MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

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COASTAL HEARING ROOM

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A P P E A R A N C E S

COMMITTEE MEMBERS:

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Jason Bush, Ph.D.

Shanaz Dairkee, Ph.D.

David A. Eastmond, Ph.D.

Joseph Landolph, Ph.D.

Peggy Reynolds, Ph.D.

Duncan Thomas, Ph.D.

Luoping Zhang, Ph.D.

STAFF:

Dr. George Alexeeff, Director

Mr. Allan Hirsch, Chief Deputy Director

Dr. John Budroe, Chief, Cancer Toxicology and Epidemiology Section

Ms. Rose Cendak, Cancer Toxicology and Epidemiology Section

Dr. Jennifer Hsieh, Cancer Toxicology and Epidemiology Section

Ms. Fran Kammerer, Staff Counsel

Ms. Cynthia Oshita, Proposition 65 Implementation

Dr. Martha Sandy, Chief, Reproductive and Cancer Hazard Assessment Branch

Dr. Meng Sun, Cancer Toxicology and Epidemiology Section

A P P E A R A N C E S C O N T I N U E D

STAFF:

Dr. Rajpal Tomar, Cancer Toxicology and Epidemiology Section

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

ALSO PRESENT:

Dr. John Butala, Consultant to Ferro Corporation

Ms. Ann Claassen, Latham and Watkins

Dr. Michael Cunningham, Cunningham & Associates

Dr. Jennifer Foreman, ExxonMobil Biomedical Sciences, Inc.

Dr. Nina Hallmark, ExxonMobil Biomedical Sciences, Inc.

Dr. Gordon Hard, Independent Consultant to BASF

Mr. Stanley Landfair, McKenna, Long & Aldridge, BASF

Mr. Alan Olson, Ferro Corporation

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P R O C E E D I N G S

DIRECTOR ALEXEEFF: Good morning, everybody. Welcome to this chilly morning in California. I'm George Alexeeff, Director of the Office of Environmental Health Hazard Assessment. A couple things I need to remind you of. In case of an evacuation, we have exit doors in the back with the green sign there. And take your valuables with you have, if you have to leave. And then you can just follow the exit signs to the street.

Also, in terms of any drinking fountains and restrooms, you can go out the back -- the doors to the back and turn left and you'll find them over there. And then there's also a restaurant downstairs or cafeteria, let's say, downstairs where you can get basic food and drink, if you need that.

So let me go ahead and introduce the members of the Carcinogen Identification Committee. I want to welcome everyone to today's meeting of the Carcinogen Identification Committee. To my left is Dr. Tom Mack, the Chairman of the Committee. And he is a professor of the Department of Preventive Medicine and pathology at the USC Keck School of Medicine.

And then to his left is Dr. Luoping Zhang. She is an associate adjunct professor of toxicology in the Division of Environmental Health Sciences in the School of

Public Health at the University of California at Berkeley.

And then to her left is Dr. Joseph Landolph, who is the associate professor of the Department of Molecular Microbiology and Immunology at the USC Keck School of Medicine.

And then to his left is Dr. Peggy Reynolds, who's a senior research scientist at the Cancer Prevention Institute of California, and a consulting professor at the Stanford University School of Medicine, Department of Health Research and Policy.

And directly to my right is Dr. David Eastmond. He's a professor and Chair of Cell Biology and Neuroscience, and a research toxicology -- toxicologist at the University of California at Riverside. And then to his right is Dr. Shanaz Dairkee. She is a senior scientist at the California Pacific Medical Center and a consulting professor for the Stanford University School of Medicine.

And then to her right is Dr. Duncan Thomas, who is a professor of biostatistics and the Verna R. Richter scale -- Richter Chair in cancer research at the University of Cal -- University of Southern California.

And to my far right is Dr. Jason Bush, associate professor of cancer biology at California State University, Fresno.

And I thought I'd just also mention the leads. Dr. Luoping Zhang and Dr. Joseph Landolph are co-lead reviewers for DINP, one of the chemicals to be discussed today. And then Dr. Eastmond, Dr. Dairkee, and Dr. Thomas are all co-leads reviewers for BBP.

I'd like to also introduce the OEHHA staff, since they may be answering questions or making presentations today. Directly in front of me is Dr. Lauren Zeise. She's our Deputy Director for Science in OEHHA. And then to her right is Dr. Martha Sandy -- Dr. Martha Sandy. She's our branch chief for our Reproductive Cancer and Hazard Assessment section. And then to her right is Dr. John Budroe, who's -- I'm sorry to our -- our branch chief. And then Dr. John Budroe who's our section chief, our cancer section chief. And to his right is Dr. Raj Tomar. And then to his right is Rose Cendak. And then Dr. Jennifer Hsieh and Dr. Meng Sun who will be giving a presentation today. And our legal counsel for the day is Fran Kammerer. Carol is not able to be with us today. And also here is Allan Hirsch, our Chief Deputy Director.

So, let's see, I think we wanted to -- I want to welcome everyone here. First, I want to welcome all the panel members for taking time out of their busy schedules to be here and help us on these important issues for this Committee. We really appreciate it. And we know that

you're donating a lot of your time and expertise to this -- to us and to the State of California.

And I also want to thank the members of the public who are here attending, either making presentations or just listening. And I also want to mention -- thank those who are listening on our webcast. And since we are having a webcast today, and actually probably any time since we are recording this as well, it's important that if you're going to speak, please speak into the microphone. And actually, you have to get pretty close. I get really close now, and it sounds much better, I can tell, but I feel like I'm almost swallowing the microphone, but I think that's what we have to do.

All right. So let's see. I think I've welcomed everybody, so I think I will now ask Fran Kammerer, our legal counsel, to give some introductory comments.

STAFF COUNSEL KAMMERER: Can you hear me?

Good morning. As Dr. Alexeeff said, my name is Fran Kammerer. I will be your counsel for the day. I'm staff counsel for OEHHA. I just want to give you a few reminders today. The first one is that there are certain criteria for listing chemicals. And you have those criteria in front of you. You're listing decisions should be based on those criteria, and the discussions you have on those criteria.

The listing criteria was determined by Proposition 65 -- well, actually, it was determined by the Panel, your Panel. And Proposition 65 states that a chemical is clearly shown, through scientifically valid testing, according to generally accepted principles to cause cancer. The clearly shown standard is that the statute is a scientific judgment call on your behalf. It's not a legal standard of proof. You're not a jury. You don't have to find reasonable doubt -- or beyond reasonable doubt that you would in a courtroom.

This Committee is also allowed to decide to list a chemical based on animal evidence only. There need not be any evidence that a chemical causes human cancer. And you don't need to consider the future impact of a listing, whether a warning will be required or whether or not the current human exposures to the chemical are sufficiently high to cause cancer. That is a dose related question. It's not something you need to make a finding on today.

You were appointed by the Governor because of your scientific expertise. And so you need not feel compelled to go outside of that charge, regardless of the comments you may hear from the public. In the event you feel that you have insufficient information or need more time to think about a listing or discuss it, there's no requirement that you make a decision today or even this

morning. You can table the discussion and ask us to get you more information. So you're not required to make a decision pro or con today.

Are there any questions about that?

Okay. Dr. Mack.

DIRECTOR ALEXEEFF: Actually, Dr. Sandy, did you have something you wanted to say in the beginning here, before we turn to her?

DR. SANDY: I did, if I may. Good morning, everyone. Because several of you members are new, this is your second meeting, I wanted to give some background on how the chemicals that are before you today reached your Committee. And so to do that, I need to tell you that we went through a multi-year prioritization process where we screened a number -- hundreds of chemicals. We brought to this Committee over a three-year period in 2009, 2010, and 2011, about 100 chemicals, and asked your Committee to rank them as to their priority for selection and hazard identification document preparation.

