

MEETING  
STATE OF CALIFORNIA  
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT  
PROPOSITION 65  
CARCINOGEN IDENTIFICATION COMMITTEE

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CAL/EPA HEADQUARTERS BUILDING  
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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

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

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

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

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

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

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

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

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

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

25           Okay, thank you.

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

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

7 Martha.

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

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

12 David.

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

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

21 --o0o--

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

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

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

7 Next slide.

8 --o0o--

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

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

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

4                           --o0o--

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

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

16                           --o0o--

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

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

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

3 --o0o--

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

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

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

21 --o0o--

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

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

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

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

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

22 --o0o--

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



1                   --o0o--

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

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

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

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

21                   --o0o--

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

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

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

6                           --o0o--

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

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

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

20                           --o0o--

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

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

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

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

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

21                           --o0o--

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



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

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

8 --o0o--

9 DR. MORRY: Now, we move on to the complicated  
10 issue of metabolism. So 1,3-Dichloropropanol is the  
11 chemical that's shown in the green box. And there are two  
12 major pathways. All of this slide is based on studies in  
13 live rats, and also with rat liver extracts. So  
14 1,3-Dichloropropanol, there are two main pathways for  
15 metabolism of it.

16 It can be metabolized directly to  
17 1,3-Dichloroacetone. And this chemical has not been  
18 evaluated by IARC, but it is a mutagen, and it is a skin  
19 tumor initiator in mice. The other pathway is to  
20 Epichlorohydrin, the same as the industrial change.  
21 Epichlorohydrin is, of course, an epoxide, which is an  
22 IARC carcinogen, highly mutagenic chemical.

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

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

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

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

13           The other pathway is from 3-MCPD over to a  
14 beta-chloroacetaldehyde, which then can be metabolized to  
15 beta-chlorolactic acid and oxalic acid or over this way to  
16 1,2-propanediol. So many of the chemicals on this slide  
17 we'll be discussing shortly with regard to structure  
18 activity relationships.

19                           --o0o--

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

24                           --o0o--

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

1 the first group are halogenated propanols. And in this  
2 group are the compound I'm talking about right now, the  
3 one that Dr. Tomar will talk about later, and then there's  
4 one more that's a halogenated propanol, and this is  
5 2,3-Dibromo-1-propanol which is an IARC 2B carcinogen, and  
6 a Prop 65 carcinogen.

7 --o0o--

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

14 --o0o--

15 DR. MORRY: Here are some other three-carbon  
16 halogenated compounds. 1,3-Dichloroacetone is the  
17 compound that can be made directly from  
18 1,3-Dichloropropanol. It's not been evaluated by IARC.  
19 1,2,3-Trichloropropane is an IARC carcinogen.

20 Telone II, which in industry is made from  
21 1,3-Dichloropropanol, is an IARC carcinogen and Prop 65  
22 listed. And DBCP, Dibromochloropropanol is an IARC  
23 carcinogen.

24 --o0o--

25 DR. MORRY: Lastly, there is two phosphate

1 triesters. The TDCPP, the one with the chlorine. This  
2 one we call chlorinated tris. And it's not been evaluated  
3 by IARC. If you break this compound here and convert this  
4 add a hydroxyl group to this oxygen here, or make this  
5 oxygen to a hydroxyl group, this compound is  
6 1,3-Dichloropropanol. So this TDCPP can be metabolized to  
7 1,3-Dichloropropanol. It's not been evaluated by IARC.

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

12           And if you -- just as I said for this compound,  
13 if you break this compound here, then you get  
14 1,3-Dibromopropanol, and that's an IARC carcinogen.

15                           --o0o--

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

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

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

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

9           2,3-Dibromo-1-propanol is the metabolite of  
10 brominated tris, is positive in the liver, and in the  
11 tongue and oral cavity. 1,2,3-Trichloropropane is  
12 positive in the liver in male and female mice, in male  
13 rats, female mice and male and female rats in the tongue.

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

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

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

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

5 --o0o--

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

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

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

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

8 --o0o--

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

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

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

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

3 --o0o--

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

5 CHAIRPERSON MACK: Thank you, David.

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

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

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

21 Is it David?

22 COMMITTEE MEMBER EASTMOND: It's Joe.

23 CHAIRPERSON MACK: Go ahead, Joe.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 are a number of genotoxic metabolites, the  
2 1,3-Dichloroacetone, the epichlorohydrin, the glycidol,  
3 two of which are epoxides. And many of these are  
4 carcinogenic and their structural isomers are carcinogenic  
5 analogs.

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

10 And thank you for your nice and thorough  
11 presentation.

12 CHAIRPERSON MACK: Thank you, Joe.

13 David? Who would you like to speak next?

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

16 David.

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

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

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

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

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

7 DR. SANDY: Martha Sandy.

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

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

24 COMMITTEE MEMBER EASTMOND: Reduced body weight  
25 gain.

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

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

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

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

18 CHAIRPERSON MACK: Joe.

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

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

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

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

6 DR. MORRY: That's correct.

7 COMMITTEE MEMBER LANDOLPH: -- as we understand  
8 it.

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

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

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

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

18 COMMITTEE MEMBER LANDOLPH: Thank you.

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

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

25 CHAIRPERSON MACK: Yeah, the structure probably

1 has something to do with that too.

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

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

6 Marty, do you have anything to add?

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

11 CHAIRPERSON MACK: Sol.

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

15 DR. MORRY: Morry.

16 COMMITTEE MEMBER HAMBURG: Thank you.

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

19 CHAIRPERSON MACK: David, anything?

20 COMMITTEE MEMBER HUNTER: No additional comment.

21 CHAIRPERSON MACK: Anna.

22 COMMITTEE MEMBER WU: No.

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

25 So let's go to the public.

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

5           So Lois Haighton.

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

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

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

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

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

15          CHAIRPERSON MACK: I couldn't hear you.

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

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

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

3 If you could find the slides that start DCP  
4 --o0o--

5 MS. HAIGHTON: I had started with MCPD.  
6 There. The next slide, please.

7 --o0o--

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

13 --o0o--

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

25 Next slide, please.

1                   --o0o--

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

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

13           Furthermore, hepatic tumors are known to arise  
14 secondary to metabolite disturbances, specifically the  
15 1,3-Dichloroacetone is a known glutathione depleter.  And  
16 glutathione, as you know, is essential for detoxifying  
17 epoxide metabolites.

18           Next slide, please.

19                   --o0o--

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

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

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

4 If you could move to the next slide, please.

5 --o0o--

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

14 Next report, please -- or next slide.

15 --o0o--

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

22 Next slide, please.

23 --o0o--

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

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

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

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

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

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

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

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

3 Next slide, please.

4 --o0o--

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

20 Last slide, please.

21 --o0o--

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

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

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

11           Last slide, please.

12                               --o0o--

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

15           CHAIRPERSON MACK: Thank you, Ms. Haighton.

16           Joe, do you have any response?

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

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

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

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

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

14 CHAIRPERSON MACK: Anybody else want to comment?  
15 Marty.

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

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

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

3 CHAIRPERSON MACK: Anybody else?

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

10 You want to say something.

11 DR. ROBERTS: Can I just make one comment.

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

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

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

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

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

15 Thank you.

16 CHAIRPERSON MACK: Thank you.

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

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

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

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

17           Joe.

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

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

1 testing.

2 CHAIRPERSON MACK: David.

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

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

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

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

22 So I will pose the voting question.

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

1           So all those voting yes, please raise your hands.

2           (Hands raised.)

3           CHAIRPERSON MACK: All of those voting no?

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

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

10          CHAIRPERSON MACK: I counted her.

11          (Laughter.)

