonella chromosomal aberrations, SCEs. There's lung tumors in four studies in animals. And there's positive subcutaneous and IP studies. And there's a drinking water study that's positive. And it's a front line TB drug. It's also used to prevent TB in people that might have been exposed to it.

Interestingly, the epidemiology study is negative, and I hope Anna and Tom will comment on that. They've looked in TB patients, and I guess that's 9 out of 10 studies. Just one observation of a mesothelioma.

So this may be one of those interesting cases where the animal studies are positive, but the epidemiology is negative for whatever reason. But I think it's used so widely, I put it in a high category myself.

CHAIRPERSON MACK: Well, we certainly have a difference of opinion about this one. I put it in a low category. And I put it in low because it was reviewed by IARC a number of years ago, and -- it was reviewed by IARC a number of years ago, and there hasn't been a darn thing that's positive since. So my inclination is to put it in the low category, because there's nothing new to evaluate.

But again --

COMMITTEE MEMBER LANDOLPH: You want to compromise on medium.

(Laughter.)

CHAIRPERSON MACK: Sure, I don't care. Does anybody else have views.

Sol, back me up.

COMMITTEE MEMBER HAMBURG: No, I back you up 100 percent. I think it's been looked at for many, many years. And actually as a relative important agent, although it's used commonly for those patients that have an indication for it, it's not generally used within the population. So exposure is high in a very small subgroup of Californians, and I don't think it needs to be highly prioritized.

CHAIRPERSON MACK: I would also say that a couple of the epidemiology studies, one by -- John -- the cohort of people who got pulmonary --

COMMITTEE MEMBER WU: No, agree. I think it's -- I can't remember the guy's name, but I --

CHAIRPERSON MACK: John, John, John -- anyway, the guy who looked at x-rays in people with tuberculosis.

It was pretty well done and it was pretty negative and he considered it negative.

COMMITTEE MEMBER WU: I would agree.

CHAIRPERSON MACK: So we have a low, a medium --

COMMITTEE MEMBER HOPP: I have another opinion.

COMMITTEE MEMBER HAMBURG: Of course.

CHAIRPERSON MACK: Low?

COMMITTEE MEMBER HOPP: While this is a medication that is used in a very specific population, that population is extremely susceptible to any type of carcinogenic activity. They're weakened. They're in a very vulnerable state. And I'm thrilled with the fact that the Committee is addressing the use in the population of how this chemical affects the people of California in a widespread manner, equally as well as what the carcinogenicity animal studies suggest for -- as a value to our investigation.

As a function of the population, I think this is a fantastic way to address things, as an importance to the people in California, as well as the importance of the scientific data that's erupting.

I think that people that receive isoniazid have -- you know, commonly have tuberculosis. And some of these people are the most susceptible to chemical affects. And if there are issues of new carcinogenicity issues that are coming up since the old studies, I'd rather see that in a relative than some of the studies that are just done with animals, no epidemiology and it's not that commonly used.

CHAIRPERSON MACK: Let's see a show of hands for medium?

(Hands Raised.)

COMMITTEE MEMBER WU: What are you voting?

CHAIRPERSON MACK: For medium as opposed to low.

So we've got two votes for medium.

How many votes for low?

(Hands raised.)

CHAIRPERSON MACK: One, two, three, four.

Okay, you win.

I call this one low.

Quinoxaline-1,4-dioxide compounds and desoxycarbadox.

Joe.

COMMITTEE MEMBER LANDOLPH: This one has got a lot of studies on it, tumors in rats, liver tumors, four out of four studies. IP liver tumors. No epidemiology on it. Genetox is positive in salmonella, E. coli, micronuclei, chromosome aberrations. And it's metabolized to hydrazine, which is a carcinogen.

And the exposure so so. It's an antimicrobial agent used to improve growth as a promoter for livestock. And banned in the EU, not approved in the U.S. So I gave it a two, medium priority.

CHAIRPERSON MACK: I actually, based on that,

thought about giving it a high priority, but I could be happy with medium. Does anybody object to medium?

COMMITTEE MEMBER HOPP: Is this completely banned in the United States?

CHAIRPERSON MACK: No. Well it is banned in the United States, but it's still in a lot of people --

COMMITTEE MEMBER HAMBURG: It's in silo.

DR. SANDY: If I could -- actually, one of the chemicals, the carbadox, has been approved by the U.S. FDA since 1998, for the control of swine dysentery and bacterial swine enteritis, and other uses.

And the desoxycarbadox is a metabolite of carbadox. So it is used in the U.S. and we also were reporting that the chemicals have been detected in the U.S. and Canadian surface waters and wastewater effluents. So we think there's exposure.

CHAIRPERSON MACK: So does anybody object to medium? Are you happy with medium, Marty? Grudgingly?

COMMITTEE MEMBER HOPP: Grudgingly.

(Laughter.)

CHAIRPERSON MACK: Anybody object?

So medium it is.

Acephate. Do you want to start, Marty?

COMMITTEE MEMBER HOPP: No. I'm getting tired of being beat up.

(Laughter.)

COMMITTEE MEMBER HOPP: Acephate. I question it -- it's a common usage for insecticides. I don't know what earwigs are, but I'm sure interested in finding out.

Again another -- no epidemiological studies whatsoever.

COMMITTEE MEMBER HUNTER: They're pincher bugs.

COMMITTEE MEMBER HOPP: I'm sorry?

COMMITTEE MEMBER HUNTER: They're pincher bugs.

COMMITTEE MEMBER HOPP: Pardon?

COMMITTEE MEMBER HUNTER: Earwigs are pincher bugs.

COMMITTEE MEMBER HOPP: Thank you.

Fairly common exposure in our fruits and vegetables. Again, no epidemiology data. Mice and rats have some activity. Seem more toxic to me than carcinogenic. It decreases cholinesterase activities. Again, seem to be more toxicity than carcinogenicity on my review. And so I gave it a low evaluation, low to medium at the most.

CHAIRPERSON MACK: I'm sorry, I didn't hear you.

COMMITTEE MEMBER HOPP: Low medium.

CHAIRPERSON MACK: Low, okay.

Joe.

COMMITTEE MEMBER LANDOLPH: I gave it a medium.

CHAIRPERSON MACK: For the same reasons?

COMMITTEE MEMBER LANDOLPH: Yeah, mainly the carcinogenicity data is positive, and cell transformation is positive. No epi. And based on the exposure, I gave it a medium, and the carcinogenicity

CHAIRPERSON MACK: So medium

Medium.

Amitraz. Marty.

COMMITTEE MEMBER HOPP: The is the insecticide group. So we have more insecticides. Again, no epidemiology. The long-term mice studies and rat studies showed a moderate amount of work. The EPA studies -- wait a second here. Just give me a minute here.

Started to -- EPA studies showed mild genotoxicity. Although, there was some P450 induction. There are no large-time reviews of this, so I thought that this was something worth evaluating. But again the insecticides that have mixed results, I put in the low to medium category.

CHAIRPERSON MACK: Low or medium?

COMMITTEE MEMBER HOPP: More on the low side.

CHAIRPERSON MACK: Low side.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, there's a positive carcinogenicity studies in mice. And let's see

the genetox is pretty much negative. It doesn't show very much. And the exposure is moderate. I put in the medium category initially

CHAIRPERSON MACK: All right, so we have one medium and one low.

COMMITTEE MEMBER LANDOLPH: I don't feel real strong about that, so you know, if you want to talk it down to low, it's okay with me.

CHAIRPERSON MACK: Okay. Does anybody object to low?

No.

So let's go to the next one, furfural.

Marty.

COMMITTEE MEMBER HOPP: Furfural. We're getting away from insecticides. Now, we're on to refinery products. This is very common in rubber cement, fungicides. It's in foods. So there is some commonality to all of this, in general. This was reviewed by IARC, and found to be not carcinogenic in 1995.

Since that time, there's been some increased genotoxicity studies. So while there's -- as affecting these DNA cross-link formations for Burkitt's lymphoma. I think it's that genotoxicity study and the mechanism of its action that's stimulated more interest in evaluating it. It's an aliphatic aldehyde, and then general are not

so good. Again, no cancer epidemiology studies.

Normally, I wouldn't even suggest looking at this, but the genotoxicity studies and mechanism of action elucidation starts to raise this level of concern to me, so I go from low to medium on this also.

CHAIRPERSON MACK: You're choosing between low and medium how?

COMMITTEE MEMBER HOPP: Because I think the new data has been available since IARC study. It makes it a little scarier. The genotoxicity and these so-called DNA protein cross-link formations, otherwise known as DPX efficacy in the development of lymphomas is positive and that kind of scared me.

CHAIRPERSON MACK: So you're going medium?