So back in 2009, DINP was ranked as a high by the CIC. And in 2009, OEHHA selected DINP to -- and announced in a notice to the public that we had selected it for hazard identification preparation. At that time, we also issued a request for relevant information, and asked the public to provide us with any information they wished to

provide us with. We did receive information, and I believe that's been -- a copy of that has been submitted to you as comments. And I wanted to let you know -- so that was -- in response to our request for relevant information, we looked at all that information as well as the information we identified through literature searches. We considered all the information in preparing the document for you.

Thank you.

DIRECTOR ALEXEEFF: Okay. Dr. Mack.

CHAIRPERSON MACK: Well, let me add my welcome to that, George. It's nice to see all these enthusiastic faces. I hope they stay enthusiastic throughout the course of the next couple hours.

Martha who's going to go be first up?

DR. SANDY: I'll turn it over to Dr. John Budroe and he'll introduce his staff.

DR. BUDROE: Good morning, Dr. Mack, members of the Committee, I'd like to present you Dr. Rajpal Tomar and Ms. Rose Cendak, who will be presenting evidence on the carcinogenicity of diisononyl phthalate.

MS. CENDAK: Good morning. Can you all hear me?

(Thereupon an overhead presentation was presented as follows.)

MS. CENDAK: I'm going to start with an -- I'm

1 going to start with an overview of our talk. We're going
2 to cover production, use, and exposure of DINP;
3 carcinogenicity studies in animals; other relevant data,
4 including pharmacokinetics and metabolism; genotoxicity
5 and other mechanistic data and structure activity
6 relationships. Then we'll cover possible mechanisms of
7 action, reviews by authoritative bodies, and then present
8 a summary of the evidence that we've given.
9 --o0o--
10 MS. CENDAK: DINP is produced by multiple
11 processes. And these different production processes yield
12 isomeric mixtures with various CAS numbers, but the
13 general structure is shown here.
14 DINP is an isomeric mixture consisting of a
15 branched alkyl diester of either 8, 9, or 10 carbons, with
16 the bulk of the mixture containing 9 carbons. Isomeric
17 mixtures of DINP produced by different production
18 processes are considered commercially interchangeable and
19 are being considered for listing today.
20 --o0o--
21 MS. CENDAK: DINP is a general purpose
22 plasticizer used in a variety of PVC products, including
23 vinyl flooring, undercoatings for cars, roofing materials,
24 and more. It's also used in non-PVC products like
25 rubbers, inks, and sealants. DINP is used in limited food

packaging materials, and it is not used in medical applications.

Among the 10 individual phthalates, DINP has the highest production volume with the American Chemistry Council predicting annual world production of DINP to be 1.5 million metric tons in 2013.

In California, use of DINP at concentrations greater than 0.1 percent is prohibited in toys and child care articles intended for use by a child under the age of three, if the product can be placed in the child's mouth.

--o0o--

MS. CENDAK: DINP has been detected in both indoor and outdoor environments. Biomonitoring studies have measured DINP in populations of pregnant women, children, and adults with no known exposure to DINP. Many studies detected DINP urinary metabolites in 75 to 100 percent of people sampled. And the study in persons with no known exposure detected metabolites in 87 to 100 percent of people sampled.

An occupational study in car manufacturing employees showed higher DINP exposure values for all workers engaged in seam sealing with DINP based plastisol compared to other workers from the same plant. Higher DINP exposure levels were also reported in PVC film manufacturing workers compared to unexposed controls.

--o0o--

DR. TOMAR: Good morning. I'll start with the carcinogenicity studies. There are no known human carcinogenicity studies with DINP. We have 12 animal carcinogenicity studies that include six dietary studies Fischer 344 rats, two dietary studies in Sprague-Dawley rats, and four dietary studies in B6C3F1 mice.

--o0o--

DR. TOMAR: This is the incidence data from a two-year feeding study conducted by Lington et al. Since all of the tables are laid out in the similar fashion, they start with the left column, indicate the organ involved. The second column indicates the tumor types, and the rest of the table gives the incidence data, except the last column, which gives the P value for the trend test. The dosages used in this study were 0, 300, 3,000, and 6,000 ppm. There's a dose dependent increase. The P value for the trend is significant for hepatocellular carcinoma.

The next, kidney tumors, were observed in the middle dose, three tumors. And they were transitional cell carcinoma arising from the urothelium. And we also have two tumors at the highest dose of the tubular cell carcinoma. These two types of tumors are considered uncommon or rare. However, there was no laboratory data

provided, so we looked at the literature and we found that there was about seven years of the data from feeding studies was collected, and by Haseman et al. in 1998. That NTP study gives about 0.1 percent for the transitional cell carcinoma with a range of 0 to 2, and about 0 to 2 percent for tubular cell carcinoma, again with the range of 0 to 2.

It was further indicated in 2013 by NTP again, giving a percentage of 0.9 for transitional cell carcinoma, and 0.8 for the tubular cell carcinoma, indicating that these tumors are rare in Fischer 344 rats.

We also have one significant increase in mononuclear cell leukemia. There's a significant dose dependent effect on the two highest doses, as well as the trend test for these two tumors.

COMMITTEE MEMBER THOMAS: Can I ask a point of clarification?

DR. TOMAR: Yes, please.

COMMITTEE MEMBER THOMAS: In the briefing book that was given to us, it gives a different P value. Which one is correct?

DR. TOMAR: I'm sorry? I didn't get that. What's the question?

COMMITTEE MEMBER THOMAS: Table 3 in the briefing book gives a different P value. Both are significant. I

would just like clarification, if you have it available.

DR. SANDY: So you're correct, it's 0.01 --

COMMITTEE MEMBER THOMAS: I can imagine you might need to go back to the raw -- the original publication to find this. So I don't want to belabor the point since both are significant.

DR. SANDY: It's 0.01, you're correct.

COMMITTEE MEMBER THOMAS: Thank you.

--o0o--

DR. TOMAR: This is a two-year study again by Lington et al. conducted in the female rats. There are no liver tumors in these female mice -- female rats. However, there's a significant increase by pairwise comparison as well as the trend test for the mononuclear cell leukemia.

--o0o--

DR. TOMAR: Moore conducted another study with F344 rats. And this is the incidence data for the male rats. There's a significant pair -- trend for the hepatocellular adenoma. Also, there's a significant increase by pairwise comparison, as well as the trend test for the hepatocellular carcinoma at the highest dose. And we also have a combined hepatocellular carcinoma/adenoma at the highest dose with a very strong positive trend.

Again, we have kidney tumors in the 6,000 ppm

dose group, which is transitional cell carcinoma. And we also have renal tubular cell carcinoma at the highest dose. As I indicated earlier, I gave the two -- both are rare tumors. We again have a very strong positive trend, as well as significant increase at the two highest doses for mononuclear cell leukemia in this study.

--o0o--

DR. TOMAR: In a related two-year feeding study in the female rat with the same dose range as in the male of 0, 500, 1,500, 6,000, 12,000 ppm, we have again a trend for hepatocellular adenoma, and as well as for hepatocellular carcinoma. And a combined hepatocellular adenoma and carcinoma is significantly increased by pairwise comparison, as well as by the trend test.

Again, in female, we have a significant increase at the two highest doses for mononuclear cell leukemia with a very strong positive trend.

--o0o--

DR. TOMAR: In a 78-week feeding study followed by 26 weeks feeding normal diet, we call it a recovery study, conducted by Moore 1998. The incidence here only for the renal tubular carcinoma, which is significantly different and only the two doses were used there.

Again, we also have a significant increase in mononuclear cell leukemia. And all these two types of

tumors were observed after 78 weeks of exposure.

--o0o--

DR. TOMAR: In a related study in the female, again fed for 78 weeks, followed by 26 weeks of the recovery, we find again there's a significant increase in mononuclear cell leukemia in this study.