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

14          CHAIRPERSON MACK: Seven is quite sufficient  
15 though.

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

18          (Laughter.)

19          (Thereupon an overhead presentation was  
20 Presented as follows.)

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

23          DR. TOMAR: Good morning,  
24 3-Monochloropropane-1,2-diol, 3-MCPD. It's a chlorinated  
25 three carbon alcohol.



1 DR. TOMAR: Now, studies in mice, there's a  
2 first -- two sets of these studies by Van Durren, et al.,  
3 1974. They were conducted for 19 months in groups of 50  
4 female Swiss mice. Mice were exposed by dermal  
5 application using 2 milligrams three times per week for 19  
6 months. There was no treatment related skin tumors were  
7 observed in this study.

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

13 --o0o--

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

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

1                   --o0o--

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

9                   --o0o--

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

15               In males -- and this is a study by Sunahara et  
16 al., 1993 -- groups of 50 Fischer rats were exposed to 0,  
17 20, 100, and 500 ppm for 104-weeks. There was a  
18 significant increase of Leydig cell adenoma in 100 and 500  
19 with a positive trend.

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

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

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

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

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

13           --o0o--

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

19           --o0o--

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

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

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

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

10 --o0o--

11 DR. TOMAR: Next is the proposed metabolic  
12 pathway. As we just heard from Dr. Morry, this is a  
13 metabolite of 1,3-DCP. And 3-MCPD is metabolized by two  
14 different pathway, either by oxidation to the glycidol or  
15 oxidation to the beta-chloroacetaldehyde. Glycidol can be  
16 converted into glycerol and can be exhaled through the  
17 lung as CO<sub>2</sub>.

18 The glycidol is deconjugated by glutathione and  
19 then finally acetylated to form the corresponding  
20 mercapturic acid. On the other side,  
21 beta-chloroacetaldehyde can be converted to  
22 beta-chlorolactic acid, and then oxalic acid, as well as  
23 it could be converted by elimination of chlorine to  
24 1,2-propanediol.

25 --o0o--

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

6 It was also positive in saccharomyces plumbe  
7 yeast forward mutation assay without metabolic activation.  
8 Again, gene mutation in mouse lymphoma cells with  
9 metabolic activation, Sister Chromatid Exchange in the  
10 Chinese hamster fibroblast cells with and without  
11 metabolic activation.

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

17 --o0o--

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

1                   --o0o--

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

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

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

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

24                   --o0o--

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

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

4 As we can see at the highest dose in 1000 and  
5 2000, it is cytotoxic to the cells and there is really no  
6 difference there. However, for the lower doses, there is  
7 a increase incidence 2/27 at 100 10/25 and 14/27. Both  
8 are highly significant.

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

14 --o0o--

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

20 --o0o--

21 DR. TOMAR: Six of the eight compounds are known  
22 to be carcinogenic by Prop 65 as well as by IARC. To name  
23 them 1,2,3-trichloropropane; tris,  
24 2,3-Dibromopropylphosphate; 2,3-dibromo-1-propanol;  
25 epichlorohydrin; dibromochloropropane and glycidol.



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

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

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

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

20 --o0o--

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

25 It causes kidney tumors in Sprague-Dawley rats,

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

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

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

12 --o0o--

13 DR. TOMAR: It is, as indicated, genotoxic in  
14 vitro. It causes malignant transformation of cells, like  
15 1,3-DCP. In fact, that if you look at the data, it is  
16 parallel to the 1,3-DCP. It's a metabolite to the  
17 glycidol, a genotoxic carcinogen and is structurally  
18 similar to the six known carcinogens.

19 Thank you.

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

22 David.

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

25 As I think was described in the presentation,

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

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

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

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

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

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

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

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

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

6           DR. TOMAR: Yes. I noted that comment many  
7 times. However, there are no data in rats and mice are  
8 labeled which indicate that one pathway is preferred over  
9 the other. And I would like to add that formation of the  
10 glycidol is an obligatory metabolite. You cannot have  
11 3-MCPD directly conjugated to the glutathione and form  
12 acetylation.

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

17           COMMITTEE MEMBER EASTMOND: Okay, thanks.

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

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

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

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

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

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

24           CHAIRPERSON MACK: Thank you, David.

25           Joe, do you have any comment?

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

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

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

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

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

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

8 CHAIRPERSON MACK: Thank you, Joe.

9 You've got another comment?

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

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

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

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

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

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

8           CHAIRPERSON MACK: Marty.

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

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

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

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

18           DR. TOMAR: Yes.

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

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

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

5           CHAIRPERSON MACK: Sol.

6           COMMITTEE MEMBER HAMBURG: I know less than he  
7 does.

8           (Laughter.)

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

13           DR. TOMAR: Thank you.

14           CHAIRPERSON MACK: David?

15           Pass.

16           Anna?

17           Pass.

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

20           No public comments.

21           COMMITTEE MEMBER EASTMOND: The same ones.

22           MS. HAIGHTON: Me again.

23           CHAIRPERSON MACK: Sorry about that.

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

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

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

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

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

9 Next slide, please.

10 --o0o--

11 MS. HAIGHTON: Next slide, please.

12 --o0o--

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

23 Next slide, please.

24 --o0o--

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

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

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

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

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

1 instance in the high dose.

2 Next slide, please.

3 --o0o--

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

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

15 Next slide, please.

16 --o0o--

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

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

25 Only a single instance of adenomas was reported



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

11           Next slide, please.

12                           --o0o--

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

22           Next slide, please.

23                           --o0o--

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



1 or is conjugated with glutathione forming mercapturic acid  
2 derivative.

3 Next slide.

4 --o0o--

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

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

19 Next slide, please.

20 --o0o--

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

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

4 Thank you for your attention.

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

7 David, do you have any response?

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

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

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

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

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

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

18           CHAIRPERSON MACK: Anybody else have anymore  
19 comments?

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

22           CHAIRPERSON MACK: Okay.

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

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

5 Thank you.

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

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

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

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

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

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

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

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

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

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

24 So the question is, has  
25 3-Monochloropropane-1,2-diol been clearly shown through

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

3 All those voting yes, please raise your hand?

4 (Hands raised.)

5 CHAIRPERSON MACK: We have 6 out of 7.

6 On those voting no?

7 (Hand raised.)

8 CHAIRPERSON MACK: One

9 So 6 yes, 1 no.

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

12 Let's take a 10-minute break.

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

14 Is everybody hungry?

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

18 (Laughter.)

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

21 Carol.

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

25 You can talk about anything you did this morning,

1 but not this afternoon.

2 Thank you.

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

5 (Laughter.)

6 (Thereupon a lunch break was taken.)

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

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

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

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

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

1                   --o0o--

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

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

12                   --o0o--

13           DR. SANDY: So at your last meeting on May 29th,  
14 2009, you considered and ranked 38 chemicals. And today,  
15 you'll be considering and ranking 27 chemicals, and  
16 presumably at your next meeting in 2011, you'll be ranking  
17 the remainder of that screening effort.

18                   --o0o--

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

25           And what you're going to be doing today is

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

4 --o0o--

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

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

15 --o0o--

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

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

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

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

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

12           Is that fair?

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

16           CHAIRPERSON MACK: This is a straw vote.

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

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

21           CHIEF COUNSEL MONAHAN-CUMMINGS: All right.

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

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

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

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

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

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

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

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

21 DIRECTOR DENTON: You need to use the microphone

22 CHAIRPERSON MACK: You have to get the mic.

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

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

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

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

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

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

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

1 MR. LANDFAIR: Perhaps I am.

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

4 MR. LANDFAIR: Yes.

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

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

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

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

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

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

1 high, medium, and low category.