COMMITTEE MEMBER HOPP: Yeah.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, the exposure, you know, making it a flavoring agent, gives it high exposure. And carcinogenicity studies are positive in male and female mice, and in male rats. It's also an initiator and a co-carcinogen. And like Marty said, the genetox data has some positives in it, destabilization of calf thymus DNA, some salmonella, some Drosophila sex-linked recessive lethal mutation assays, mouse lymphoma, cell mutation assay is positive in mammalian

cells. And SCE's, chromosomal aberrations in Chinese hamster V79 cells.

So based on the genetox data, the two animal studies which are positive, one in male and females, the other one in males. Initiator co-carcinogen and its widespread use as a flavoring agent. I would give it a medium comfortably.

CHAIRPERSON MACK: Thank you.

Does anybody object to a medium for furfural?

Phosmet. Marty.

COMMITTEE MEMBER HOPP: Back to insecticides, common usage. Grapes, fruit trees, nuts, fairly common. And the carcinogenicity studies show uncommon tumors, but there was a trend for adenocarcinomas. It's a methylating agent. It's a potent mutagen. And I think there's some direct evidence for development of lymphomas.

This was evaluated by the EPA in 2001. Thought to be toxic and potentially carcinogenic, but no evidence for that in humans. Since that time, there hasn't been a lot more specific studies on this that impressed me dramatically, I must say.

So I was on the low side, mostly because of the lack of -- or I mean more current information that would suggest increased carcinogenicity to a level of increased concern considering some of the other subjects which I

think had newer information that was significant.

CHAIRPERSON MACK: So where are you?

COMMITTEE MEMBER HOPP: So I'm on low.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: So the mice show studies positive in adenomas and carcinomas of the liver for males and females, and mammary gland tumors in the females. The rat studies by feeding are negative. The genetox is a pretty consistent positive database: salmonella, V79 cells, single strand breaks in human fibroblasts, chromosome aberrations, cell transformation in the hamster embryo cells, and L5178YTK plus/minus assay are all positive. So it's clearly a genotoxin carcinogenic in male and female mice. No epi studies.

And I guess it devolves upon the exposure and its uses in insecticides. So, you know, I could live with low medium somewhere in there. I'm not real strong as to exactly where we place it.

COMMITTEE MEMBER HOPP: You know, I completely agree with you reviewing those studies, but when the EPA in 2001 included all -- none of that as new information. That's all old information. And their conclusion was that this was not consistent with a human carcinogenic potential or at least it was low. And if there were more studies since that time that would elucidate it's

carcinogenicity, I'd be more in favor of making it higher.

But since there's no further information since the EPA reviewed it in 2001, I can't get excited about reviewing that same information all over again.

COMMITTEE MEMBER LANDOLPH: Yeah, it's okay. I suppose I could drop down to a low too. I'm not that excited about this one either.

CHAIRPERSON MACK: Any objections to low?

Biphenylamine and its salts.

Sol.

COMMITTEE MEMBER HAMBURG: Yes, sir. The next agent is 2-Biphenylamine and its salts. It is a chemical intermediate in the manufacture of acid red 15.

There's not a lot of data available. All the data seems to be from 1987 or before. There is one study in 1982 looking at hemangiosarcomas in female mice.

I don't believe that there's a lot of data to review. I don't think we'll be able to come to an easy conclusion about this. And I would hold off and make it low.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: I also gave it a low for the same reasons, limited data, and also appears to be fairly limited -- relatively limited exposure.

CHAIRPERSON MACK: Okay. Does anybody object to

a low?

Okay, 4-Chloro-m-phenylenediamine.

COMMITTEE MEMBER HAMBURG: Let me just find it in my list here.

4-Chloro-m-phenylenediamine it's also a dye intermediate. There's no epidemiological data. The data on animals is relatively old going back nearly 30 years -- over 30 years. I don't think it's really in widespread use, so I would make it low again.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: I also put it as low. It's been around since the forties and no epidemiologic data. And so I don't think that use of staff time is going to do a whole lot.

CHAIRPERSON MACK: We're on a roll.

Okay, Acid Orange 3.

Sol.

COMMITTEE MEMBER HAMBURG: Acid Orange 3. It's got a bad name. It's like Agent Orange.

Dinitrophenyl amine, its another dye derivative. Similarly, the data is very old, very limited, and the degree of exposure is high though. There's a great deal of concern among patients and consumers about what the role of hair dye is.

With that in mind, I think it's -- I would place

it on a medium level, simply because of the interest that the public has in understanding what the risks associated with hair dyes are.

CHAIRPERSON MACK: Okay. Darryl.

COMMITTEE MEMBER HUNTER: Yeah, I did exactly the same thing, but also because I started dying my own hair a couple months ago.

(Laughter.)

COMMITTEE MEMBER HAMBURG: It doesn't show.

COMMITTEE MEMBER HUNTER: Well, that's because I'm due.

(Laughter.)

CHAIRPERSON MACK: Okay. Does anybody object to medium?

Okay, 2,6-Dichloro-p-phenylenediamine.

COMMITTEE MEMBER HAMBURG:

2,6-Dichloro-p-phenylenediamine. It's always fun to say these, I think. There is another dye intermediate. This does not appear to have the extent in the population of use as the prior agent does. There's also very limited data, and I would again put this as a low.

COMMITTEE MEMBER HUNTER: I also did a low.

CHAIRPERSON MACK: All right. Does anybody object to a low?

Okay, Darryl. Budesonide.

COMMITTEE MEMBER HUNTER: Let me find that.

Yeah, this is interesting and certainly you've got significant clinical relevance. It's been in use since about '81 in the setting intranasally for allergies, and inhalationally for asthma, COPD, and then a little more recently for Crohn's Disease I think around 2005.

I put it as a low. And the reason I put it as a low is despite -- it is frequent -- high frequency of use for a limited population. But if you look at the data that has been put forth, the studies in the mice -- well, it was actually in the Sprague-Dawley rats. Although, one positive for glioma. It was refuted in a secondary study.

The thing that's also interesting, and I think it's probably the only chemical that we have here on the list, that has at least as many studies indicating that there may be a chemo preventive role. And that was brought out in the public comments by AstraZeneca.

So they provided a fairly, I thought, convincing argument, in terms of refuting some of the studies that indicate that there may be some carcinogenicity, but also demonstrating that there's animal data indicating, in at least four that they cited, and they did indicate it wasn't exhaustive, but at least four that cited evidence of chemo prevention. So for that reason, I put it as a low.

CHAIRPERSON MACK: Anna, do you wish to say anything?

COMMITTEE MEMBER WU: I don't have anything to add.

CHAIRPERSON MACK: So anybody object to a low for Budesonide?

COMMITTEE MEMBER HAMBURG: I object.

CHAIRPERSON MACK: All right. Let's hear it.

COMMITTEE MEMBER HAMBURG: You know, this class of compounds, the synthetic glucocorticoids, I think are in such common use, and there are so many questions about this, that I think if it's come before the Committee, we're almost obliged to review the data on this and see whether it should be classified or not.

There is a large body of information on the uses of glucocorticoids. I think it's something we could review and actually either put aside or put onto the list. So I would highly recommend that we look at this class and this particular --

CHAIRPERSON MACK: I mean --

COMMITTEE MEMBER HUNTER: Well, low priority doesn't mean we're not looking at it. Low priority means --

COMMITTEE MEMBER HAMBURG: No, no, no. But I think it's urgent that we look at this drug.

CHAIRPERSON MACK: So you want to put it high.

COMMITTEE MEMBER HAMBURG: High.

CHAIRPERSON MACK: Okay. Does anybody else want to weigh in.

Marty.

COMMITTEE MEMBER HOPP: I think again, I agree with Sol, this is a very common medication. However, the data that I see here doesn't make me as greatly concerned since I use it almost every day for patients. I think that I'd put them in the medium category, because if its commonality of usage. But lack of data takes, you know, away from the high priority.

CHAIRPERSON MACK: Okay. Have they talked you into it, Darryl?

COMMITTEE MEMBER HUNTER: Well, no. I mean, I think you prioritize something based upon the fact that you think there's public harm. And right now, again, this is the only chemical that's showing that there may actually be working in the opposite direction.

I mean, we're supposed to be listing things that are going to cause cancer. We've got something that may prevent it. So calling it a priority, I think is going to be taking staff time away from things that cause cancer and don't prevent cancer.

CHAIRPERSON MACK: I hate to weigh in on an

AstraZeneca drug that both causes and prevents cancer, potentially --

(Laughter.)

CHAIRPERSON MACK: -- because there's been previous AstraZeneca drugs which both caused and prevent cancer, and I just don't think we can necessarily use the preventive side as a moderator of the causation side, because the two mechanisms are likely to be very different. And it's our job not to decide what is the net effect of a drug, but whether or not it causes cancer.