--o0o--

DR. TOMAR: This is another study conducted by Bio\dynamics. It's a two-year feeding study in Sprague-Dawley rats. And this is the incidence data in the male -- this is the incidence data in the male rat. And we see again there's a significant -- there's an increase at the highest dose for interstitial cell carcinoma.

Here we indicated in our HID that this is outside the range of the historical control. This was misquoted there by CPSC 2001. In fact, this is slightly -- indeed, slightly increased compared to the mean, but not to the study control historical range. We also have pancreatic islet cell carcinoma which is 4 out of 70. And these two tumor types are considered uncommon or rare in S-D rats.

We did not have control data for the islet cell carcinoma. So we looked at the literature and we found a paper by Chandra et al., which gives a percentage of 0.07 for the islet cell carcinoma in Sprague-Dawley rat. These

two tumors are also considered rare.

--o0o--

DR. TOMAR: In a related study at the same does level by -- in Sprague-Dawley rat, we have a significant increase for hepatocellular carcinoma at the two highest doses, as well as a very strong positive trend test for hepatocellular carcinoma. We also have some uterine tumors endometrial adenocarcinoma at the highest dose, two out of the 69.

--o0o--

DR. TOMAR: This is another study in the B6C3F1 mice conducted by Moore 1998 with a slightly different dose range as we have seen in the previous study, which is 0, 500, 1,500, 4,000, and 8,000 ppm in the diet. And only the liver tumors were observed in this male study. We have a positive trend test for the adenoma. We have a pairwise, as well as very strongly positive trend for the hepatocellular carcinoma. And we have a significant increase at the two highest doses, the 4,000 and 8,000 with a very strong positive trend for combined hepatocellular adenoma and carcinoma in this study.

--o0o--

DR. TOMAR: This is a related study conducted by Moore 1998 in the B6C3F1 mice, female. And we have again a significant increase at the highest dose for the

hepatocellular adenoma with a very strong positive trend. We also have a significant increase at the two highest doses of hepatocellular carcinoma along with the very strong positive trend, as well as hepatocellular adenoma and carcinoma combined on the three highest doses of 1,500, 4,000, and 8,000 with a very strong trend -- positive trend.

In this study, we also have again pancreatic islet cell carcinoma at the highest dose 2 of 70. As I indicated earlier that this we consider a rare tumor.

--o0o--

DR. TOMAR: This is another study in the female mice -- this is another recovery study where the mice were fed for 78 weeks and there was a recovery for 26 weeks making it a full two year study. And only thing we have in male mice here is a significant increase in the hepatocellular adenoma and carcinoma.

COMMITTEE MEMBER EASTMOND: Rajpal, how confident are you in those statistics, because that looks very hard to believe the P value --

DR. TOMAR: Which tumor?

COMMITTEE MEMBER EASTMOND: The hepatocellular carcinoma. You're got a P value there of less than 0.001 and the -- no, the previous -- next slide. The one you were talking about.

DR. TOMAR: I have a statistician sitting next to me who did most of the statistics and I'm pretty confident.

COMMITTEE MEMBER EASTMOND: Go the next -- the one you were talking on. I was asking about the slide you were looking at.

DR. TOMAR: This one?

COMMITTEE MEMBER EASTMOND: Yes. The P value seems very hard to believe, given the numbers there.

DR. TOMAR: 16 out 70 compared to the 19 out of 50?

COMMITTEE MEMBER EASTMOND: Yeah. That seems very hard to believe.

MS. CENDAK: We used the standard pairwise comparison that we use for the other -- you know, the other P values that we calculated here. I can run it and get the back number for you.

COMMITTEE MEMBER EASTMOND: Yeah, if you could check that one, because this one looks really suspicious. Most of the others -- this one just looks really questionable. I mean if you look at the numbers themselves, that P value should barely be significant, if it's significant at all, and certainly not at a less than 0.001 significance.

DR. SANDY: Again, I'll -- let me just point out

that the denominators are quite different.

COMMITTEE MEMBER EASTMOND: Oh, I know, but they're not that different.

DR. SANDY: So we'll have Rose run that again and get back to you.

--o0o--

DR. TOMAR: Okay. This is another study, same recovery type in B6C3F1 mice in females. And we have a significant increase in hepatocellular carcinoma, as well as hepatocellular adenoma and carcinoma. And this I can be sure that this is correct.

(Laughter.)

--o0o--

DR. TOMAR: Pharmacokinetics and metabolism in humans. In single oral dose studies multiple metabolites were observed. More than 90 percent of the metabolites were excreted in the first 24 hours. There was a biphasic elimination pattern. Elimination half-life was three to five hours in the first phase, and 12 to 18 hours in the second phase. Essentially, similar pharmacokinetics and metabolism was observed in animals.

--o0o--

DR. TOMAR: This is proposed metabolism for DINP. DINP is hydrolyzed to MINP. MINP is oxidized at the ultimate carbon, then conjugated with either hydroxy,

carboxy, or oxo metabolites.

This carboxy octyl phthalate can change to -- I can hardly see that -- hexyl, then butyl, and then ethyl, and finally to phthalic acid. So it's kind of a soup of long chain, as well as the small chain. And the notion of that only the long chain or small chain work differently, it just doesn't seems to work when we talk about the metabolism of this compound.

--o0o--

DR. TOMAR: Genotoxicity. Reverse gene mutation was conducted in salmonella typhimurium. There was a forward mutation in mouse lymphoma cells, and chromosomal aberrations in Chinese hamster ovary cells with and without metabolic activation, and all three were negative.

There's also unscheduled DNA synthesis in primary rat hepatocytes, which is also negative, and in vivo Micronucleus assay in rats and mice, which was also negative. I should mention here that we missed this study by unscheduled DNA synthesis in primary rat hepatocytes we did not include in our HID.

--o0o--

DR. TOMAR: In vitro cell transformation. DINP has been tested in seven studies using BALB/c-3T3 A31 mouse cells. We indicated again in our HID there were eight studies, and that was my mistake. It should be

seven. Also, DINP was found to be positive in one study, negative in three studies, and a non-significant increase in transformed foci in the three studies.

--o0o--

DR. TOMAR: Yes, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Sorry to interrupt you. Did they get dose responses in any of those studies where they're called positive for the cell transformation assays?

DR. TOMAR: There was one study which was positive. And --

COMMITTEE MEMBER LANDOLPH: What does that mean positive, just at one point or --

DR. TOMAR: A significance increase in the foci.

COMMITTEE MEMBER LANDOLPH: Was the trend test positive for the trend for dose response?

DR. TOMAR: No, there was no trend test. There was not -- just only I think on one dose.

COMMITTEE MEMBER LANDOLPH: Just the one dose. Um-hmm. Thank you.

DR. TOMAR: There was no number of studies.

--o0o--

DR. TOMAR: And those were non-significant increase, some of the foci, you know, were increased, but they were not -- there was neither the dose response or

nor it was, you know, highly significant.

DINP effects on steroidogenesis.

Multiple perinatal DINP exposure studies in rats indicate reduced testosterone levels in male pups and reduced ex vivo testosterone production. Reduced messenger RNA expression of genes involved in steroid production, example, insulin-like-3, cytochrome P455 11A, and steroidogenic acute regulatory protein(StAR)

Reduced anogenital distance in the male pups, and reduced absolute weight of seminal vesicles.

Disturbances of testosterone production in humans are associated with testicular dysgenesis syndrome in children. And TDS is associated with germ cell cancer. However, according to NAS report of 2008, rats do not get germ cell cancer. They get Leydig cell cancer, Leydig cell tumor, as we have seen in the Sprague-Dawley rat studies.

Excuse me, I have to go back. Dr. Landolph, there is a dose response for cell transformation assay, the one positive study.