2 MR. LANDFAIR: Yes.

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

6 MR. LANDFAIR: Right.

7 CHAIRPERSON MACK: Okay.

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

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

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

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

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

19 (Laughter.)

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

23 (Laughter.)

24 CHAIRPERSON MACK: It's not a simple process.

25 MR. LANDFAIR: Thank you.

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

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

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

13 Did you want to comment on that?

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

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

21 So the next one is omeprazole.

22 COMMITTEE MEMBER HAMBURG: Omeprazole.

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

25 COMMITTEE MEMBER HAMBURG: I would consider

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

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

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

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

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

19           CHIEF COUNSEL MONAHAN-CUMMINGS: And the third  
20 one.

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

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

4 COMMITTEE MEMBER WU: Okay. Well --

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

7 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 COMMITTEE MEMBER HAMBURG: I can certainly  
23 support that.

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

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

3           David.

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

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

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

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

1 significance of those mammary tumors.

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

8           CHAIRPERSON MACK: Thank you, David.

9           Anna.

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

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

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

23           Hearing no opposition.

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

1 David.

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

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

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

17 CHAIRPERSON MACK: Anna.

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

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

1           Now, we come to Malathion.

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

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

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

21           CHAIRPERSON MACK: Okay. Anna.

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

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

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

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

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

25 So I think there's a question about Malathion and

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

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

8 COMMITTEE MEMBER WU: Yes.

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

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

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

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

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

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

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

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

19           DR. ALEXEEFF: Dr. Mack.

20           CHAIRPERSON MACK: Yeah.

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

1 reports by tomorrow, but we can talk with DPR.

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

4 (Laughter.)

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

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

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

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

20 DR. ALEXEEFF: Is he still here?

21 COMMITTEE MEMBER HUNTER: Well, he drank it.

22 (Laughter.)

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

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

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

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

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

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

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

18 David.

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

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

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

14           CHAIRPERSON MACK: Anna, did you look at this?

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

17           CHAIRPERSON MACK: Medium category?

18           COMMITTEE MEMBER WU: Yeah.

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

21           Anybody object?

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

25           COMMITTEE MEMBER HOPP: Alpha-methyl styrene is

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

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

18 CHAIRPERSON MACK: David.

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

25 The one that drives it is essentially the

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

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

10 Marty, is that okay with you?

11 COMMITTEE MEMBER HOPP: That's fine.

12 CHAIRPERSON MACK: Okay. Now, we're to decaBDE.  
13 Marty, you want to take that.

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

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

25 CHAIRPERSON MACK: David.

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

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

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

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

19 Does anybody object to that?

20 Okay, decalin.

21 Marty.

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

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

10           CHAIRPERSON MACK: David.

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

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

25           So this would be one of these examples where I

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

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

7 COMMITTEE MEMBER HOPP: Yeah, low is fine.

8 COMMITTEE MEMBER WU: I think Marty is right.

9 COMMITTEE MEMBER HOPP: I didn't hear you.

10 CHAIRPERSON MACK: Do you agree with low.

11 COMMITTEE MEMBER HOPP: I'll take low.

12 CHAIRPERSON MACK: The next special --

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

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

16 COMMITTEE MEMBER EASTMOND: Hypolipidemia.

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

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

24 CHAIRPERSON MACK: That's what I thought.

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

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

3 CHAIRPERSON MACK: Okay. Joe, go ahead.

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

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

17 And I'll defer to the exposure.

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

21 So do we agree on low?

22 COMMITTEE MEMBER LANDOLPH: Yeah, that's fine.

23 CHAIRPERSON MACK: Any object to low?

24 Okay, the next one is gentian violet.

25 Joe.

1 DR. ALEXEEFF: I can report back on Malathion.

2 CHAIRPERSON MACK: My God.

3 (Laughter.)

4 DR. ALEXEEFF: Computers are great.

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

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

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

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

17 COMMITTEE MEMBER HAMBURG: It shows the tonnage?

18 COMMITTEE MEMBER EASTMOND: Yeah, that's  
19 available.

20 CHAIRPERSON MACK: Okay. Joe.

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

1 cancer in rodents. So that woke me up.

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

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

9 COMMITTEE MEMBER HAMBURG: Yeah, sure.

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

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

14 COMMITTEE MEMBER HOPP: I think medium is fine.

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

17 Joe.

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

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

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

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

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

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

21 CHAIRPERSON MACK: So does anybody object to  
22 medium?

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

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

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

7 CHAIRPERSON MACK: Is everybody --

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

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

12 (Laughter.)

13 COMMITTEE MEMBER HAMBURG: So just to keep it  
14 confusing.

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

17 COMMITTEE MEMBER LANDOLPH: Ours do, our medical  
18 students.

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

21 (Laughter.)

22 COMMITTEE MEMBER HAMBURG: That's number one.

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

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

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

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

13 (Hands raised.)

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

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

18 CHAIRPERSON MACK: How many people want low?

19 (Hands raised)

20 CHAIRPERSON MACK: One, two. You lose.

21 COMMITTEE MEMBER HOPP: Okay.

22 COMMITTEE MEMBER HAMBURG: Okay, not the first  
23 time.

24 CHAIRPERSON MACK: Isoniazid.

25 Joe.

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

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

10 Interestingly, the epidemiology study is  
11 negative, and I hope Anna and Tom will comment on that.  
12 They've looked in TB patients, and I guess that's 9 out of  
13 10 studies. Just one observation of a mesothelioma.

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

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

25 But again --

1 COMMITTEE MEMBER LANDOLPH: You want to  
2 compromise on medium.

3 (Laughter.)

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

6 Sol, back me up.

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

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

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

20 CHAIRPERSON MACK: John, John, John -- anyway,  
21 the guy who looked at x-rays in people with tuberculosis.  
22 It was pretty well done and it was pretty  
23 negative and he considered it negative.

24 COMMITTEE MEMBER WU: I would agree.

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

1 COMMITTEE MEMBER HOPP: I have another opinion.

2 COMMITTEE MEMBER HAMBURG: Of course.

3 CHAIRPERSON MACK: Low?

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

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

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

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

3 (Hands Raised.)

4 COMMITTEE MEMBER WU: What are you voting?

5 CHAIRPERSON MACK: For medium as opposed to low.

6 So we've got two votes for medium.

7 How many votes for low?

8 (Hands raised.)

9 CHAIRPERSON MACK: One, two, three, four.

10 Okay, you win.

11 I call this one low.

12 Quinoxaline-1,4-dioxide compounds and

13 desoxycarbadox.

14 Joe.

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

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

25 CHAIRPERSON MACK: I actually, based on that,

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

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

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

7 COMMITTEE MEMBER HAMBURG: It's in silo.

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

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

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

19 COMMITTEE MEMBER HOPP: Grudgingly.

20 (Laughter.)

21 CHAIRPERSON MACK: Anybody object?

22 So medium it is.

23 Acephate. Do you want to start, Marty?

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

1 (Laughter.)