So I don't know the mechanism of the prevention. I'm sure we'll hear about that from the AstraZeneca folks, if not from you.

COMMITTEE MEMBER HUNTER: Aren't they speaking?

CHAIRPERSON MACK: But the real question is, do we think it's likely that it might be a carcinogen, whether or not it's a preventive in other respects.

COMMITTEE MEMBER HUNTER: Well, even if you look at the studies that have been cited as positive, there's no statistically significant increase in the cancers that were caused. There were some where if you lumped benign and malignant, there was some. But none of the studies that I've read showed cancer.

There was a citation in the CD-1 mice study, but that didn't lump all the tumors together. And when you

lumped them all together, it actually decreased the total tumors seen. And again, that kind of goes with the chemo preventive.

CHAIRPERSON MACK: Okay, Joe, do you want to weight in?

COMMITTEE MEMBER LANDOLPH: Yeah, I'm kind of dead in the middle. The brain gliomas worries me and there's primary hepatocellular neoplasms in males and primary mammary neoplasms in females, and they stayed by pairwise comparison and trend.

And then the increase in hepatocellular adenomas and carcinomas in the second rat study. And so that, and the fact that the genetox database is largely negative, but they say that it's metabolized by human and animal liver microsomes to a metabolite which is a mutagenic toward salmonella typhimurium and that it -- when it's incubated with rat liver and brain S9 it covalently binds to tissue macro-molecules.

So there's a lot that needs to be known about this compound. But based on the two physician's arguments about the widespread use as a medication, and the potential carcinogenicity, I would feel comfortable parking it in the medium category. I think we should look at it, not with the highest priority, but we should look at it.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, Carol over here. Just as a process issue, I know that the reporter is having difficulty hearing the speakers, you all up here. And so if you could all put your microphones closer to your mouth and try not to turn away from them. It's much easier. I'm sure that the people behind us would also appreciate that.

Sorry to interrupt.

CHAIRPERSON MACK: That's really nice, Carol, but of course we're almost finished now.

(Laughter.)

CHAIRPERSON MACK: Okay. We'll all try hard. Now, let's discuss this again, because we have the whole range of proposals.

What do you think about medium, Sol?

COMMITTEE MEMBER HAMBURG: I can live with medium.

CHAIRPERSON MACK: You can live with a medium. How about you, Marty?

COMMITTEE MEMBER HOPP: I suggested medium.

CHAIRPERSON MACK: You suggested medium.

(Laughter.)

CHAIRPERSON MACK: All right. Does anybody object to a medium now for this drug?

Okay, going, going, gone.

4-Hydroxymethyl, 4-Methyl, and 4-Hydroxy Benzenediazonium and their salts. Darryl.

COMMITTEE MEMBER HUNTER: I put that as a medium. Let me see if I can find my.

I'm sorry, I called it a medium. I'm just trying to find my notes here.

CHIEF COUNSEL MONAHAN-CUMMINGS: Is your microphone on, Darryl?

COMMITTEE MEMBER HUNTER: Yeah, the light is on.

CHIEF COUNSEL MONAHAN-CUMMINGS: Can you push it over closer to your -- there you go.

COMMITTEE MEMBER HUNTER: Okay. So this is something that is sort of, I think, is a three for one here. The 4-MB, which may form from a 4-HMB, which is naturally found in the edible mushroom before HB found in inedible mushroom that could be mistaken for the edible. So there's some ingestion issues that come into play with this.

No epidemiologic data to talk about this. In the animal data, certainly some evidence with contact through subcutaneous injection or gastric lavage of increasing tumors. And one of the concerns is the product that's in the edible mushroom having a break -- as far as one of the things that metabolites to being something that actually may be carcinogenic.

And some of the -- I think there was some structural -- let's see, yeah the structural similarities with these three also make them concerning. I thought overall a medium.

CHAIRPERSON MACK: Just out of curiosity are these in commercial mushrooms or just woodland mushrooms.

COMMITTEE MEMBER HUNTER: Yeah, I didn't see that.

DR. SANDY: I think, Dr. Mack -- this is Martha. I believe the first one, the commonly cultivated edible mushroom Agaricus bisporus, or however you say that. We believe that's the common mushroom, the white mushroom, you find in the stores. That's what we think. We're not mushroom experts.

DR. MORRY: It's the close relative to argaricus campestris which is the most common one. This is the same genus, so I think it's similar.

COMMITTEE MEMBER HUNTER: It has a high frequency of ingestion, and you know, thought that certainly there could be a public issue that warrants investigation.

CHAIRPERSON MACK: And, Darryl, you came down with a medium.

COMMITTEE MEMBER HUNTER: I came down with a medium.

CHAIRPERSON MACK: Anna and you?

COMMITTEE MEMBER WU: I came down with a medium. Does anybody object to a medium?

CHAIRPERSON MACK: Now, we're at 7-Methylbenz[a]anthracene.

Darryl.

COMMITTEE MEMBER HUNTER: This is something that product of incomplete combustion. It's in some oil refinery emissions, gasoline exhaust, cooking emissions. So certainly a high degree of prevalence. I gave it a medium, largely due to that. There is lacking of epidemiologic data, but I thought it had enough of the animal studies and the prevalence of this warranted a medium.

CHAIRPERSON MACK: Anna, did you have anything?

COMMITTEE MEMBER WU: Well, I was put it in medium in terms of its exposure, but you the data they seemed -- they were all relatively old, so I didn't know whether there are more recent things, that people are just not interested, or -- so, I mean, there's not a whole lot, because most of the citations are from the 1960s. So, I mean, there are things from, you know -- anyway, I just thought it would be helpful to know whether there is really anything.

CHAIRPERSON MACK: David, did you look at it?

COMMITTEE MEMBER EASTMOND: I did a little bit.

My concern on this is going to be with how old these studies are and whether they're generally accepted. So I mean, if you come back to looking at what the criteria is, scientifically valid testing according to generally accepted principles. This was commonplace 50 years ago, but these injection sites sarcomas I think have really fallen out of favor in evaluations. So I think we're going to lose a lot of the data as they go through the evaluation.

Now, on its face value, I think it's actually a fairly important one. I just don't know if we're going to have the data to do any sort of evaluation, but that's --

CHAIRPERSON MACK: It sounds as though, you'd be going for medium too.

Sol.

COMMITTEE MEMBER HAMBURG: Do we know whether the levels of this particular hydrocarbon is going down or up in air?

Anybody?

DR. SANDY: (Shakes head.)

DR. ALEXEEFF: Repeat that again, Sol.

COMMITTEE MEMBER HAMBURG: Do we know if the levels of this particular hydrocarbon is going up or down in ambient air, has increased or decreased, have things changed over the decades?

DR. SANDY: We didn't find anything, but we didn't do an exhaustive search. We did a search. We didn't find any information.

COMMITTEE MEMBER HAMBURG: Thank you.

CHAIRPERSON MACK: Marty.

Marty or David?

COMMITTEE MEMBER EASTMOND: Both of us are going to go. Go ahead, Marty.

Or I guess my suggestion is more of one for OEHHA as they get into this, if they realize that there really is just not enough data to carry this forward not to do it, because I mean just the superficial evaluation that I'm doing here, is I think you're going to have real problems.

I think the chemical by itself merits an investigation, because it's one of these class of polycyclic aromatic hydrocarbons, which are generally carcinogenic. And this is one that would be flagged that way. But it just doesn't look like there's going to be a lot of data to support it that would be considered currently acceptable. I mean that's a decision you'll have to make as you go forward, I think.

COMMITTEE MEMBER HAMBURG: It also may not be common enough in air right now to really have any great impact, so that may be of some value to find that out.

CHAIRPERSON MACK: George.

DR. ALEXEEFF: Yeah, this is George Alexeeff. Well, what we could do is we could check with the Air Resources Board and other agencies to see, one, is it being detected. It may or may not be measured, but if there is, if we can determine there's widespread exposure, maybe the alternative is for us to make a recommendation to the National Toxicology Program to do some studies on it.

COMMITTEE MEMBER HAMBURG: I think that's correct.

COMMITTEE MEMBER HOPP: Yeah, I think in terms of priority, although the studies are just fairly old, and there's only three studies since 1982. So I think we're going to have a hard time evaluating this, tend to go back to evaluate the Millers who are very famous people. But it's -- to reevaluate data from 1960, I don't think is a high priority for our Committee at this point.

CHAIRPERSON MACK: So what are we doing? I'm sorry. Do we call it a low, George? Would that be consistent with your recommendation?

DR. ALEXEEFF: My recommendation could occur under any circumstance. Although, it wouldn't make sense under a high recommendation, that's for sure. I'm just thinking in terms of timewise, probably a medium or a low

would allow sufficient time to gather more information, and do some studies.