COMMITTEE MEMBER LANDOLPH: There was?

DR. TOMAR: Yes.

DR. SANDY: So if I can point you to the HID. It's page 31 and 32 where we discuss that, but we are -- we did not have the original studies. The study that is

positive, it's -- we're taking what -- how it was cited by the ECJRC report of 2003. So we're going off a secondary review, but we did report that apparently there was a dose response.

COMMITTEE MEMBER LANDOLPH: It was a dose response. And was the trend statistically significant?

DR. SANDY: We don't have that information.

COMMITTEE MEMBER LANDOLPH: That's good. Thank you.

DR. SANDY: No, I'm sorry. Misspoke. We have written here that the increases were statistically significant and thought to be dose related. Again, this is what's reported by the ECJRC 2003 report.

COMMITTEE MEMBER LANDOLPH: Thank you.

DR. TOMAR: Before I go further, I might as well mention one thing that we do not have most of the original studies. We requested it, but we were denied for confidentiality. So there might be a difference here and there, because one study has been reported three different places by three different names. So it was not always possible to keep track of those studies.

MS. CENDAK: I just want to mention, Dr. Eastmond, you're correct. It was a typo. It should have been two asterisks, not three for that table. Good eye.

DR. TOMAR: Structure Activity Comparisons.

We're comparing DINP with DEHP, as well BBP, which you'll be listening in afternoon today. And we see that there is common tumor types for all three phthalates together. We have a mononuclear cell leukemia by DINP in male and female. We have with BBP in male and female rats, and with the DEHP. So all three phthalates produce mononuclear leukemia.

Also, they all three produce pancreatic tumors, DINP, DEHP, BBP. Only difference is that DINP produces islet cell carcinoma, while DEHP and BBP produces acinar cell carcinoma. They also have in common DINP and DEHP produces liver tumors in mice, as well as in rats, and in both sexes, male and female.

Also, we have testicular and testes carcinoma for DINP and DEHP. So all these three phthalates, it's remarkable that they all produce the common type of tumors.

--o0o--

DR. TOMAR: This is a structure activity comparison for other parameters. And if you see that all these three phthalates have many of the parameters in common.

To start with the DNA damage, it's not evaluated for the DINP, but DEHP and BBP both are positive. For gene -- what is this? There's only DEHP. And we have

chromosomal damage with the two of the phthalates, DEHP and BBP. In vitro cell transformation, all three phthalates, BBP, DEHP, and DINP show transformation. However, DINP has only one tested positive.

They're all three phthalates are agonist for PPAR alpha and gamma. They all affect the estrogen receptor, aryl hydrocarbon receptor, and they also are agonist to pregnane X receptor as well as constitutive androstane receptor. They're all -- two of them, at least DINP and DEHP, affect the gap junction intercellular communication. And there all -- they all are anti-androgenic, all of them. So it's marked similarity in all the phthalates together.

--o0o--

DR. TOMAR: Now, what's the possible mechanism of action of all the various kinds of tumors we just observed?

We start with the genotoxicity. We know that available data for DINP is negative. However, the DINP has not been tested for oxidative DNA damage in comet assay or in some of the strains of the salmonella typhimurium, which can detect the oxidated DNA damage.

It is important especially, because it produces a lot of reactive oxygen species, permit acyle coA oxidase activities when it metabolized the lipid or it will

1 produce a lot of the hydroxyl radical as well as the
2 hydrogen peroxide, which will change in the hydroxyl
3 radical again.
4 Inhibition of steroidogenesis. As we know that
5 testosterone production play an important role during
6 fetal and early postnatal life, and thus disturbances of
7 testosterone production in fetal life are important, and
8 may lead to the male reproductive malformation. This has
9 been suggested that postnatal phenotype of hypospadias,
10 cryptorchidism, testes germ cell cancer, and poor semen
11 quality are manifestations of the aberrant fetal testes
12 development.
13 Tumor necrosis factor. This is the most
14 interesting. Tumor necrosis factor is produced by
15 macrophages, activated macrophages, as well as T&B cells
16 in a normal situation. However, tumor necrosis factor can
17 be produced by endothelial cell or many neutrophils or
18 many other types of cells under stress.
19 Tumor necrosis factor is a two-way factor. In a
20 normal situation, it regulates your immune system and it
21 keeps you healthy. However, if you increase the tumor
22 necrosis factor above a certain level, it can cause
23 cancer. An as a matter of fact for liver cancer, this is
24 considered one of the most important factor. And it's of
25 course got -- many of the autoimmune diseases arthritis,

they all have high concentration of the TNF.

Decreased gap junction intercellular communication, it's simply the way for a process by which exchange of small molecule cell maintain homeostasis. The inhibition of gap junction has been proposed as a known genotoxic carcinogenic mechanism. Several types, including hepatocellular carcinoma, have been shown to inhibit gap junction.

CAR -- activation of CAR and PXR. They both have transcription regulator and affect the phase 1 and phase 2 enzymes for the metabolism. They also affect induction of CYP 2B, CYP 2C, and CYP 3 enzyme. And testosterone is a substrate for all these three enzymes. So there's a good reason why we might have a problem with the reduced testosterone in the case of many of the phthalates.

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DR. TOMAR: Possible mechanisms of action.

Activation of PPAR alpha. It was hypothesized that activation of PPAR alpha is a necessary event in liver tumor induction in rat and mice. And it was further suggested that the liver tumors induced are not relevant to humans.

Findings inconsistent with the PPAR mode of action. Initially, it was because in null mice one of the agonists WY 14,640 very strong agonist for PPAR alpha, did

not produce any tumor in null mice or the peroxisome proliferation. So this was the basis that it is not relevant to the humans.

Now, recently we have found that DEHP induces liver tumors in PPAR alpha null mice, Ito 2007. And we also know that receptor activation in a mouse model does not produce liver tumors. So you could have constituted activation of the receptors for PPAR alpha, that alone would not produce the liver tumor. In fact, based on these two studies and some other data, IARC re-reviewed the DEHP. And now in 2013, from -- they changed from Group 3 to Group 2B. Group 3 is not carcinogenic. Group B possible human carcinogenic.

DINP-specific data related to PPAR activation suggests the hypothesized mode of action may not be operative in DINP-induced liver tumors. Inconsistent observations of a short-term hepatocellular proliferation, lack of sustained long-term hepatocellular proliferation with DINP.

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DR. TOMAR: Possible mechanism of actions continued with alpha 2 globulin nephropathy. Usually, it is believed that in case of the F344 rats, if the tumors is because of alpha 2 globulin, then they are not considered relevant to the humans. And there are five or

1 six criteria given by the International Agency of Research
2 on Cancer, as well as there are some other criteria which
3 are not necessary, but they could be, you know, used.
4 So as a matter of fact here, I have criteria
5 that's really handy. Renal tumors only in the male rats.
6 Acute exposure cause hyaline droplets. Alpha 2 globulin
7 accumulates in hyaline droplets. Other characteristics,
8 histopathology kidney changes, like granular cast
9 formation and mineralization.
10 No such kidney changes in female rats. This
11 would not be -- it should be completely clean, in order to
12 have the alpha 2 globulin nephropathy as a cause. And it
13 should be negative for genotoxicity. However, what we see
14 here that some of the criteria for alpha 2 globulin
15 nephropathy are not met by DINP.
16 Acute exposure does not exacerbate hyaline
17 droplet formation, because only time they observed it
18 after 12 months. They did not observe six months. And I
19 think 12 months is not acute exposure, to the best of my
20 knowledge.
21 Again, the subchronic histopathological changes
22 including granular cell cast formation, and linear
23 papillary mineralization was not observed.
24 Next one. Renal histopathological changes in
25 female rats were observed, which was not supposed to be,

in renal tubular, Lington, et al. 1997. And so it does not eliminate the criteria for alpha 2 globulin nephropathy, so the tumor should be considered relevant in cases of the human.