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

5 Again another -- no epidemiological studies  
6 whatsoever.

7 COMMITTEE MEMBER HUNTER: They're pincher bugs.

8 COMMITTEE MEMBER HOPP: I'm sorry?

9 COMMITTEE MEMBER HUNTER: They're pincher bugs.

10 COMMITTEE MEMBER HOPP: Pardon?

11 COMMITTEE MEMBER HUNTER: Earwigs are pincher  
12 bugs.

13 COMMITTEE MEMBER HOPP: Thank you.

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

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

22 COMMITTEE MEMBER HOPP: Low medium.

23 CHAIRPERSON MACK: Low, okay.

24 Joe.

25 COMMITTEE MEMBER LANDOLPH: I gave it a medium.

1 CHAIRPERSON MACK: For the same reasons?

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

6 CHAIRPERSON MACK: So medium  
7 Medium.

8 Amitraz. Marty.

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

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

20 CHAIRPERSON MACK: Low or medium?

21 COMMITTEE MEMBER HOPP: More on the low side.

22 CHAIRPERSON MACK: Low side.

23 Joe.

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

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

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

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

9 CHAIRPERSON MACK: Okay. Does anybody object to  
10 low?

11 No.

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

13 Marty.

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

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

1 so good. Again, no cancer epidemiology studies.

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

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

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

14 CHAIRPERSON MACK: So you're going medium?

15 COMMITTEE MEMBER HOPP: Yeah.

16 CHAIRPERSON MACK: Joe.

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

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

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

8 CHAIRPERSON MACK: Thank you.

9 Does anybody object to a medium for furfural?  
10 Phosmet. Marty.

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

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

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

1 think had newer information that was significant.

2 CHAIRPERSON MACK: So where are you?

3 COMMITTEE MEMBER HOPP: So I'm on low.

4 CHAIRPERSON MACK: Joe.

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

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

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

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

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

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

8 CHAIRPERSON MACK: Any objections to low?

9 Biphenylamine and its salts.

10 Sol.

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

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

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

21 CHAIRPERSON MACK: Darryl.

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

25 CHAIRPERSON MACK: Okay. Does anybody object to

1 a low?

2 Okay, 4-Chloro-m-phenylenediamine.

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

5 4-Chloro-m-phenylenediamine it's also a dye  
6 intermediate. There's no epidemiological data. The data  
7 on animals is relatively old going back nearly 30 years --  
8 over 30 years. I don't think it's really in widespread  
9 use, so I would make it low again.

10 CHAIRPERSON MACK: Darryl.

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

15 CHAIRPERSON MACK: We're on a roll.

16 Okay, Acid Orange 3.

17 Sol.

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

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

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

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

4 CHAIRPERSON MACK: Okay. Darryl.

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

8 (Laughter.)

9 COMMITTEE MEMBER HAMBURG: It doesn't show.

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

12 (Laughter.)

13 CHAIRPERSON MACK: Okay. Does anybody object to  
14 medium?

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

16 COMMITTEE MEMBER HAMBURG:

17 2,6-Dichloro-p-phenylenediamine. It's always fun  
18 to say these, I think. There is another dye intermediate.  
19 This does not appear to have the extent in the population  
20 of use as the prior agent does. There's also very limited  
21 data, and I would again put this as a low.

22 COMMITTEE MEMBER HUNTER: I also did a low.

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

25 Okay, Darryl. Budesonide.

1 COMMITTEE MEMBER HUNTER: Let me find that.

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

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

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

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

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

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

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

7 COMMITTEE MEMBER HAMBURG: I object.

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

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

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

20 CHAIRPERSON MACK: I mean --

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

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

1 CHAIRPERSON MACK: So you want to put it high.

2 COMMITTEE MEMBER HAMBURG: High.

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

5 Marty.

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

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

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

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

25 CHAIRPERSON MACK: I hate to weigh in on an

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

3 (Laughter.)

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

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

14 COMMITTEE MEMBER HUNTER: Aren't they speaking?

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

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

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

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

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

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

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

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

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

8 Sorry to interrupt.

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

11 (Laughter.)

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

15 What do you think about medium, Sol?

16 COMMITTEE MEMBER HAMBURG: I can live with  
17 medium.

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

20 COMMITTEE MEMBER HOPP: I suggested medium.

21 CHAIRPERSON MACK: You suggested medium.

22 (Laughter.)

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

25 Okay, going, going, gone.

1           4-Hydroxymethyl, 4-Methyl, and 4-Hydroxy  
2 Benzenediazonium and their salts. Darryl.

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

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

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

9           COMMITTEE MEMBER HUNTER: Yeah, the light is on.

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

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

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

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

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

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

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

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

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

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

23           COMMITTEE MEMBER HUNTER: I came down with a  
24 medium.

25           CHAIRPERSON MACK: Anna and you?

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

3 CHAIRPERSON MACK: Now, we're at  
4 7-Methylbenz[a]anthracene.

5 Darryl.

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

14 CHAIRPERSON MACK: Anna, did you have anything?

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

24 CHAIRPERSON MACK: David, did you look at it?

25 COMMITTEE MEMBER EASTMOND: I did a little bit.

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

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

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

15 Sol.

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

19 Anybody?

20 DR. SANDY: (Shakes head.)

21 DR. ALEXEEFF: Repeat that again, Sol.

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

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

4 COMMITTEE MEMBER HAMBURG: Thank you.

5 CHAIRPERSON MACK: Marty.

6 Marty or David?

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

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

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

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

1 CHAIRPERSON MACK: George.

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

10 COMMITTEE MEMBER HAMBURG: I think that's  
11 correct.

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

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

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

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

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

5 COMMITTEE MEMBER HAMBURG: I'm for low.

6 CHAIRPERSON MACK: Okay, we've got it.

7 COMMITTEE MEMBER EASTMOND: 60 years.

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

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

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

1 CHAIRPERSON MACK: Anna, did you look at it?

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

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

13 Any mushroom eaters in the group?

14 (Laughter.)

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

17 Anybody else want to weigh in on this?

18 Joe.

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

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

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

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

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

12 CHAIRPERSON MACK: What do you think, Darryl?

13 COMMITTEE MEMBER HUNTER: I mean I could do  
14 medium.

15 CHAIRPERSON MACK: Medium.

16 Anybody object to medium?

17 Sorry, anybody object to medium?

18 Okay, that's it.

19 So now we go to the public comments.

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

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

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

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

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

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

25 These findings are not replicated in other

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

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

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

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

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

1 CHAIRPERSON MACK: Thank you.

2 Does anybody have any other questions for Mr.  
3 Marin?

4 DR. MARIN: Doctor.

5 CHAIRPERSON MACK: Dr. Marin, excuse me.  
6 Thank you very much.

7 DR. MARIN: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17           Thank you. Any questions?

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

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

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

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

8 DR. PASTOOR: Correct.

9 CHAIRPERSON MACK: Do you have any questions?

10 COMMITTEE MEMBER WU: I have nothing.

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

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

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

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

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

8           COMMITTEE MEMBER LANDOLPH: Thank you.

9           CHAIRPERSON MACK: Does anybody else have  
10 questions?

11           David.

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

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

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

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

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

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

22           CHAIRPERSON MACK: Thank you.

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

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

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

3 DR. ALEXEEFF: Yes.

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

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

16 COMMITTEE MEMBER HOPP: Thank you.

17 CHAIRPERSON MACK: Thank you, sir.

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

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

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

24 (Laughter.)

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

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

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

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

21 CHAIRPERSON MACK: Thank you very much.

22 MR. LANDFAIR: Well, thank you.

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

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

1 will remain silent.

2 CHAIRPERSON MACK: Thank you.

3 (Laughter.)

4 MR. LANDFAIR: Thank you.

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

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

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

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

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

1 budesonide in humans.