CHAIRPERSON MACK: I figured low would be short to allow that time. So does anybody object to a low?

COMMITTEE MEMBER HAMBURG: I'm for low.

CHAIRPERSON MACK: Okay, we've got it.

COMMITTEE MEMBER EASTMOND: 60 years.

CHAIRPERSON MACK: N-Methyl-N-formylhydrazine. Darryl.

COMMITTEE MEMBER HUNTER: I actually put this as a high. This is another chemical from -- it's a hydrazine. It comes from an edible mushroom. It would be interesting to find out what the -- you know, what mushrooms constitute the ones that are being most frequently eaten. But this -- one of the things is this is in a mushroom that apparently has at least six different compounds that have association with carcinogenic activity. There's some animal studies, predominantly published studies by one author Toth, that's shown some increase in malignancies, both in drinking water and injection studies.

But also as far as the structural data, there are, it looks like, seven or eight hydrazine compounds that are currently listed as Prop 65 carcinogens. So, you know, for those reasons, I thought it would be a high.

CHAIRPERSON MACK: Anna, did you look at it?

COMMITTEE MEMBER WU: Well, I have to say, these mushroom compound are a surprise to me, because we're always looking at mushroom for chemo prevention. So I didn't -- I mean -- I would have listed -- and I also don't know what's the difference between this one and the previous mushroom. So I would have put it at medium, but I just thought that since these are such highly commonly consumed products that we probably should look at it, but they were a surprise to me.

CHAIRPERSON MACK: Does anybody else want to weigh in on this one?

Any mushroom eaters in the group?

(Laughter.)

CHAIRPERSON MACK: I'm speaking to my colleagues. It doesn't make any difference if they hear me.

Anybody else want to weigh in on this?

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. Toth is a well known guy who's worked in these types of compounds for many years, hydrazine-like compounds. And they're a little bit unusual because they make radical intermediates, which are a little tough to track sometime.

But the animal data looks pretty good. I thought, in particular, the lifetime drinking water

studies. You got positives in male and female mice in one study, male and female mice in another study, and in a third study. And you also have positives in male and female hamsters. So I think that animal database is pretty sturdy, so I would argue for a medium on that.

CHAIRPERSON MACK: He actually suggested a high. Would you prefer medium to a high?

COMMITTEE MEMBER LANDOLPH: I think medium is reasonable. I'm not sure how good the exposure is on this how much of these false morels are eaten. I don't know the answer to that.

CHAIRPERSON MACK: What do you think, Darryl?

COMMITTEE MEMBER HUNTER: I mean I could do medium.

CHAIRPERSON MACK: Medium.

Anybody object to medium?

Sorry, anybody object to medium?

Okay, that's it.

So now we go to the public comments.

And we basically have public comments about three compounds. The first on our list is -- oops, here's some more.

Okay, the first one on the list is omeprazole. And the person representing AstraZeneca would like to speak to that. So Mr. Marin.

DR. MARIN: Good afternoon, everyone. My name is Dr. Matthew Marin. I am a Board Certified Internist. About four years ago, after more than 30 years in academic medicine, I joined AstraZeneca as a senior director and field medical physician.

AstraZeneca is the inventor and maker of prilosec, known generically as omeprazole. I have a very brief statement today, but I believe you all have copies of our submission, which includes the scientific underpinnings for the information at hand.

Omeprazole was first approved in the United States by the Food and Drug Administration in 1989, and has over 970 million treatment courses. AstraZeneca believes that it is both safe and effective.

When it was first approved, the original package insert for omeprazole contained a box warning relating to gastric carcinoids found in rats. In 1995, based upon a recommendation from the an FDA advisory board, the FDA removed the box warning and granted a long-term indication for a omeprazole use. Subsequently, the FDA approved the over-the-counter omeprazole in June 2003. As noted in the background document, carcinoid findings occurring in rats identified by this Committee review are delineated in our product insert.

These findings are not replicated in other

species. For instance, they are not observed in the mouse and they are not observed in the dog. These findings seem to be uniquely sensitive to acid suppression. And, in fact, other means of acid suppression in the rat result in hypergastrinemia, ECLC, cell hyperplasia, and carcinoids.

In over 3,000 patients treated with omeprazole in long-term clinical studies, no case of ECL cell, carcinoids dysplasia or neoplasia was found. Based on the extensive evidence in the FDA review, and the information provided to this committee, AstraZeneca requests that omeprazole be removed from further consideration under Proposition 65.

Thank you for the opportunity of speaking. And I would be pleased to entertain questions.

CHAIRPERSON MACK: Do you know if AstraZeneca has any hypothesis about the increasing incidents of adenocarcinoma of the esophagus in especially men.

DR. MARIN: We have not seen that data. Actually, we've looked for epidemiologic data that would tie specifically omeprazole to cancer and have not been able to find that. So we will -- obviously, I am not a toxicologist. I am going to carry this information back home and we will look very carefully at that information and be willing to be forthcoming with the results of that investigation.

CHAIRPERSON MACK: Thank you.

Does anybody have any other questions for Mr. Marin?

DR. MARIN: Doctor.

CHAIRPERSON MACK: Dr. Marin, excuse me.

Thank you very much.

DR. MARIN: Thank you.

CHAIRPERSON MACK: The next speaker should be Timothy Pastoor from Syngenta speaking -- addressing the issue of atrazine, which we also have classified as high.

DR. PASTOOR: Thank you, Dr. Mack. I appreciate the time that you're spending on this and I appreciate OEHHA's willingness to let the public speak on some of these issues.

What I'll be addressing here is on atrazine's listing that you have right now as being high. I'm going to request that you put it as a low, and I'm going to tell you some reasons why.

Part of it is that there's a tremendous amount of interest in atrazine certainly, I think, Dr. Eastmond as you pointed out. But I think even overshadowing that is a tremendous amount of study that's gone on over the last 15 to 20 years on this very valuable agricultural product. And what I tried to do in an August submission is summarize all that in one place, because there's a

tremendous amount of information that all of us need to go over to make any good decision. So I tried to condense that into one spot.

And so what I'd like to say right here is to condense that even more into a couple of very, very brief points.

Number one is that the listing -- that choice and prioritization should be based on a criteria, one of which is exposure. Atrazine is not used in the state of California to any significant degree.

But secondly, and probably more important, is the consideration of the toxicological data and epidemiological data that would indicate any likelihood of cancer causation in humans. And I can summarize it very simply this way.

Atrazine is not genotoxic in well over 100 mutagenicity studies. The mode of action for the mammary tumors in Sprague-Dawley female rats is well understood, and is understood as not being relevant to human health. Thirdly, the epidemiology is strong and getting stronger, that there is no causal linkage between atrazine and human health.

In 36 studies reviewed by Dr. Sathiakumar from the University of Alabama, there is no consistent linkage found there. Furthermore the ag health study, which is in

nearly 50,000 farmers from North Carolina and Iowa, there have been no linkages made to cancer in any of these people.

A recent review by Dr. Weichenthal, 2010, further reiterated that looking at the agricultural health study atrazine was not related to any cancer in humans.

So on those three bases, I can say that on the criteria, it certainly deserves a low rating, but I would have to add to that, that there's one other reason. And that reason is that on the basis of six authoritative body reviews, atrazine has been declared not to be carcinogenic to humans.

And that's based on not only the animal studies that were done but also on the epidemiology. Those six agencies are represented by the United States Environmental Protection Agency, who declared atrazine not to be carcinogenic in the year 2000, after review by a scientific advisory panel. They reiterated that statement in 2006 in the reregistration of atrazine for usage.

IARC has also weighed in on this, the United Kingdom on behalf of the European Union as a rapporteur state. Canada's Pest Management Regulatory Agency, Australia, and the World Health Organization have all concluded that atrazine is not carcinogenic to humans, based on the animal and the epidemiology data.

So along with the low usage in California, I'd have to say that this careful review by six different agencies over the last decade have firmly established that atrazine is not going to be a causative agent in cancer for humans.

So I'm pleased asking very simply that you take a moment, reconsider, that this is an effort that has been looked at extensively by regulatory agencies around the world, and you'll see in the abstract that I have that I submitted in August the checklist of those various agencies that have come to those conclusions.

And, of course, that has a lot to do with the time that would be spent on retreading the steps that these regulatory agencies have made.

So I very, very respectfully request that you reconsider the prioritization of atrazine to low.

Thank you. Any questions?

CHAIRPERSON MACK: I'm going to ask the others if they have questions, but I'd like to make one comment. I don't think you'll find that those agencies all declared atrazine to be not causal of cancer. What they declared was that there was no evidence that was convincing that it was carcinogenic. And there's a big difference between these two things.