Now, we talk about later.

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DR. TOMAR: Review by authoritative bodies.

DINP has not been classified as to its carcinogenicity by United States Environmental Protection Agency, Food and Drug Administration, National Toxicology Program, National Institute of Occupational Safety and Health, and International Agency for Research on Cancer.

Yes, sir.

COMMITTEE MEMBER LANDOLPH: Could I ask you a question about that. Is that it's too hot potato, they don't want to touch it or have they looked at it? You know, have they looked at it and shelved it, or have they just not looked at it at all?

DR. TOMAR: U.S. EPA has reviewed in 2005, but they still have their judgment -- they're waiting for certain things, and they can wait for another long time with my experience. So I really don't know why.

FDA has been looking for it.

DR. SANDY: Excuse me. If I can just add to what Dr. Tomar said about U.S. EPA. They have looked at the

1 different phthalates under different programs, but they
2 have not done a review and classified it as to its
3 carcinogenicity.
4 COMMITTEE MEMBER LANDOLPH: And what about the
5 other agencies?
6 DR. TOMAR: As far as the FDA is concerned, they
7 deal with mostly the drug for alpha-1, which is in case of
8 the hyperlipidemia. And in case of the diabetes 2, both
9 the drugs are there. They reviewed in 2005 I think 11
10 alpha and B -- gamma agonist, and they finally decided
11 that they require -- because they found multiple tumors in
12 multiple species, multiple strains and they decided that
13 they would require a two-year study. That's all I have.
14 COMMITTEE MEMBER LANDOLPH: They would require it
15 to be what?
16 DR. SANDY: Well, this --
17 DR. TOMAR: Now, before you could --
18 COMMITTEE MEMBER LANDOLPH: No, I missed your
19 last word of your last sentence.
20 DR. TOMAR: Before it can go for the clinical
21 trial, they need to have a two-year carcinogenicity study
22 for rats and mice.
23 DR. SANDY: So Dr. Tomar is referring in general
24 to PPAR alpha and gamma agonists, and the review of those
25 agonists by FDA, but FDA has not reviewed DINP, to our

knowledge.

COMMITTEE MEMBER LANDOLPH: And how about NIOSH and IARC?

DR. SANDY: They have not. They have not.

DR. TOMAR: They have not.

DR. SANDY: We don't know why. NTP has not conducted a bioassay on DINP. That may be why. And most of this literature -- all of the studies we're reporting are not published. There's Lington et al., which has a male rat study and a female rat study, but the other studies are not published in the literature.

COMMITTEE MEMBER LANDOLPH: Thank you.

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DR. TOMAR: Summary of carcinogenicity evidence. We know that human evidence there are no data. As for animal evidence is concerned, we divided the tumors in two different groups. A statistically significant increase in tumor incidence, we have liver tumors in male and female rats and mice. Mononuclear cell leukemia, we have male and female rats. And we have renal tubular cell carcinoma in male rats, which is a rare tumor.

Tumor incidence increase not statistically significant, but tumor type considered to be rare or uncommon. Pancreatic islet cell carcinoma, which is rare; uterine adenocarcinoma, again which is rare; renal

transitional cell carcinoma, again which is rare; and Leydig cell carcinoma, which is considered to be uncommon.

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DR. TOMAR: Summary carcinogenicity evidence, other relevant date. DINP activates several nuclear receptors, PPAR alpha, PPAR gamma, constitute androgen receptor, and pregnane X receptor. DINP has anti-androgenic activity and causes steroidogenesis disruption. DINP induces tumor necrosis factor, which is possibly main cause for liver tumor. DINP inhibits gap junction intercellular communication. And the common tumor site/types observed in animal studies of DINP are structurally related phthalates.

Thank you.

CHAIRPERSON MACK: Thank you, Raj. We obviously will be getting the opinions of the members of the Committee later, but are there any questions to require clarification on anything from anybody on the Committee?

COMMITTEE MEMBER EASTMOND: If I could ask, Raj you'd mentioned that for the rare tumors you talked about the historical ranges and the variability. What about the mononuclear cell leukemia? How did these -- that's one that I think is highly variable and can meet present high incidence. How did these frequencies --

DR. TOMAR: The first thing is most of the

mononuclear cell leukemia I specifically would like to indicate that there was a positive trend for almost all -- wherever we find the mononuclear cell leukemia. It means there was a greater incident with dose -- it decreased with the dose. And beside those studies were done in 1986 and we are talking 2013. Tumor incidence does not stay the same over that many years. So, yes, I can understand that there's more mononuclear cell leukemia nowadays indicated, and I'm sure Dr. John Budroe has some more information on it.

DR. BUDROE: There is a good deal of variability in the historical control data between different laboratories. Haseman '98, the male MNCL data in the study cited in the HID tended to fall within the historical control range. The female data tended to fall outside. And there's at least one other study that didn't describe a range, but described a mean. And the mean was actually below both the male and female doses that were significant.

COMMITTEE MEMBER EASTMOND: Okay. Thanks.

CHAIRPERSON MACK: Anybody else?

I have one general question that relates to both of these compounds. In the material that was submitted by the regulated community, there were a lot of -- got to get it closer -- there were a number of allegations that there

1 were a lots of other studies that hadn't been reviewed.
2 So I guess I just want your views on the completeness of
3 the search.
4 DR. SANDY: So we have presented all the
5 long-term cancer bioassay studies, and we have tried to
6 present all of the types of other relevant data that we
7 thought were important. We have addressed some of the
8 mechanistic hypotheses, but have not written a
9 comprehensive document citing every single study that was
10 done looking at those hypotheses, or else you'd have a
11 much longer document. We've tried to expedite this and
12 look at new more recent literature and thinking on those
13 hypotheses, such as --
14 CHAIRPERSON MACK: I'm just referring to the
15 actual animal carcinogenicity studies, not the mechanistic
16 information. In other words, are there -- for example,
17 there was a suggestion that NTP studies over and above the
18 ones that you mentioned were available.
19 DR. SANDY: Actually, there are no NTP studies on
20 DINP. I believe Dr. Budroe may have -- in speaking about
21 historical control data that NTP has, we used that -- he
22 was referring to that to compare to these studies done in
23 other laboratories, contract laboratories. But to our
24 knowledge, NTP has not conducted any studies on DINP.
25 CHAIRPERSON MACK: How about BBP?

DR. SANDY: When we discuss the BBP, again to our knowledge, we have included all the cancer bioassays we know about on BBP.

CHAIRPERSON MACK: That's what I want to know. Thank you.

Okay. There was a request for a discussion to be provided on behalf of ExxonMobil and other members of the regulated community BASF. And we had asked -- we have a long list here. Okay. I'm sorry, let me take a few minutes to look at this.

All right. I have a list of four people who together will take up 30 minutes of discussion on this compound.

So let's begin with Stanley Landfair.

Please, please try really hard to fit it into the 30 minutes.

MR. LANDFAIR: Of course, Dr. Mack.

I'll introduce myself as Stanley Landfair, law firm of McKenna, Long and Aldridge. I represent BASF Corporation, and I'd like to introduce this presentation on behalf of BASF, ExxonMobil, and the American Chemistry Council. I want to thank the panel and you in particular, Dr. Mack, for allowing us to make this presentation. I think you'll find it far more efficient in this forum than had we spoken separately.

(Thereupon and overhead presentation was presented as follows.)

MR. LANDFAIR: So proceeding with the introductions, I won't waste further time by going through their credentials one by one or their academic backgrounds. I want you to know that we've brought each of the speakers here before you because they have a particular connection with this chemical or with items of research regarding this chemical that should be of interest to you. And I want to emphasize what we are trying to encourage here and provide you is the opportunity for professional dialogue with some people who are truly experts in these fields.