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

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

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

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

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

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

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

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

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

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

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

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

10          David.

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

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

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

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

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

4 COMMITTEE MEMBER EASTMOND: Thank you.

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

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

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

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

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

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

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

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

23 CHAIRPERSON MACK: Thank you very much.

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

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

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

11          DR. MARIN: Thank you very much.

12          CHAIRPERSON MACK: Thank you.

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

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

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

20          DIRECTOR DENTON: There's one more comment.

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

23          CHAIRPERSON MACK: No, I think we've gone through  
24 them all.

25          MS. OSHITA: There should be on for acephate.

1 CHAIRPERSON MACK: Maybe I missed acephate.

2 Oh, all right. Ms. Plunkett.

3 Sorry.

4 CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, the  
5 court reporter needs a break soon.

6 CHAIRPERSON MACK: Pardon me?

7 CHIEF COUNSEL MONAHAN-CUMMINGS: The court  
8 reporter needs a break soon, like maybe 10 minutes. Maybe  
9 after this comment before the Committee discusses.

10 CHAIRPERSON MACK: Yes. I think that's an  
11 excellent idea. We'll break right after this comment, and  
12 caucus.

13 DR. PLUNKETT: Thank you very much. I was  
14 wondering if I was going to get a chance to speak. I'm  
15 going to keep it very short. My name is Laura Plunkett.  
16 I'm a pharmacologist and Board Certified Toxicologist.  
17 And my colleague and I Judith McGregor wrote a letter that  
18 came in actually a little late, I think, to the -- a  
19 couple days after the comment period had ended. So I hope  
20 that some of you may have actually seen the letter on  
21 acephate.

22 We are consulting on behalf AMVAC Chemical  
23 corporation, which is the registrant for acephate. And a  
24 couple of comments that I just wanted to make. In the  
25 letter I actually provide -- Judith and I provide some

1 additional detail on interpretation of the animal studies.  
2 If you look at the database for acephate and the animal  
3 data that's there, I think it was acknowledged by someone  
4 on the panel that indeed the issue with the chemical tends  
5 to be toxicity in those studies, and the fact that  
6 anything that you're seeing occurring is occurring at high  
7 doses where you have significant levels of cholinesterase  
8 inhibition and confounding issues related to  
9 interpretation of the data.

10           So I'm not going to go into those comments again  
11 here, but I just wanted to point two things out. First, I  
12 don't know whether the panel realized that there was a  
13 significant number of in vivo genotox studies that I don't  
14 think were listed in the table that was provided to you,  
15 at least in the submission that we saw that was on the  
16 website from OEHHA. And if you look at that in vivo  
17 genotox data, I mean, it appears to indicate that there is  
18 no genotoxic risk to the chemical.

19           And the other thing I wanted to point out is that  
20 this is a chemical, that like some of the other  
21 pesticides, has been looked at by several international  
22 regulatory bodies. And this is not a chemical that has  
23 been regulated based on cancer hazard by bodies in the  
24 past.

25           So I would hope that that information and the

1 issues with the interpretation of the data itself for the  
2 database would indicate that this should be a low priority  
3 chemical, instead of a medium priority chemical.

4 Thank you.

5 CHAIRPERSON MACK: Thank you.

6 Joe, do you have any questions?

7 COMMITTEE MEMBER LANDOLPH: Just a second.

8 CHAIRPERSON MACK: Or Marty.

9 COMMITTEE MEMBER LANDOLPH: Yes. What about  
10 the -- what is your opinion of the genetox database? And  
11 I didn't read your and Judy McGregor's letter. I mean, I  
12 see a number of positives in this database. Mutagenicity  
13 In lymphoma, cell assay, sister chromatid exchange,  
14 unscheduled DNA synthesis, in vivo tests in mice, bone  
15 marrow chromosomal aberrations positive, micronucleus,  
16 some positive, some negative, dominant lethal tests,  
17 positive and negative.

18 So what is your -- and cell transformation  
19 positive. What is your assessment of that data?

20 DR. PLUNKETT: Are you talking about the in vitro  
21 studies, primarily?

22 COMMITTEE MEMBER LANDOLPH: Yes.

23 DR. PLUNKETT: Well, in our experience, like  
24 other organophosphates, you will sometimes find that they  
25 have activity in vitro, but when you put them into the in

1 vivo testing, you see a different result with the  
2 chemical. We believe that the in vivo data, and  
3 genotoxicity is highly relevant for then interpreting what  
4 you get in vivo in animals when you do have two studies, a  
5 mouse and a rat study, to look at with the chemical.

6 So we felt that the genotox data was somewhat  
7 weak as far as putting a signal forward for a genotoxic  
8 mechanism of action in vivo in the cancer studies.

9 COMMITTEE MEMBER LANDOLPH: And the animal data,  
10 you've got positive studies in -- positive results in  
11 feeding studies in mice, for both male and female mice.  
12 And then you've got positive data in males and females for  
13 28-month feeding studies in rats. So that's mice and  
14 rats, two species. You think that data is not relevant or  
15 useful, what is your opinion?

16 DR. PLUNKETT: I think the issue here is looking  
17 at the data itself. Not that it's not relevant. You need  
18 to look at the study. For example, I think as we pointed  
19 out in our comments, when you look at the mouse study, the  
20 results that you're seeing are -- if they're occurring,  
21 it's only at the highest dose, where you have significant  
22 levels of toxicities that are interfering with the  
23 interpretation, I believe, of the study and the data that  
24 you're seeing. You're seeing significant deaths, for  
25 example, in some of the study groups due to the toxicity

1 of the chemical, not just due to the actual activity of  
2 it.

3           And I believe that that would be consistent with  
4 how EPA has looked at those data sets and has described  
5 its review of that data as well.

6           In the rat study, I think we pointed out that in  
7 the rat study the issue you had was looking at the lack of  
8 a dose response relationship for the chemical, where you  
9 see some increase incidence mid-dose but not in the  
10 high-dose group. And the fact that these were benign  
11 adrenal tumors in the animals not malignant tumors. And  
12 again, I think that would be consistent with looking at  
13 the way that the EPA had interpreted that data as well,  
14 and why it's not listed as B-2 carcinogen.

15           COMMITTEE MEMBER LANDOLPH: Thank you.

16           COMMITTEE MEMBER EASTMOND: I might mention, I  
17 was looking at my notes. And I believe the EPA when they  
18 did evaluate the rat data said something on that they  
19 didn't think this was indicative of a true carcinogenic  
20 effect. I think that was the way they worded it.

21           DR. PLUNKETT: Yes.

22           COMMITTEE MEMBER EASTMOND: Although there were  
23 some trends seen there, the EPA looked at it, they weren't  
24 convinced by that data.

25           DR. PLUNKETT: Right.

1 CHAIRPERSON MACK: Any others?

2 Marty.

3 COMMITTEE MEMBER HOPP: I think the review of  
4 this was due to high toxicity, but it's overall usage,  
5 it's commonality, was the reason that I thought this had  
6 some more value to the public than a low priority. Highly  
7 toxic and wide usage, although, the carcinogenicity  
8 effects may be limited. I think, because of its use in  
9 the public, it's something to be looked at. And if it  
10 turns out to be safe, I hope so.

11 But with a high utilization exposure of the  
12 public, I believe it should be in the medium category.

13 DR. PLUNKETT: Okay. Thank you very much. We  
14 just want to be able to get on the record the issues that  
15 are related to it. I think the actual data themselves and  
16 the details in the data that I think are important for any  
17 decision that you might make.

18 CHAIRPERSON MACK: Thank you, Dr. Plunkett.

19 DR. PLUNKETT: Thanks.

20 CHAIRPERSON MACK: All right. Okay, how much  
21 time do you need?

22 THE COURT REPORTER: About 10 minutes.

23 CHAIRPERSON MACK: Ten minutes. So let's  
24 reconvene at 5 to 3:00.

25 (Thereupon a recess was taken.)