DR. PASTOOR: Dr. Mack, that's a very important

point. And I think the language that's used and I've quoted it in the submission that I made in August, and the reason I put it in there is that there's a variety of different ways that these agencies make that conclusion, so that's a very good point.

CHAIRPERSON MACK: It's impossible to declare something that's not carcinogenic.

DR. PASTOOR: Correct.

CHAIRPERSON MACK: Do you have any questions?

COMMITTEE MEMBER WU: I have nothing.

COMMITTEE MEMBER LANDOLPH: I just had a question. I rotated off the U.S. EPA's Science Advisory Board. And I went down to Research Triangle Park and they were conducting research on atrazine. Steve Nesnow who's a good friend of mine was leading that effort.

And I recall them doing microarray studies, because it didn't seem like it had a genotoxic mechanism of action. And I recall them being very interested in this, and this was a couple of years ago. And I wondered if you were aware of those studies or if the agency had taken an official position recently?

DR. PASTOOR: Yes. Dr. Landolph, those studies were done on aromatase. And I think, Dr. Eastmond, you appropriately brought that up as an alternative mode of action, which has been discounted by the EPA, Australia

and a number of other regulatory agencies as having a role in atrazine.

What Dr. Nesnow, who I know very well as well, was looking at the underlying evidence for any potential change in aromatase. And what he has found is that you can cause this in vitro, but you cannot cause it in vivo. You cannot find it in an in tact animal.

COMMITTEE MEMBER LANDOLPH: Thank you.

CHAIRPERSON MACK: Does anybody else have questions?

David.

COMMITTEE MEMBER EASTMOND: I had a question. There were, I guess, a number of articles -- epidemiological studies cited that indicated there was an increased risk of non-Hodgkin's lymphoma. Can you briefly comment on that? There were like four or five of them in the document we saw just briefly mentioned.

DR. PASTOOR: I understand. And as I mentioned, there's a lot of information there. And Dr. Sathiakumar looked add at that in 36 different studies. And I can't recall exactly how many were related to non-Hodgkin's lymphoma, but in each one she found the same kinds of difficulties that exist in so many of those epidemiology studies. Either there was very poor relationship to exposure, very difficult to tabulate, or it was low

participation rates, and a number of other features that rendered those studies more hypothesis generating, as she said than anything else.

And what she said on those particular studies if I could quote her is that, "Collectively these studies do not provide a consistent scientifically convincing evidence of a causal relationship between exposure to atrazine or triazine herbicides and these cancers...". These cancers being the non-Hodgkin's lymphoma, "...breast and prostate cancer in particular".

CHAIRPERSON MACK: Just to remind you, we're not making a decision on whether or not it causes cancer. We're making a decision on whether or not we should prioritize it for looking at that question. And there's big, again, difference between those two.

DR. PASTOOR: Yes, Dr. Mack, I understand that that's exactly what you're about here. And I think what I'm trying to make a point here is that there has been an extensive amount of study already done. And I'm suggesting that this is not one that requires the extensive time of the staff here within OEHHA.

CHAIRPERSON MACK: Thank you.

COMMITTEE MEMBER HAMBURG: May I ask the staff a question.

Dr. Alexeeff, maybe you'll be the best one. When

we review and decide not to list, is that information made public?

DR. ALEXEEFF: Yes.

COMMITTEE MEMBER HAMBURG: So reviewed and unlisted items. So there would be some value in reviewing the data and then deciding that this was not to be listed, is that right?

CHIEF COUNSEL MONAHAN-CUMMINGS: There's a public record of your decisions, in terms of listing or not listing. The actual Prop 65 list that's published only has those chemicals that have been found to cause cancer. And so one would have to look, you know, on our website or other, you know, publications, like the California Notice Register. But they would be able to tell that you had not listed a chemical, yeah.

COMMITTEE MEMBER HOPP: Thank you.

CHAIRPERSON MACK: Thank you, sir.

The next chemical to be discussed is PFOS and I have Sue Chang, Geary Olsen, Stan Landfair, and Larry Zobel.

I don't know if you have a different order.

MR. LANDFAIR: I've made that decision, Judge.

Judge.

(Laughter.)

MR. LANDFAIR: Chairman Mack, thank you. I'm

Stan Landfair, law firm of McKenna, Long, and Aldridge representing 3M.

In considering our chemical, you have tentatively assigned it a priority of medium. As partly a digression, I would like to thank the Panel for the way it has organized its proceedings this way. In contrast to a different proceeding we had last year, where we think, you know, we've been privy to a good deal of discussion among the panel members. And I think in light of the written -- you are aware that we have submitted written comments recommending low.

I want to speak primarily just to point out that our client, our company, Dr. Zobel and others believe very sincerely that low is the absolute highest it should receive, and that ultimately the data do not justify lifting. But in light of listening to your comments and your proceeding, your deliberations, we can recognize some reasonable room for disagreement, and we're in a reasonable zone, and we can waive the rest of our comments if the judgment is to be medium.

CHAIRPERSON MACK: Thank you very much.

MR. LANDFAIR: Well, thank you.

CHAIRPERSON MACK: So there's no more speakers on PFOS.

MR. LANDFAIR: No, if we're agreed on medium, we

will remain silent.

CHAIRPERSON MACK: Thank you.

(Laughter.)

MR. LANDFAIR: Thank you.

CHAIRPERSON MACK: And so the final comment is back to AstraZeneca to comment on budesonide.

DR. MARIN: Good afternoon again. I'm still Dr. Matthew Marin. I guess the only way my credentials have changed is that I should add I'm also board certified in pulmonary disease. And in addition to being senior director, I am the respiratory field medical physician. I'm still not a toxicologist however.

In our written responses to the Office of Environmental Health Hazard, we provided detailed responses to each of the issues raised in the preliminary toxicological evaluation of budesonide by this office.

In the interests of time, I'm not going to reiterate these responses but permit me to summarize as follows:

As of June 30th, 2010, more than 90 million patient treatment years have been achieved with various medications containing budesonide. A review of the post-marketing safety data for the AstraZeneca budesonide-containing products does not reveal any safety signal for an increased risk of neoplasms associated with

budesonide in humans.

Your office has conducted an epidemiology data screen on budesonide, and we have also performed an extensive literature search. In neither circumstance were any epidemiological studies identified, which suggested evidence of carcinogenicity in humans.

This absence of data indirectly lends support to the safety profile of budesonide in man as approved by the FDA and numerous regulatory agencies worldwide.

During the 1980s, animal carcinogenicity studies were to support the registration requirements for budesonide. The initial carcinogenicity study in Sprague-Dawley rats there were low but statistically significant increases in brain gliomas and primary hepatocellular neoplasms in males and primary mammary neoplasms in females.

Two additional carcinogenicity studies conducted in male rats failed to confirm a treatment-related effect on brain gliomas, while demonstrating that the liver tumor was a class effect shared by other glucocorticoids and is thus related to the pharmacological action of budesonide on liver, as well as the sensitivity of the rat to glucocorticoid effects.

In the mouse carcinogenicity study, although there was a trend of increase in lung alveolar bronchiolar

carcinomas in a subset of lung tumors, the total lung alveolar bronchiolar tumor incidences were actually lower in the budesonide treated groups than in the concurrent control groups. The decreased lung tumors in mice is consistent with the reported literature that budesonide has a chemopreventive action on lung tumor development.

Budesonide has been extensively investigated in the National Cancer Institute's Chemoprevention Drug Program. Investigators in the United States and other regions of the world have shown that budesonide can prevent the development of tumors in mice by various carcinogens and have elucidated some of the underlying mechanisms.

The hope that I would be able to explain those mechanisms I'm afraid is not going to be forthcoming in this setting. However, if that's necessary, we can bring in our experts to do that.

Finally, utilizing a battery of genotoxicity tests, we have summarized in our comments that budesonide is not genotoxic. AstraZeneca believes that a review of the submitted comments combined with the fact that no increase risk of carcinogenicity from clinical use of budesonide has been documented leads to the reasonable conclusion that budesonide is not a candidate for further consideration as a carcinogen.

In summary, AstraZeneca requests that the Office of Environmental Health Hazard Assessment remove budesonide from the list of chemicals, or at least place it in a low priority as you consider the review of possible carcinogens under Proposition 65.

Thank you very much. And again, I would be pleased to address questions.

CHAIRPERSON MACK: Does anybody have any questions for Dr. Marin?

David.

COMMITTEE MEMBER EASTMOND: I have one. Thank you. You had mentioned some post-market studies that had been done on the carcinogenicity, can you describe those in a little more detail?

DR. MARIN: Yeah. Post-marketing surveillance is done routinely according to the FDA mandates on all of our medications, so that we collect information about the occurrence of a variety of adverse events as well as cancers.

COMMITTEE MEMBER EASTMOND: So if someone is taking this drug for five years, and then they stopped, and they developed cancer 15 years later, would you pick that up?