The first is Dr. Michael Cunningham, who's presently working as an independent consultant in toxicology. But of relevance here, he worked for over 25 years as an intramural researcher at NIEHS. From the years 1995 through 2006, he managed NTP's peroxisome proliferation research initiative. Of course, that's an issue very relevant here. In particular, Dr. Cunningham is here and he's available to speak to you regarding the tumors that were observed in the liver in the rat.

Our next speaker will be Dr. Gordon Hard. I'd like to say with respect to Dr. Hard, we in particular, and we hope you, owe him some thanks for making plans on

1 such short notice to come here from New Zealand to speak.
2 We had requested the opportunity that he might address the
3 panel by telephone. The answer was no. That's quite a
4 reasonable response under the circumstances. We don't
5 contest that, but I do want to thank Dr. Hard for making
6 these arrangements to be here in person so quickly.
7 Dr. Hard is now an independent consultant also,
8 but of relevance here he was the director of the British
9 Industry Biological Research Association. And he has
10 particular expertise to discuss the tumors that were
11 observed in the kidney.
12 Dr. Hard also has been involved in the study of
13 kidney carcinogenesis for over 40 years, and he helped
14 draft the U.S. EPA purple book on glamma(sic) 2 -- I'm
15 sorry, gamma 2u-globulin kidney tumors, and he was also
16 involved in the 1997 deliberations by IARC on the very
17 same topic. We think his testimony will be of interest to
18 you.
19 And finally, our third speaker is Dr. Jennifer
20 Foreman. She's a toxicologist with ExxonMobil Biomedical
21 Sciences, Incorporated. Dr. Foreman has spent five years
22 of study on the PPAR-alpha mode of action under an NRSA
23 fellowship funded by the NIEHS. She will speak in
24 particular to the issue of mononuclear cell leukemia, and
25 also she will sum up to address the weight of the evidence

for us.

We want you to know that some speakers of note or authors of note have submitted papers for your consideration. We hope you saw the paper by Dr. James Klaunig. He couldn't be here because of his duties as a professor. And in your background you might find it of interest, he was involved in a defense of a Ph.D. dissertation today, and he couldn't abandon that student after years of study. So we hope you understand why he's absent today. But we hope you're aware that he's watching via webcast, and he's interested in your reaction to his paper that he presented also.

Dr. James Felton also delivered a paper for you on the issue of genotoxicity. We hope you saw that. And Dr. Tim Zacharewski from the University of -- or, I'm sorry, from Michigan State University is also observing on webcast. We bring this up, because these are experts in the field, and if there's an extraordinary circumstance where you'd have a question regarding any of their work, they're available one way or another.

So without further ado, I'd like to introduce Dr. Cunningham.

CHAIRPERSON MACK: Can I just make one comment.

MR. LANDFAIR: Certainly.

CHAIRPERSON MACK: Thank you very much, Dr.

Landfair for organizing it in the way you have. I would request that questions to the individual experts that you're going to provide us with be held until after all of them have presented. That would make, I think both time and logic sensibility.

MR. LANDFAIR: Well, that's certainly within your discretion, Dr. Mack, if you'd like to do it that way. And we'll ask them to go through their presentations and stand available. I did omit just the briefest word about the standard for listing. I know that's sort of de rigueur these days. And I don't want to dwell on it, except that we all know the standard is clearly shown. So those are two words, two English words. It's up to you to decide whether or not the evidence is clearly shows.

What we want to convey in this context is we're not looking for closed cases, hard cases, or cases where, you know, the precautionary principle might be invoked or we believe that there's likely to be a carcinogen and we want to err on the side of human safety. This is a whole different statutory regime.

And the question is it clearly shown to cause cancer. If I were to reduce that to a numerical analysis, I'd say on 1 to 10, we're looking for 10s, not five, six, and seven. So thanks very much.

CHAIRPERSON MACK: Thank you.

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DR. CUNNINGHAM: Members of the Committee, thank you for giving me time today to talk about some of my experiences in the world of DINP. My comments have been submitted in summary form, so they are available I think in your packet.

As you know, DINP and phthalates in general as a class are some of the most widely studied industrial chemicals in commerce today. My personal experience with DINP dates back to my participation in the -- as a member of the Consumer Product Safety Commission Chronic Hazard Advisory Panel in 2000/2001. This panel was composed of university and government scientists, including your own Dr. Lauren Zeise here at the CalEPA.

This expert panel considered the weight of evidence of DINP toxicity in rodents and whether or not that would be relevant in human exposure conditions. Since then, there's also been new data relevant to this evaluation. And I'll talk about that in the next presentation that was scheduled to be presented by Dr. Klaunig. But today, I'd like to describe the relevance of these findings for your present deliberations.

This CHAP meeting by the Consumer Products Safety Commission engendered three face-to-face meetings with two or three days long, including many, many conference calls

between these meetings. And the following then are the conclusions that were based on these meetings back in 2001 on DINP itself.

The mononuclear cell leukemia in Fischer 344 rats was considered of questionable significance, and was not used in any further human cancer hazard assessments. And this will be discussed in more detail in another presentation.

Also, the kidney tumors were not relevant to human -- were determined to be not relevant to human cancer assessment due to meeting the U.S. EPA criteria for alpha 2u-globulin nephropathy in male rats. Another speaker will talk about that in much greater detail.

The rest of this presentation and the following presentation will talk about PPAR mediated mechanisms of hepatocarcinogenesis that have been clearly shown today to exist in rats. But I'd like to provide some data that demonstrates that they're not readily induced in humans, especially of importance to the CPSC, especially at doses resulting from the current use of DINP in consumer products. And therefore, it was thought at the time that human hazard was seen therefore as negligible or non-existent due to differential effects of DINP in rodents and in humans.

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DR. CUNNINGHAM: PPAR alpha activation by any compound be it an environmental compound, a fibrate hypolipidemic drug in endogenous fatty acid in rodents causes induction of peroxisomal, mitochondrial, and Microsomal fatty acid metabolizing enzymes including hydrogen peroxide-generating fatty acyl-CoA oxidase, carnitine acetyl transferase, and cytochrome P450 4A isozymes.

In rodents, this results in the commonly observed hepatomegaly, increases in oxidative stress, and ultimately, after long-term exposure, liver cancer in rodents.

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DR. CUNNINGHAM: However, in humans and non-human primates, the effects of PPAR alpha activation are quite different. PPAR activation in humans is actually the basis for the beneficial effects of the hypolipidemic compound gemfibrozil and the class of fibrates that are very widely used to lower serum triglycerides and cholesterol in humans.

It's shown not to induce increases in cell -- peroxisome proliferation in humans, and has as its mechanism of action not increases in peroxisome proliferation like in rodents, but increases in Apolipoprotein A-II, lipoprotein lipase transcription and

reduction of apolipoprotein C-III.

These are not associated with increased oxidative stress or hepatotoxicity. They don't breakdown lipids. They're very simply transport proteins that pull the triglycerides and cholesterol-containing compounds out of the serum and transport them into the liver cells.

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DR. CUNNINGHAM: These data were more fully analyzed by a -- I've got to get my glasses here make sure I'm on the right -- this mode of action was reviewed in a NIEHS workshop in 2011, which confirmed these results, and extended them to the entire field of nuclear receptor PPAR alphas. These are published in a recent paper by Corton, et al. The citation is here at the bottom, and I'll talk more about that in -- this is the citation here. And the authors of that paper were the members of the Committee that basically confirmed the CPSC results and really confirmed that the significant quantitative differences in PPAR alpha activator induced effects that related to liver cancer in rodents were not operative in humans after PPAR activation.