1 CHAIRPERSON MACK: All right. Let's get the show  
2 on the road. My record says that we have five compounds  
3 that we had public comment on, omeprazole -- I never can  
4 pronounce that correctly.

5 Omeprazole and its salts we judged to be of high  
6 priority; atrazine, high priority; PFOS, medium priority;  
7 acephate, medium priority; and budesonide, medium  
8 priority.

9 So let's go through those five and see whether or  
10 not anybody votes to change the prioritization.

11 So first is omeprazole. Does anybody want to  
12 change the prioritization from high?

13 I don't see any hands raised, so I'm going to  
14 presume that we leave that prioritization at high.

15 Atrazine. Does anybody want to change the  
16 prioritization from high?

17 Seeing no flurry of activity, I will presume that  
18 that one will also stay as high.

19 PFOS and its salts. Even though Stan has given  
20 his largesse, we still will ask the question, do any of us  
21 want to change that categorization from medium?

22 I guess not, so we leave that one at medium.

23 Acephate, currently categorized as medium. Does  
24 anybody want to vote to change that prioritization from  
25 medium?

1           No.

2           I think everybody is awake.

3           (Laughter.)

4           CHAIRPERSON MACK: And finally, budesonide,  
5 currently classified as medium. Does anybody suggest  
6 changing that classification from medium?

7           Well, what a solid bunch.

8           (Laughter.)

9           CHAIRPERSON MACK: So we're not changing our  
10 classifications. They stand as originally done.

11          And now Carol wishes to address the crowd.

12          DR. ALEXEEFF: Dr. Mack, George Alexeeff, just a  
13 point of order. Maybe I misunderstood what you said in  
14 the introduction. But it seemed to me as though, it would  
15 be worth to ask the question if any of the chemicals  
16 should be reprioritized, even though they weren't  
17 commented on.

18          CHAIRPERSON MACK: I'd be happy to ask that  
19 question.

20          Having now gone through five that we had public  
21 comment on, to be complete and honest and fair, do we want  
22 to change any of the other criteria -- I'm sorry, do we  
23 want to change any of the other classifications?

24          I will go through them one by one, so everybody  
25 remembers what they are.

1           Methylphenidate and its salts we've classified as  
2 high

3           COMMITTEE MEMBER EASTMOND: Probably better go  
4 off the screen.

5           CHAIRPERSON MACK: You want to go do the screen?

6           Well, that doesn't seem very right to me, but  
7 I'll do it anyway, if that's what you want.

8           (Laughter.)

9           CHAIRPERSON MACK: I don't have it listed there.  
10 I have to look for it on here, then.

11           Oh, I see it is listed there. Fancy that.

12           (Laughter.)

13           CHAIRPERSON MACK: All right. Acephate is listed  
14 as medium, we just did that.

15           Alpha-methyl styrene is classified as medium.  
16 Does anybody want to change that?

17           Amitraz is listed as low. Any suggestions for  
18 change on that?

19           Atrazine is high. We've done that.

20           Biphenylamine and its salts was categorized as  
21 low. No change there.

22           We've done budesonide.

23           4-Chloro-m-phenylenediamine is classified as  
24 medium.

25           No changes there.

1 COMMITTEE MEMBER EASTMOND: It's low.

2 CHAIRPERSON MACK: I'm sorry, low. You're right.

3 Thank you.

4 4-Chloro-m-phenylenediamine is classified as low.

5 That stays as is.

6 C.I. Acid Orange 3 is classified as medium.

7 Stay as is.

8 Ciprofibrate is classified as low.

9 Stay as is.

10 Clomiphene and its salts as high.

11 Stay as is.

12 Decabromophenyl ether. I'm sorry,  
13 decabromodiphenyl ether, classified as medium.

14 Stay as is.

15 DecaBDE is not listed here. And I think we  
16 called it low and we're going to look it up.

17 COMMITTEE MEMBER EASTMOND: That's the acronym  
18 for the one you just did.

19 CHAIRPERSON MACK: Oh, that's the acronym. It  
20 takes a toxicologist.

21 (Laughter.)

22 CHAIRPERSON MACK: Decalin is classified as low.

23 That stays as is.

24 2,6-Dichloro-p-phenylenediamine classified as  
25 low.

1 Stay as is.

2 Furfural classified as medium.

3 Stays as is.

4 Gentian violet, medium. Stays as is.

5 4-Hydroxymethyl, 4-Methyl, and 4-Hydroxy,

6 benzenediazonium -- I can't get through that --

7 benzenediazonium -- is that right -- and their salts.

8 COMMITTEE MEMBER EASTMOND: You're doing fine.

9 CHAIRPERSON MACK: It's classified as medium.

10 Stays as is.

11 Isoniazid low.

12 Stays as is.

13 Malathion medium.

14 Stays as is.

15 7-Methylbenz[a]anthracene as low.

16 Stays as is.

17 Joe.

18 COMMITTEE MEMBER LANDOLPH: Just if OEHHA speaks

19 with the Air Resources Board and they decide there is

20 substantial exposure, then we could -- I would recommend

21 we revisit that since it's a mutagen tumor initiator skin

22 carcinogen. But our vote was mainly based on our lack of

23 knowledge of exposure, which we think might be low.

24 CHAIRPERSON MACK: Can I ask a question that may

25 be stupid?

1 I thought that this was a product of incomplete  
2 combustion, which means that it has the same exposure as  
3 any other product of incomplete combustion, when you burn  
4 something you get this as well as a lot of other things.  
5 Is that true or not?

6 COMMITTEE MEMBER HAMBURG: Sounds right.

7 DR. SANDY: In general, yes. As far as we know,  
8 that's the general --

9 CHAIRPERSON MACK: It's coming out of your  
10 fireplace. It's coming out of your cigarettes. It's  
11 coming out of your barbecue, and all those things. So I  
12 think it's pretty clear that it is wide exposure. The  
13 question is whether the evidence warrants upgrading it  
14 from low.

15 DR. ALEXEEFF: Dr. Mack, George Alexeeff. I did  
16 say we would check with the Air Resources Board in terms  
17 of if they had any measurements in the air and that kind  
18 of stuff. And if so, we'll report back to you and then  
19 you can --

20 CHAIRPERSON MACK: I was just making it clear  
21 that it was not the exposure they were going to look back  
22 to, but the actual empirical information.

23 Okay. Anyway, so it is currently classified as  
24 low and we're going to hear about whether that's to be  
25 changed later.

1           Methylphenidate and its salts is classified as  
2 high.

3           No changes there, unless somebody speaks up.

4           N-Methyl-N-formylhydrazine is medium.

5           And that stays as is.

6           We've already discussed omeprazole and actually  
7 Pantoprazole and Rabeprazole, presumably.

8           All stay high.

9           Perfluorooctane sulfonate, PFOS, we've already  
10 done that. Sorry.

11          Phosmet stays low, unless somebody complains.

12          Quinoxaline-1,4-dioxide compounds and  
13 desoxycarbadox -- I'm very proud of myself for getting  
14 through that -- is classified as medium.

15          And I just spoke about the other one. So we've  
16 gone through all 27, and there are no changes. So we're  
17 going to stand pat as a group.

18          I will now turn it over to -- Carol, go for it.

19          CHIEF COUNSEL MONAHAN-CUMMINGS: Okay, the next  
20 agenda item for you is the update of the Sections 2700  
21 list of chemicals, which have not been adequately tested  
22 as required. You received some information on this, I  
23 think, towards the middle of all the binders that you  
24 received.