DR. MARIN: I don't know the answer to that specific question, in that I don't know what the mandate

is, in terms of how long we need to follow people for. But certainly, that's something that I can get and supply you with.

COMMITTEE MEMBER EASTMOND: Thank you.

CHAIRPERSON MACK: Let me ask you a related question. What do you compare it to?

DR. MARIN: Well, that's an interesting question. I think what you're asking is --

CHAIRPERSON MACK: It's the answer that's interesting.

DR. MARIN: Right -- is what is the denominator.

CHAIRPERSON MACK: No. No. What is the rate that you would expect in those people?

DR. MARIN: And again, I'm on thin ground, but my understanding is that we use FDA guidelines, in terms of statistical evaluation to see if we are getting clusters or out of the normal occurrence of cancers. But, you know, we can certainly give you a much more learned answer on that question.

CHAIRPERSON MACK: I'm afraid your ground is very thin. There is no more learned answer.

DR. MARIN: Okay, well, I -- yeah.

CHAIRPERSON MACK: Thank you very much.

DR. MARIN: You say there's no more learned answer than that?

CHAIRPERSON MACK: No, there isn't, because post-marketing surveys don't have control groups. They just look for something that's very common. And as you say, clustering, but it's clustering of diseases that are very common, which do not include cancer, because they're too uncommon.

And especially when it relates to long-term follow-up, that's going to be the case. And it would be nice if it were otherwise, but it's not. And it's not just AstraZeneca, it's the whole world of pharmacology.

DR. MARIN: Thank you very much.

CHAIRPERSON MACK: Thank you.

Now, my proposal is that we look at the compounds that have been responded to by the public community, and ask the question, do we wish to change our classification?

DIRECTOR DENTON: It looks like Cindy has another one for us.

CHAIRPERSON MACK: Oh, you've got another one, Cindy.

DIRECTOR DENTON: There's one more comment.

MS. OSHITA: You have one more comment for acephate.

CHAIRPERSON MACK: No, I think we've gone through them all.

MS. OSHITA: There should be on for acephate.

CHAIRPERSON MACK: Maybe I missed acephate.

Oh, all right. Ms. Plunkett.

Sorry.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, the court reporter needs a break soon.

CHAIRPERSON MACK: Pardon me?

CHIEF COUNSEL MONAHAN-CUMMINGS: The court reporter needs a break soon, like maybe 10 minutes. Maybe after this comment before the Committee discusses.

CHAIRPERSON MACK: Yes. I think that's an excellent idea. We'll break right after this comment, and caucus.

DR. PLUNKETT: Thank you very much. I was wondering if I was going to get a chance to speak. I'm going to keep it very short. My name is Laura Plunkett. I'm a pharmacologist and Board Certified Toxicologist. And my colleague and I Judith McGregor wrote a letter that came in actually a little late, I think, to the -- a couple days after the comment period had ended. So I hope that some of you may have actually seen the letter on acephate.

We are consulting on behalf AMVAC Chemical corporation, which is the registrant for acephate. And a couple of comments that I just wanted to make. In the letter I actually provide -- Judith and I provide some

additional detail on interpretation of the animal studies. If you look at the database for acephate and the animal data that's there, I think it was acknowledged by someone on the panel that indeed the issue with the chemical tends to be toxicity in those studies, and the fact that anything that you're seeing occurring is occurring at high doses where you have significant levels of cholinesterase inhibition and confounding issues related to interpretation of the data.

So I'm not going to go into those comments again here, but I just wanted to point two things out. First, I don't know whether the panel realized that there was a significant number of in vivo genotox studies that I don't think were listed in the table that was provided to you, at least in the submission that we saw that was on the website from OEHHA. And if you look at that in vivo genotox data, I mean, it appears to indicate that there is no genotoxic risk to the chemical.

And the other thing I wanted to point out is that this is a chemical, that like some of the other pesticides, has been looked at by several international regulatory bodies. And this is not a chemical that has been regulated based on cancer hazard by bodies in the past.

So I would hope that that information and the

issues with the interpretation of the data itself for the database would indicate that this should be a low priority chemical, instead of a medium priority chemical.

Thank you.

CHAIRPERSON MACK: Thank you.

Joe, do you have any questions?

COMMITTEE MEMBER LANDOLPH: Just a second.

CHAIRPERSON MACK: Or Marty.

COMMITTEE MEMBER LANDOLPH: Yes. What about the -- what is your opinion of the genetox database? And I didn't read your and Judy McGregor's letter. I mean, I see a number of positives in this database. Mutagenicity In lymphoma, cell assay, sister chromatid exchange, unscheduled DNA synthesis, in vivo tests in mice, bone marrow chromosomal aberrations positive, micronucleus, some positive, some negative, dominant lethal tests, positive and negative.

So what is your -- and cell transformation positive. What is your assessment of that data?

DR. PLUNKETT: Are you talking about the in vitro studies, primarily?

COMMITTEE MEMBER LANDOLPH: Yes.

DR. PLUNKETT: Well, in our experience, like other organophosphates, you will sometimes find that they have activity in vitro, but when you put them into the in

vivo testing, you see a different result with the chemical. We believe that the in vivo data, and genotoxicity is highly relevant for then interpreting what you get in vivo in animals when you do have two studies, a mouse and a rat study, to look at with the chemical.

So we felt that the genotox data was somewhat weak as far as putting a signal forward for a genotoxic mechanism of action in vivo in the cancer studies.

COMMITTEE MEMBER LANDOLPH: And the animal data, you've got positive studies in -- positive results in feeding studies in mice, for both male and female mice. And then you've got positive data in males and females for 28-month feeding studies in rats. So that's mice and rats, two species. You think that data is not relevant or useful, what is your opinion?

DR. PLUNKETT: I think the issue here is looking at the data itself. Not that it's not relevant. You need to look at the study. For example, I think as we pointed out in our comments, when you look at the mouse study, the results that you're seeing are -- if they're occurring, it's only at the highest dose, where you have significant levels of toxicities that are interfering with the interpretation, I believe, of the study and the data that you're seeing. You're seeing significant deaths, for example, in some of the study groups due to the toxicity

of the chemical, not just due to the actual activity of it.

And I believe that that would be consistent with how EPA has looked at those data sets and has described its review of that data as well.

In the rat study, I think we pointed out that in the rat study the issue you had was looking at the lack of a dose response relationship for the chemical, where you see some increase incidence mid-dose but not in the high-dose group. And the fact that these were benign adrenal tumors in the animals not malignant tumors. And again, I think that would be consistent with looking at the way that the EPA had interpreted that data as well, and why it's not listed as B-2 carcinogen.

COMMITTEE MEMBER LANDOLPH: Thank you.

COMMITTEE MEMBER EASTMOND: I might mention, I was looking at my notes. And I believe the EPA when they did evaluate the rat data said something on that they didn't think this was indicative of a true carcinogenic effect. I think that was the way they worded it.

DR. PLUNKETT: Yes.

COMMITTEE MEMBER EASTMOND: Although there were some trends seen there, the EPA looked at it, they weren't convinced by that data.

DR. PLUNKETT: Right.

CHAIRPERSON MACK: Any others?

Marty.

COMMITTEE MEMBER HOPP: I think the review of this was due to high toxicity, but it's overall usage, it's commonality, was the reason that I thought this had some more value to the public than a low priority. Highly toxic and wide usage, although, the carcinogenicity effects may be limited. I think, because of its use in the public, it's something to be looked at. And if it turns out to be safe, I hope so.

But with a high utilization exposure of the public, I believe it should be in the medium category.

DR. PLUNKETT: Okay. Thank you very much. We just want to be able to get on the record the issues that are related to it. I think the actual data themselves and the details in the data that I think are important for any decision that you might make.

CHAIRPERSON MACK: Thank you, Dr. Plunkett.

DR. PLUNKETT: Thanks.

CHAIRPERSON MACK: All right. Okay, how much time do you need?

THE COURT REPORTER: About 10 minutes.

CHAIRPERSON MACK: Ten minutes. So let's reconvene at 5 to 3:00.

(Thereupon a recess was taken.)

CHAIRPERSON MACK: All right. Let's get the show on the road. My record says that we have five compounds that we had public comment on, omeprazole -- I never can pronounce that correctly.

Omeprazole and its salts we judged to be of high priority; atrazine, high priority; PFOS, medium priority; acephate, medium priority; and budesonide, medium priority.

So let's go through those five and see whether or not anybody votes to change the prioritization.

So first is omeprazole. Does anybody want to change the prioritization from high?

I don't see any hands raised, so I'm going to presume that we leave that prioritization at high.

Atrazine. Does anybody want to change the prioritization from high?

Seeing no flurry of activity, I will presume that that one will also stay as high.