And most of the panel members indeed agreed that based on the mode of action that PPAR alpha activators, including DINP, were not relevant to humans or the remaining members concluded was unlikely to be relevant to

humans.

Thank you very much.

CHAIRPERSON MACK: Thank you, Dr. Cunningham.

Dr. Hard.

DR. CUNNINGHAM: May I continue with the next presentation?

CHAIRPERSON MACK: Yes, I'd prefer that we ask questions after you finish.

DR. CUNNINGHAM: I'm sorry?

CHAIRPERSON MACK: I would prefer that we ask questions after the four of you have made your presentations, please.

DR. CUNNINGHAM: Okay. This was originally --

CHAIRPERSON MACK: I'm sorry, go ahead.

DR. CUNNINGHAM: -- going to be represented by Dr. Klaunig, so I hope I represent his views properly.

His comments have been -- his written comments have been provided to the Committee, so they should be able to be easily accessed.

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DR. CUNNINGHAM: In the next presentation, I'd like to discuss the results of the workshop held at NIEHS on the mode of action in general of PPAR alpha agonists in rodents and in humans in 2011. And I participated in this as an organizer, as well as a participant. And basically

the outcome of this report demonstrated that the CPSC results were valid, and they actually extended the results to a more broader regulatory framework that I'll discuss later. The manuscript from this workshop has recently been published and should be included in your handouts.

A mode of action framework used in this meeting identifies key events that are associated with rodent hepatocarcinogenesis that may or may not occur in humans. Such a mode of action framework is actually very helpful in understanding the weight of evidence of the data and the human relevance of the mode of action developed in experimental animals and forms the basis for the conclusion of this work group that the rodent MOA of PPAR alpha agonist is not relevant or is unlikely to be relevant in humans.

So the mode of action of -- in rodents is described here that begins with metabolic activation of the compound, if necessary, to produce the proper structural binding metabolite that can then activate a PPAR alpha receptor. In rodents -- this slide is all on rodents. This is associated with lipid metabolizing enzyme increases, particularly peroxisomes and all the associated enzymes that are associated with the phenomenon of peroxisome proliferation in rodents.

It also includes alterations in cell growth

pathways, such as increases in cell proliferation that are observed in -- particularly in liver tissue, perturbation of cell growth and survival, which refers to decreases in apoptosis that are observed in rodent studies, clonal expansion of pre-neoplastic foci, and liver tumors which are confounded by increased oxidative stress NF kappa B activation, as well as inhibition of gap junctional cell communication.

These have all been highly studied and demonstrated exhaustively in rodents, but they differ in non-human primates, and in humans, as described in the following slide.

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DR. CUNNINGHAM: In the two red bars, I'd like to highlight. The key events in rodents are PPAR alpha activation, and that's been demonstrated widely in rodent models, in non-human primates, and in humans that may or may not exist.

This is about as far as the two models are in similarity. The rest of the key events -- associative events and modulating factors that we observed in the rodent models are not -- do not exist in humans or non-human primates, such as the increases in transient cell proliferation that occur in rodents are widely seen not to occur in humans or non-human primates. The

decreases in apoptosis that you see in rodents when and seen, when observed, when looked for don't occur in humans. Increases in liver to body weight ratio, which are very significant in rodents. By far, never are seen in humans or non-human primates. Other modulating factors, such as alterations in gap junctions that are seen to -- and are mechanistically related to the hepatocarcinogenesis mechanisms when observed in rodents and non-human primates -- in humans and non-human primates don't exist.

And so the tumors that result from all this activation of all these associative and causative factors that you see in rodent species would really not exist in humans, and are therefore really not likely to occur after exposure to PPAR alpha activators.

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DR. CUNNINGHAM: And getting close to the end. Putting this into a more formalized IPCS, International Program for Chemical Safety, framework for the relevance of rodent and human data from the World Health Organization, the common factors of metabolism of these compounds, particularly phthalates, are common in rodents. They do activate the PPAR receptor. However, any other downstream effects are not common in rodents, and in humans, such as cell proliferation. It doesn't show up in

human models. Pre-neoplastic liver foci that show up in rodents, there's no evidence for that in humans. And then, of course, tumors that are very prevalent in rodents exposed to long-term PPAR alpha agonists are really unlikely to show up.

And therefore, the conclusion that the mode of action of rodent hepatocarcinogenesis is really not relevant or considered unlikely to exist in a human exposure scenario.

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DR. CUNNINGHAM: And then finally, the work group really did conclude that PPAR alpha activators are highly unlikely to cause tumors in humans, and that the PPAR activator effects related to liver cancer formation in rodents are quantitatively not relevant or not likely to be -- exist in human exposure conditions.

Thank you very much.

CHAIRPERSON MACK: Thank you, Dr. Cunningham.

DR. CUNNINGHAM: And then I'd like to introduce Dr. Gordon Hard. You get the real reward for coming from the furthest away.

DR. HARD: Thank you. You've received my written submission, I hope. But I really want to thank you for this opportunity to address you in person about the -- woops.

--o0o--

DR. HARD: -- about the kidney effects of DINP. So thank you very much, Mr. Chairman and Committee.

The key histopathologic features of alpha 2u-globulin nephropathy in male rats commenced with hyaline droplet formation containing alpha 2u-globulin in the S2 or the second segment of the proximal tubule. There is single cell loss because epithelial cells crammed with droplets drop out into the lumen. And these sloughed cells form granular casts, at the so-called corticomedullary junction. Usually, this is seen at 13 weeks.

These tend to disappear, but many months after the start of treatment, mineralized cell debris formed streaks in the tubules of the papilla. And this is usually not seen unless there's a 15 month interim sacrifice. And, of course, by study termination, there can be a low incidence of renal tubule tumors. I've got variable there, because it's important to recognize that chemicals can be strong, moderate, or weak in inducers of alpha 2u-globulin nephropathy. And so the renal tumor incidence varies accordingly.

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DR. HARD: This is a ribbon diagrammatic likeness of the alpha 2u-globulin molecule. There is a hydrophobic

pocket in the center. And under normal conditions, this low molecular weight protein has a very long half-life of five to eight hours.

And the process driving this mechanism is the loose binding of the chemical or its metabolite into that hydrophobic pocket. And this interferes with degradate -- enzymatic degradation of the protein and leads to engorgement of cells with indigestible crystal-like protein that causes them to drop out and cause the cell loss.

So this process is really a perturbation of a male rat physiological process involving a protein that does not occur in humans.

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DR. HARD: How does DINP measure up against the IARC criteria for this mode of action?

Well, renal tumors have been seen in male rats, as you've heard. I'll dwell a little bit on the hyaline droplet though, because the awareness of the hyaline droplets in alpha 2u-globulin nephropathy came to prominence in the mid to late eighties. And this pre- -- and some of these subacute studies of DINP predated this emerging awareness of hyaline droplets. And so the lesions were probably not recognized.

There are also other reasons why this could have

1 happened. But anyway, Schoonhoven -- and I think you've
2 been give this abstract. Schoonhoven described
3 accumulation of alpha 2u-globulin in the cortex of rat
4 kidneys at five days. And this implies the acute presence
5 of hyaline droplets in the cortex. Caldwell also
6 identified protein droplets much later at 12 months still
7 persisting. And both of these authors identified the
8 accumulating protein as alpha 2u.
9 --o0o--
10 DR. HARD: Criterion 4 I considered to be one of
11 the most important for DINP, and that is because granular
12 casts and linear papillary mineralization are very
13 distinctive lesions, and together, they are virtually
14 pathognomonic for an alpha 2u-globulin nephropathy. And
15 in each case for these lesion -- in each lesion case, two
16 studies have identified them. And in the case of Myers,
17 granular casts were actually described as being located at
18 the corticomedullary junction and containing epithelial
19 cell -- degenerative epithelial cells. And this also
20 implies that there was hyaline droplets further up in the
21 cortex to lead to that particular lesion.
22 None of the subchronic or chronic studies have
23 recorded any of these kidney changes in female rats or
24 mice of either sex. And you will have read in Dr.
25 Felton's written submission that DINP is negative for

genotoxicity, and with -- from a variety of short-term tests.