25          This is just for background. We talked about

1 this last time at the last meeting that there's a somewhat  
2 little known provision of Prop 65 that requires you, as  
3 the State's qualified experts to --

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

6 CHIEF COUNSEL MONAHAN-CUMMINGS: -- maintain a  
7 list of chemicals that need further testing -- that are  
8 required to have further testing by U.S. EPA or the  
9 Department of Pesticide Regulation or other relevant  
10 programs within those agencies. And there's a list  
11 actually that we provided you of -- well, we gave you two  
12 different pieces of information.

13 One was the actual request we made to U.S. EPA  
14 and Department of Toxic Substances Control and their  
15 responses to us asking whether or not any of these  
16 chemicals should be removed from the list, because the  
17 testing requirements have been satisfied, and whether or  
18 not there's any additional chemicals that they would  
19 recommend being added to the list that haven't been  
20 adequately tested.

21 We gave you an underline and strike-out version  
22 of the current regulation that is somewhat hard to follow,  
23 in terms of -- it's all strike-out by the way, because we  
24 don't have any chemicals that are being recommended to add  
25 to this list. So essentially what we're asking you to do

1 is in reliance on the statements from U.S. EPA and the  
2 Department of Toxic Substances Control, to find that the  
3 chemicals that are listed up here on the slide -- I'm  
4 going to make no effort to try and read these -- there's  
5 one, two, three, four, five, six, seven, eight, nine of  
6 them. And we'll include the names of those in the record.

7 But we're asking you to find based on these  
8 representations from U.S. EPA and DPR that these chemicals  
9 have been adequately tested and can be taken off the  
10 Section 2700 list.

11 Does anybody have any questions on that?

12 So, Dr. Mack, if you want the take a vote.

13 CHAIRPERSON MACK: Based on the information  
14 you've been provided from U.S. EPA, should the nine  
15 chemicals noted on Exhibit A be removed from the list of  
16 chemicals required by State or federal law to be tested,  
17 but which have not been adequately tested as required?

18 Does everybody who will vote yes to that  
19 proposition, please raise their hand.

20 (Hands raised.)

21 CHAIRPERSON MACK: No?

22 Hearing no knows, there are seven yes votes. The  
23 measure passes, 7 to 0.

24 CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

25 CHAIRPERSON MACK: The next item. Cynthia is

1 going to do her annual review.

2 MS. OSHITA: Good afternoon. Since you last met  
3 in May of 2009, OEHHA has administratively added 28  
4 chemicals to the Prop 65 list, nine chemicals as known to  
5 cause cancer, and then 19 as known to cause reproductive  
6 toxicity.

7 And rather than recite all the names of these  
8 chemicals, there is a summary sheet within your meeting  
9 materials behind the staff updates that list all the  
10 chemicals as well as their effective listing dates.

11 Presently, there remain four chemicals that are  
12 under consideration for administrative listing, which  
13 includes 4-Methylimidazole, metam potassium,  
14 spirodiclofen, as known to cause cancer. And then one  
15 also under consideration for methanol as causing  
16 reproductive toxicity.

17 And each of these four chemicals are in the  
18 Notice of Intent to List phase. And we have received  
19 comments on each of them, which are under review.

20 In addition, on three separate occasions since  
21 May of 2009, OEHHA announced the proposed administrative  
22 listing of yet some other chemicals. Two chemicals are  
23 under consideration for listing as causing cancer. That  
24 includes epoxiconazole and DEF. And those are now also in  
25 the Notice of Intent to List phase.

1           We received comments on epoxiconazole, and that  
2 is under review. And an extension to the public comment  
3 period has been granted for DEF, and that will close on  
4 October 13th, 2010.

5           Comments were also received on a third chemical  
6 that's under consideration, and that is BPA for causing  
7 reproductive toxicity. And we are also in the process of  
8 reviewing those comments.

9           Then additionally since last May, OEHHA has  
10 adopted two No Significant Risk Levels NSRLs. One for  
11 para-chloroaniline and another for para-chloroaniline  
12 hydrochloride. These levels became effective on August  
13 12th, 2010.

14           Currently, OEHHA has proposed to adopt two new  
15 NSRLs. One for 2,4,6-Trinitrotoluene, or TNT. And the  
16 other is for glycidol.

17           We are also proposing two new MADLs, which stands  
18 for Maximum Allowable Dose Levels. They are for DIDP and  
19 hexavalent chromium.

20           No comments were received for TNT or glycidol.  
21 And so the rule-making packages will be finalized for  
22 those and submitted to the Office of Administrative Law  
23 for approval.

24           Comments were received in support of the MADL for  
25 DIDP. And so we will also finalize its rule-making

1 package, and similarly submit it to OAL for approval.

2 The MADL for hexavalent chromium is still open  
3 for public comment. And that comment period will close on  
4 September 27th, 2010.

5 Thank you.

6 CHIEF COUNSEL MONAHAN-CUMMINGS: I'm back.

7 (Laughter.)

8 CHIEF COUNSEL MONAHAN-CUMMINGS: This is Carol  
9 Monahan-Cummings again. I promise hopefully this is the  
10 last time I'll say anything. This is the point at which I  
11 update you on Prop 65 litigation.

12 And given the fact that you are all parties to  
13 one of the cases, you might have some interest in that  
14 one. That's the Sierra Club versus Schwarzenegger case.

15 And as you may recall, that is in the trial  
16 court. It deals with various listing mechanisms under  
17 Prop 65, including listings by this Committee and also the  
18 prioritization process that you were involved in today.

19 That case has proceeded slowly, as civil cases  
20 tend to do, but we have gone through a number of motions  
21 in the case, and we are in the discovery process right  
22 now. As you recall, you produced some documents  
23 yourselves. And there's potential for additional  
24 discovery, like depositions and that sort of thing. I  
25 can't advise you whether or not you'd be involved in that.

1           We expect that if -- assuming that discovery goes  
2 as expected, that the trial in that case would occur early  
3 next year.

4           There are also two cases pending in the  
5 California appellate courts regarding the proposed listing  
6 of the chemical styrene, and the chemical -- well, the  
7 first one being the proposed listing of the chemical  
8 styrene and vinyl acetate under our Labor Code provision  
9 of the statute.

10           Those were proposed for listing based on an IARC  
11 2B designation. However, the information from IARC is  
12 that there's insufficient animal or human data, but  
13 there's other relevant scientific data to support a  
14 finding that they are possible human carcinogens.

15           We were actually ordered at the trial level not  
16 to list those two chemicals. And because the IARC said  
17 there was insufficient evidence. And so that question is  
18 now before the third district court of appeal.

19           That also affects a handful of other chemicals  
20 that we had proposed at the same time for this listing  
21 mechanism, both of these chemicals were proposed for  
22 listing as carcinogens.

23           The last case that I would mention is the one  
24 that's related to the Sierra Club case, which is pending  
25 in the first district court of appeal, and that is the

1 Chamber of Commerce versus Schwarzenegger case that had  
2 also to do with Labor Code listings under Prop 65. And  
3 that case is still pending in the court. It's been fully  
4 briefed and we're expecting to have oral argument at any  
5 time.

6 I should also mention on the styrene, vinyl  
7 acetate cases those are also nearly fully briefed and  
8 we're expecting oral argument, either late this year or  
9 earlier next year.

10 Any questions on those?

11 Yes. Dr. Landolph.

12 COMMITTEE MEMBER LANDOLPH: Do we have to keep  
13 recent copies of the prioritization or will you keep those  
14 and forward them for us, if they ask for them? I just  
15 can't store anything in my office anymore.