PFOS and its salts. Even though Stan has given his largesse, we still will ask the question, do any of us want to change that categorization from medium?

I guess not, so we leave that one at medium.

Acephate, currently categorized as medium. Does anybody want to vote to change that prioritization from medium?

No.

I think everybody is awake.

(Laughter.)

CHAIRPERSON MACK: And finally, budesonide, currently classified as medium. Does anybody suggest changing that classification from medium?

Well, what a solid bunch.

(Laughter.)

CHAIRPERSON MACK: So we're not changing our classifications. They stand as originally done.

And now Carol wishes to address the crowd.

DR. ALEXEEFF: Dr. Mack, George Alexeeff, just a point of order. Maybe I misunderstood what you said in the introduction. But it seemed to me as though, it would be worth to ask the question if any of the chemicals should be reprioritized, even though they weren't commented on.

CHAIRPERSON MACK: I'd be happy to ask that question.

Having now gone through five that we had public comment on, to be complete and honest and fair, do we want to change any of the other criteria -- I'm sorry, do we want to change any of the other classifications?

I will go through them one by one, so everybody remembers what they are.

Methylphenidate and its salts we've classified as high

COMMITTEE MEMBER EASTMOND: Probably better go off the screen.

CHAIRPERSON MACK: You want to go do the screen?

Well, that doesn't seem very right to me, but I'll do it anyway, if that's what you want.

(Laughter.)

CHAIRPERSON MACK: I don't have it listed there. I have to look for it on here, then.

Oh, I see it is listed there. Fancy that.

(Laughter.)

CHAIRPERSON MACK: All right. Acephate is listed as medium, we just did that.

Alpha-methyl styrene is classified as medium. Does anybody want to change that?

Amitraz is listed as low. Any suggestions for change on that?

Atrazine is high. We've done that.

Biphenylamine and its salts was categorized as low. No change there.

We've done budesonide.

4-Chloro-m-phenylenediamine is classified as medium.

No changes there.

COMMITTEE MEMBER EASTMOND: It's low.

CHAIRPERSON MACK: I'm sorry, low. You're right. Thank you.

4-Chloro-m-phenylenediamine is classified as low.

That stays as is.

C.I. Acid Orange 3 is classified as medium.

Stay as is.

Ciprofibrate is classified as low.

Stay as is.

Clomiphene and its salts as high.

Stay as is.

Decabromophenyl ether. I'm sorry, decabromodiphenyl ether, classified as medium.

Stay as is.

DecaBDE is not listed here. And I think we called it low and we're going to look it up.

COMMITTEE MEMBER EASTMOND: That's the acronym for the one you just did.

CHAIRPERSON MACK: Oh, that's the acronym. It takes a toxicologist.

(Laughter.)

CHAIRPERSON MACK: Decalin is classified as low.

That stays as is.

2,6-Dichloro-p-phenylenediamine classified as low.

Stay as is.

Furfural classified as medium.

Stays as is.

Gentian violet, medium. Stays as is.

4-Hydroxymethyl, 4-Methyl, and 4-Hydroxy, benzenediazonium -- I can't get through that -- benzenediazonium -- is that right -- and their salts.

COMMITTEE MEMBER EASTMOND: You're doing fine.

CHAIRPERSON MACK: It's classified as medium.

Stays as is.

Isoniazid low.

Stays as is.

Malathion medium.

Stays as is.

7-Methylbenz[a]anthracene as low.

Stays as is.

Joe.

COMMITTEE MEMBER LANDOLPH: Just if OEHHA speaks with the Air Resources Board and they decide there is substantial exposure, then we could -- I would recommend we revisit that since it's a mutagen tumor initiator skin carcinogen. But our vote was mainly based on our lack of knowledge of exposure, which we think might be low.

CHAIRPERSON MACK: Can I ask a question that may be stupid?

I thought that this was a product of incomplete combustion, which means that it has the same exposure as any other product of incomplete combustion, when you burn something you get this as well as a lot of other things. Is that true or not?

COMMITTEE MEMBER HAMBURG: Sounds right.

DR. SANDY: In general, yes. As far as we know, that's the general --

CHAIRPERSON MACK: It's coming out of your fireplace. It's coming out of your cigarettes. It's coming out of your barbecue, and all those things. So I think it's pretty clear that it is wide exposure. The question is whether the evidence warrants upgrading it from low.

DR. ALEXEEFF: Dr. Mack, George Alexeeff. I did say we would check with the Air Resources Board in terms of if they had any measurements in the air and that kind of stuff. And if so, we'll report back to you and then you can --

CHAIRPERSON MACK: I was just making it clear that it was not the exposure they were going to look back to, but the actual empirical information.

Okay. Anyway, so it is currently classified as low and we're going to hear about whether that's to be changed later.

Methylphenidate and its salts is classified as high.

No changes there, unless somebody speaks up.

N-Methyl-N-formylhydrazine is medium.

And that stays as is.

We've already discussed omeprazole and actually Pantoprazole and Rabeprazole, presumably.

All stay high.

Perfluorooctane sulfonate, PFOS, we've already done that. Sorry.

Phosmet stays low, unless somebody complains.

Quinoxaline-1,4-dioxide compounds and desoxycarbadox -- I'm very proud of myself for getting through that -- is classified as medium.

And I just spoke about the other one. So we've gone through all 27, and there are no changes. So we're going to stand pat as a group.

I will now turn it over to -- Carol, go for it.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay, the next agenda item for you is the update of the Sections 2700 list of chemicals, which have not been adequately tested as required. You received some information on this, I think, towards the middle of all the binders that you received.

This is just for background. We talked about

this last time at the last meeting that there's a somewhat little known provision of Prop 65 that requires you, as the State's qualified experts to --

(Thereupon an overhead presentation was Presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: -- maintain a list of chemicals that need further testing -- that are required to have further testing by U.S. EPA or the Department of Pesticide Regulation or other relevant programs within those agencies. And there's a list actually that we provided you of -- well, we gave you two different pieces of information.

One was the actual request we made to U.S. EPA and Department of Toxic Substances Control and their responses to us asking whether or not any of these chemicals should be removed from the list, because the testing requirements have been satisfied, and whether or not there's any additional chemicals that they would recommend being added to the list that haven't been adequately tested.

We gave you an underline and strike-out version of the current regulation that is somewhat hard to follow, in terms of -- it's all strike-out by the way, because we don't have any chemicals that are being recommended to add to this list. So essentially what we're asking you to do

is in reliance on the statements from U.S. EPA and the Department of Toxic Substances Control, to find that the chemicals that are listed up here on the slide -- I'm going to make no effort to try and read these -- there's one, two, three, four, five, six, seven, eight, nine of them. And we'll include the names of those in the record.

But we're asking you to find based on these representations from U.S. EPA and DPR that these chemicals have been adequately tested and can be taken off the Section 2700 list.

Does anybody have any questions on that?

So, Dr. Mack, if you want the take a vote.

CHAIRPERSON MACK: Based on the information you've been provided from U.S. EPA, should the nine chemicals noted on Exhibit A be removed from the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required?

Does everybody who will vote yes to that proposition, please raise their hand.

(Hands raised.)

CHAIRPERSON MACK: No?

Hearing no knows, there are seven yes votes. The measure passes, 7 to 0.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

CHAIRPERSON MACK: The next item. Cynthia is

going to do her annual review.

MS. OSHITA: Good afternoon. Since you last met in May of 2009, OEHHA has administratively added 28 chemicals to the Prop 65 list, nine chemicals as known to cause cancer, and then 19 as known to cause reproductive toxicity.

And rather than recite all the names of these chemicals, there is a summary sheet within your meeting materials behind the staff updates that list all the chemicals as well as their effective listing dates.

Presently, there remain four chemicals that are under consideration for administrative listing, which includes 4-Methylimidazole, metam potassium, spirodiclofen, as known to cause cancer. And then one also under consideration for methanol as causing reproductive toxicity.

And each of these four chemicals are in the Notice of Intent to List phase. And we have received comments on each of them, which are under review.

In addition, on three separate occasions since May of 2009, OEHHA announced the proposed administrative listing of yet some other chemicals. Two chemicals are under consideration for listing as causing cancer. That includes epoxiconazole and DEF. And those are now also in the Notice of Intent to List phase.

We received comments on epoxiconazole, and that is under review. And an extension to the public comment period has been granted for DEF, and that will close on October 13th, 2010.

Comments were also received on a third chemical that's under consideration, and that is BPA for causing reproductive toxicity. And we are also in the process of reviewing those comments.

Then additionally since last May, OEHHA has adopted two No Significant Risk Levels NSRLs. One for para-chloroaniline and another for para-chloroaniline hydrochloride. These levels became effective on August 12th, 2010.