16 CHIEF COUNSEL MONAHAN-CUMMINGS: We do have a  
17 litigation hold. And so I would recommend that you keep  
18 those items that you have actually prepared yourself. And  
19 you should also keep notes and those kinds of things that  
20 you kept, you know, for the meeting. The materials that  
21 we've provided to you, we can produce, you know, if  
22 they're required. But your own personal notes or  
23 materials that you've created ought to be kept under that  
24 for now.

25 CHAIRPERSON MACK: So if you don't ever write any

1 notes, and you don't keep any documents you don't have  
2 anything to do, right?

3 CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry?

4 CHAIRPERSON MACK: I said if you never write any  
5 notes and you don't keep any documents, there's nothing to  
6 do, right?

7 CHIEF COUNSEL MONAHAN-CUMMINGS: Right. If you  
8 don't haven't it, you can't produce it, that's true.

9 COMMITTEE MEMBER EASTMOND: Let me ask a very  
10 practical point. The court cases have to do with previous  
11 things. Do I have to keep the notes I made for this  
12 meeting, because it deals with prioritization?

13 CHIEF COUNSEL MONAHAN-CUMMINGS: It's an ongoing  
14 case, and so the litigation hold is still current.  
15 There's a possibility that we'll get a second set of  
16 requests for discovery. There usually is one just before  
17 trial. And we would have to produce anything from the  
18 time that we last produced up to the date that the new  
19 request was made.

20 COMMITTEE MEMBER EASTMOND: Okay.

21 CHIEF COUNSEL MONAHAN-CUMMINGS: Anything else?  
22 Lucky for you we've only got one hold for you.  
23 We have about seven or eight holds pending right now.

24 DIRECTOR DENTON: George.

25 DR. ALEXEEFF: Yeah, I just wanted to thank the

1 panel for considering the two chemicals today for possible  
2 listing. And I also wanted to thank them for their advice  
3 on the prioritization.

4 And I just -- so as Dr. Sandy was pointing out so  
5 far, the staff have gone through -- well as of for this  
6 meeting -- 285 chemicals, okay, in terms of -- and then  
7 from those, we brought you two batches to consider.

8 And of those, you've prioritized 15 as high. So  
9 just on the math side, that's five percent of the  
10 chemicals that we've had in our database. So I just think  
11 that's a very -- you know, we were wondering how this  
12 effort would work when we thought of this prioritization  
13 procedure, and had advice from you. So I think it's  
14 working very well.

15 So thank you.

16 CHAIRPERSON MACK: As we all thought, of course.

17 (Laughter.)

18 DIRECTOR DENTON: Okay. I'm just going to take a  
19 minute or so to summarize what happened at our meeting  
20 today.

21 Obviously, the Committee has concluded its  
22 deliberations on the agenda items, so there will be no  
23 meeting tomorrow. So this is a one-day meeting.

24 So this morning, the panel, the Committee, voted  
25 unanimously to list 1,3-DCP and by a vote of six to one to

1 list 3-MCPD, both as chemicals known to the State to cause  
2 cancer.

3           This afternoon the Committee prioritized 27  
4 chemicals, six in the high category, 12 in the medium  
5 category and nine in the low category, and zero in the no  
6 priority. There is one chemical,  
7 7-methylbenz[a]anthracene in the low category, which the  
8 Committee would like us to look at to see if there's any  
9 air data, any other exposure data. And here's where I'm a  
10 little unclear. Regardless of our findings, do you want  
11 us to come back and report what we found to you or if  
12 there's really no significant air data out there, then  
13 just keep it in the low category?

14           CHAIRPERSON MACK: I'll ask the question of the  
15 group.

16           DIRECTOR DENTON: Would you like to hear about it  
17 regardless?

18           CHAIRPERSON MACK: I would like -- I would  
19 recommend that we keep it in the low category, unless  
20 there's something that dramatically warrants a change, and  
21 then you can --

22           DIRECTOR DENTON: Bring it back.

23           CHAIRPERSON MACK: -- get back to us. Does  
24 everybody agree with that?

25           COMMITTEE MEMBER HOPP: I think we voted for it

1 to be low, but if there's some new information that would  
2 be appropriately reviewed, we'd be glad to hear it next  
3 time or it should be brought to us, and if we think it's  
4 significant, I think we could always change the category.

5           DIRECTOR DENTON: Okay. All right, so if we  
6 don't bring it back, then we have not really found any  
7 significant exposure from the chemical.

8           Okay. And then also the Committee unanimously  
9 voted to remove nine chemicals from the list of chemicals  
10 required by the State or federal to be tested -- federal  
11 law to be tested, but which have not been adequately  
12 tested as required.

13           So I want to again thank the Committee very much  
14 for your deliberations, for your very efficient  
15 deliberations today. I'd also like to thank the audience  
16 and the stakeholders who came to the meeting. Some of you  
17 testified. Some of you did not. But we always appreciate  
18 and acknowledge that you came and attended and are  
19 interested in the deliberations of the Committee.

20           And then I would really want to thank my staff.  
21 Martha, you're great. You have a tremendous staff. Dave  
22 Morry, Rajpal, Feng, Jennifer, Rose, George, Lauren,  
23 Carol. Anyway -- oh, and all also Susan and Cindy, you  
24 always provide such an incredible support to the  
25 Committee. So I'd like to personally thank them. I'm

1 very proud to be the director of this group.

2           So with that, and thanking the Committee -- okay,  
3 Marty.

4           COMMITTEE MEMBER HOPP: I just want to comment  
5 about how proud I am that this Committee is taking into  
6 its deliberations the effect of these chemicals on the  
7 public, and not just the scientific information that comes  
8 up and burbles up through the spectacular amount of work  
9 that the OEHHA does regarding these. But by looking at  
10 not only the chemicals, but how the public need for  
11 information about these chemicals affects our  
12 deliberations, I think, is a major step and a change in  
13 the Committee, and something to be very proud of.

14           And I think it's very productive and it's  
15 something that we, as a Committee, should be proud of what  
16 we're doing, because it's a direction that I think is  
17 consistent with the way Prop 65 really was intended, but  
18 not written that way.

19           And now we're elucidating in, I think, a much  
20 more effective means for the people of California. And  
21 I'm very proud the way we're doing it this way.

22           DIRECTOR DENTON: We've always had exposure as  
23 part of prioritization, but we always -- we haven't always  
24 had this methodology for prioritizing. So exposure has  
25 always been part, but it hasn't been so public.

1           Of course, when we talk about the hazard  
2 identification, HIM, exposure is not the consideration of  
3 whether it's a carcinogen, but it is -- it's an essential  
4 part of the deliberation of whether we should look at it  
5 or not.

6           Joe.

7           COMMITTEE MEMBER LANDOLPH: Yeah, I want to thank  
8 Dr. Denton, Dr. Alexeeff, OEHHA staff for all the work we  
9 did on the prioritization in the subcommittee. I think  
10 that lasted about a year and a half or so. And I think it  
11 streamlined it. It's coming through pretty clear now.  
12 We're getting the stuff with the epidemiology data first,  
13 then the animal, then the epi. And it's worked out pretty  
14 well, I think. We're getting much better -- more toxic  
15 chemicals to look at.

16           DIRECTOR DENTON: I shouldn't forget to thank our  
17 audio visual person too.

18           Okay. Well, we won't see you for the rest of the  
19 year, so we want to wish you a Happy Holidays.

20           (Laughter.)

21           CHAIRPERSON MACK: I know it's early, but thank  
22 you very much.

23           (Thereupon the Carcinogen Identification  
24 Committee adjourned at 3:30 p.m.)

25