Currently, OEHHA has proposed to adopt two new NSRLs. One for 2,4,6-Trinitrotoluene, or TNT. And the other is for glycidol.

We are also proposing two new MADLs, which stands for Maximum Allowable Dose Levels. They are for DIDP and hexavalent chromium.

No comments were received for TNT or glycidol. And so the rule-making packages will be finalized for those and submitted to the Office of Administrative Law for approval.

Comments were received in support of the MADL for DIDP. And so we will also finalize its rule-making

package, and similarly submit it to OAL for approval.

The MADL for hexavalent chromium is still open for public comment. And that comment period will close on September 27th, 2010.

Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm back.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: This is Carol Monahan-Cummings again. I promise hopefully this is the last time I'll say anything. This is the point at which I update you on Prop 65 litigation.

And given the fact that you are all parties to one of the cases, you might have some interest in that one. That's the Sierra Club versus Schwarzenegger case.

And as you may recall, that is in the trial court. It deals with various listing mechanisms under Prop 65, including listings by this Committee and also the prioritization process that you were involved in today.

That case has proceeded slowly, as civil cases tend to do, but we have gone through a number of motions in the case, and we are in the discovery process right now. As you recall, you produced some documents yourselves. And there's potential for additional discovery, like depositions and that sort of thing. I can't advise you whether or not you'd be involved in that.

We expect that if -- assuming that discovery goes as expected, that the trial in that case would occur early next year.

There are also two cases pending in the California appellate courts regarding the proposed listing of the chemical styrene, and the chemical -- well, the first one being the proposed listing of the chemical styrene and vinyl acetate under our Labor Code provision of the statute.

Those were proposed for listing based on an IARC 2B designation. However, the information from IARC is that there's insufficient animal or human data, but there's other relevant scientific data to support a finding that they are possible human carcinogens.

We were actually ordered at the trial level not to list those two chemicals. And because the IARC said there was insufficient evidence. And so that question is now before the third district court of appeal.

That also affects a handful of other chemicals that we had proposed at the same time for this listing mechanism, both of these chemicals were proposed for listing as carcinogens.

The last case that I would mention is the one that's related to the Sierra Club case, which is pending in the first district court of appeal, and that is the

Chamber of Commerce versus Schwarzenegger case that had also to do with Labor Code listings under Prop 65. And that case is still pending in the court. It's been fully briefed and we're expecting to have oral argument at any time.

I should also mention on the styrene, vinyl acetate cases those are also nearly fully briefed and we're expecting oral argument, either late this year or earlier next year.

Any questions on those?

Yes. Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Do we have to keep recent copies of the prioritization or will you keep those and forward them for us, if they ask for them? I just can't store anything in my office anymore.

CHIEF COUNSEL MONAHAN-CUMMINGS: We do have a litigation hold. And so I would recommend that you keep those items that you have actually prepared yourself. And you should also keep notes and those kinds of things that you kept, you know, for the meeting. The materials that we've provided to you, we can produce, you know, if they're required. But your own personal notes or materials that you've created ought to be kept under that for now.

CHAIRPERSON MACK: So if you don't ever write any

notes, and you don't keep any documents you don't have anything to do, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry?

CHAIRPERSON MACK: I said if you never write any notes and you don't keep any documents, there's nothing to do, right?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. If you don't haven't it, you can't produce it, that's true.

COMMITTEE MEMBER EASTMOND: Let me ask a very practical point. The court cases have to do with previous things. Do I have to keep the notes I made for this meeting, because it deals with prioritization?

CHIEF COUNSEL MONAHAN-CUMMINGS: It's an ongoing case, and so the litigation hold is still current. There's a possibility that we'll get a second set of requests for discovery. There usually is one just before trial. And we would have to produce anything from the time that we last produced up to the date that the new request was made.

COMMITTEE MEMBER EASTMOND: Okay.

CHIEF COUNSEL MONAHAN-CUMMINGS: Anything else?

Lucky for you we've only got one hold for you. We have about seven or eight holds pending right now.

DIRECTOR DENTON: George.

DR. ALEXEEFF: Yeah, I just wanted to thank the

panel for considering the two chemicals today for possible listing. And I also wanted to thank them for their advice on the prioritization.

And I just -- so as Dr. Sandy was pointing out so far, the staff have gone through -- well as of for this meeting -- 285 chemicals, okay, in terms of -- and then from those, we brought you two batches to consider.

And of those, you've prioritized 15 as high. So just on the math side, that's five percent of the chemicals that we've had in our database. So I just think that's a very -- you know, we were wondering how this effort would work when we thought of this prioritization procedure, and had advice from you. So I think it's working very well.

So thank you.

CHAIRPERSON MACK: As we all thought, of course.

(Laughter.)

DIRECTOR DENTON: Okay. I'm just going to take a minute or so to summarize what happened at our meeting today.

Obviously, the Committee has concluded its deliberations on the agenda items, so there will be no meeting tomorrow. So this is a one-day meeting.

So this morning, the panel, the Committee, voted unanimously to list 1,3-DCP and by a vote of six to one to

list 3-MCPD, both as chemicals known to the State to cause cancer.

This afternoon the Committee prioritized 27 chemicals, six in the high category, 12 in the medium category and nine in the low category, and zero in the no priority. There is one chemical, 7-methylbenz[a]anthracene in the low category, which the Committee would like us to look at to see if there's any air data, any other exposure data. And here's where I'm a little unclear. Regardless of our findings, do you want us to come back and report what we found to you or if there's really no significant air data out there, then just keep it in the low category?

CHAIRPERSON MACK: I'll ask the question of the group.

DIRECTOR DENTON: Would you like to hear about it regardless?

CHAIRPERSON MACK: I would like -- I would recommend that we keep it in the low category, unless there's something that dramatically warrants a change, and then you can --

DIRECTOR DENTON: Bring it back.

CHAIRPERSON MACK: -- get back to us. Does everybody agree with that?

COMMITTEE MEMBER HOPP: I think we voted for it

to be low, but if there's some new information that would be appropriately reviewed, we'd be glad to hear it next time or it should be brought to us, and if we think it's significant, I think we could always change the category.

DIRECTOR DENTON: Okay. All right, so if we don't bring it back, then we have not really found any significant exposure from the chemical.

Okay. And then also the Committee unanimously voted to remove nine chemicals from the list of chemicals required by the State or federal to be tested -- federal law to be tested, but which have not been adequately tested as required.

So I want to again thank the Committee very much for your deliberations, for your very efficient deliberations today. I'd also like to thank the audience and the stakeholders who came to the meeting. Some of you testified. Some of you did not. But we always appreciate and acknowledge that you came and attended and are interested in the deliberations of the Committee.

And then I would really want to thank my staff. Martha, you're great. You have a tremendous staff. Dave Morry, Rajpal, Feng, Jennifer, Rose, George, Lauren, Carol. Anyway -- oh, and all also Susan and Cindy, you always provide such an incredible support to the Committee. So I'd like to personally thank them. I'm

very proud to be the director of this group.

So with that, and thanking the Committee -- okay, Marty.

COMMITTEE MEMBER HOPP: I just want to comment about how proud I am that this Committee is taking into its deliberations the effect of these chemicals on the public, and not just the scientific information that comes up and burbles up through the spectacular amount of work that the OEHHA does regarding these. But by looking at not only the chemicals, but how the public need for information about these chemicals affects our deliberations, I think, is a major step and a change in the Committee, and something to be very proud of.

And I think it's very productive and it's something that we, as a Committee, should be proud of what we're doing, because it's a direction that I think is consistent with the way Prop 65 really was intended, but not written that way.

And now we're elucidating in, I think, a much more effective means for the people of California. And I'm very proud the way we're doing it this way.

DIRECTOR DENTON: We've always had exposure as part of prioritization, but we always -- we haven't always had this methodology for prioritizing. So exposure has always been part, but it hasn't been so public.

Of course, when we talk about the hazard identification, HIM, exposure is not the consideration of whether it's a carcinogen, but it is -- it's an essential part of the deliberation of whether we should look at it or not.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I want to thank Dr. Denton, Dr. Alexeeff, OEHHA staff for all the work we did on the prioritization in the subcommittee. I think that lasted about a year and a half or so. And I think it streamlined it. It's coming through pretty clear now. We're getting the stuff with the epidemiology data first, then the animal, then the epi. And it's worked out pretty well, I think. We're getting much better -- more toxic chemicals to look at.

DIRECTOR DENTON: I shouldn't forget to thank our audio visual person too.

Okay. Well, we won't see you for the rest of the year, so we want to wish you a Happy Holidays.

(Laughter.)

CHAIRPERSON MACK: I know it's early, but thank you very much.

(Thereupon the Carcinogen Identification Committee adjourned at 3:30 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of September, 2010.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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