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DR. HARD: So DINP fulfills the six IARC criteria, but also three additional items, which -- of supporting evidence proposed by IARC. The most important of these is that Schoonhoven showed reversible binding of DINP to alpha 2u-globulin.

He also -- they, that group, also showed a doubling of cell proliferation in male rat cortex at five days. And Caldwell indicated a sustained increase, although modest, at 12 months. And so these various changes, renal changes, that I've described have been seen at doses which matched those where the renal tumors occurred.

So to sum up, DINP ticks all of the boxes for an alpha 2u-globulin nephropathy. And the kidney -- resulting kidney tumors are not relevant for human cancer hazard assessment.

And my indulgence, if you are wondering where I come from. I'll give you Paku Hill, Tairua, New Zealand.

Thank you very much.

CHAIRPERSON MACK: Thank you, Dr. Hard.

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DR. FOREMAN: Okay. Moving along. In the

incidence of time, I would like to thank Dr. Mack and the Committee for the opportunity to speak today in front you.

As I'm sure you all know, the Committee is charged with responsibility to carefully evaluate the weight of evidence. This importance of the independent nature of this body is the ability to objectively look at that data and come to a science-based conclusion.

Our conclusion, based on the scientific assessment of the date is that DINP is not a human carcinogen.

The following slides are going to be organized in three parts. First a review of the secondary tumors, then a quick look at the MNCL, and then finally a summary of the data that compellingly shows that DINP is not a human carcinogen.

At this point, I was going to welcome the Committee to interrupt with questions. But given Dr. Mack's statement, I'll ask that you hold them till the end, and please make a note of any really pertinent questions you might have.

Thank you.

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DR. FOREMAN: Okay. Moving onto the first slide. These are low frequency tumors that were highlighted. They're not statistically significant, and they are within

historical control ranges. Given time limitations and the fact that the principles are consistent across all three tumors, I'm going to summarize them as a whole.

As you can see, you have the treatment incidence levels of all three tumor types that were highlighted. They are all within the historical control ranges that are implemented on the slides, the 5.7 for the islet cell tumor is less than the six percent. The 2.9 percent in the female mice is less than the four percent of historical controls. The 11.7 percent for the testicular cell carcinomas is less than the 3.4 to 23.4 percent of historical control ranges found in the literature.

And finally, for the endometrial cell carcinoma -- adenocarcinomas, the range of -- the value of 2.9 percent is less than the spontaneous frequencies that have been reported up to 18 percent. I would also like to highlight that these were not statistically significant within the own studies that were conducted from the controls in those studies.

And as was reported earlier, the amount of studies that were conducted were six in Fischer rats, two in Sprague-Dawley, and four in the B6. So these were tumors the were found in only one or two of the studies. Whenever you have multiple different studies, you don't have consistency of tumor type across multiple studies,

which is often looked for.

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DR. FOREMAN: Next I'm going to look into a little bit more depth into MNCL. This is a high frequency aging legion, which occurs -- aging lesion which occurs spontaneously in the Fischer rats. Its spontaneous incidence ranges from 32 to 74 percent. This is extremely high incidence level for these animals. As you can look, the tumor data in the DINP studies is similar to the historical averages. And it was indicated in the earlier talk that the female data are outside that range. But if you look, it's 53.8 percent and the top end of the range is 52 percent.

Additionally, many factors affect tumor frequency, which are unrelated to treatment. Dosing methods have been shown by oral gavage will increase incidence in the male animals and not the female incidence. Variability has been seen by caging, diet, different vehicle, as well as incredible variability between testing in the laboratory. So it's really difficult to put these into context for a treatment related issue.

Also, these tumors are not found in the Sprague-Dawley rats or mice that were found. Additionally, it's probable that most, if not all, of the

Fischer MNCL is derived from a natural killer cell subset of large granular cell lymphocytes.

In the Fischer rats MNCL is an aggressive and often fatal disease in older animals. The closest analog in humans is a natural killer cell LGL derived malignancy that is extremely aggressive, but only occurs in young adults. Additionally, the human disease is rare and is believed to involve a viral mechanism. There has been no association with exposure to chemicals, and the high susceptibility has only been seen in these Fischer animals, which is one of the reasons the NTP has stopped using these animals in their studies.

Now quickly, before moving onto my last slide, I'd like to discuss the Ito paper which was brought up earlier as being a issue with the PPAR alpha mode of action. In that paper, there was reported to be a statistically significant increase in the knockout animals after treatment.

There's one -- there's a couple of issues with this conclusion. First, the tumors are grouped in an unusual fashion, which includes a bile duct tumor with the liver adenomas and carcinomas. Without the bile duct tumor, the data are not significantly -- statistically significant. And this is a point that was pointed out in the IARC document as well.

Also, the values are within historical control levels as reported by Halroid et al. And I would like to say that the Halroid et al., they use the same animals and they're indicated as having come from the same colony. So it should be indicative of background incidence that would expected to be seen in these animals. The specific data from the Halroid et al. they had six out of 12 animals with adenomas, in comparison to the two out of -- six out of -- sorry, six out of 12 adenomas in comparison to the six out of 31 adenomas seen in the Ito paper.

And there was two out of 12 carcinomas in the Halroid paper in comparison to the two -- or the one out of 31 carcinomas seen in the Ito paper, because you can see these are very similar numbers. And this is based on untreated similarly aged animals from the Halroid using the same model and the same colony.

Also, I have some personal experience with these animals, given that my NRSA was on conducting species sensitivity on a high affinity PPAR alpha agonist using humanized, knockout, and wild type animals. And we saw similar incidence levels in the knockout animals in the untreated groups that were unrelated to treatment.

So this is likely a background incident tumor that could be due to having knocked out a gene that is really important to liver function or possibly just the

creation of another inbred strain that has a unique level of background incidence.

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DR. FOREMAN: Finally, I'm going to move onto my summary slide. So the weight of evidence does not support DINP as a human carcinogen. I would like to point out in reference to an earlier question by the Committee, that the FDA recently did review phthalates with food contact uses and found no issues. And DINP does have food contact issues, so it would have been included in that evaluation. Additionally, it has been evaluated extensively in Europe and not classified.

So back to the slide. So tumors observed in rodents are not relevant to human cancer assessment. In the liver, DINP meets both IARC and ILSI criteria, as peroxisome proliferator, a mode of action that is relevant to humans.

The kidney, as explain by Dr. Hard, satisfies IARC and U.S. EPA criteria for lack of relevance. The MNCL is a spontaneous lesion with high prevalence in the test strain. I'd like to emphasize again that this test strain has stopped being used by the NTP, because of this high incidence -- or in part because of this high incidence level.

Also, the non-statistically significant increase

in the other tumors, which are not consistent across multiple cancer studies. DINP is not genotoxic. And if the Committee would like, I'd be happy to read in Dr. Felton's remarks on this topic, if you have further questions given he is the expert on this.

There is also no evidence of DINP inducing cancer in humans. And I'd like to make a quick point about that, is that there is evidence from the fibrate drugs, which are a much higher affinity for PPAR alpha, and they do cause tumors in the rodent model, the fibrate drugs.

So you do see a differentiation between human and rodents for this mode of action, and it's clear when you look at that data.

Finally, to highlight the weight of evidence discussed, I would like to call your attention to the following reference pages.

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DR. FOREMAN: As you can see, the highlight text on this and the next text, the bolded ones on this slide and the next slide, are all references that have been included in making this PowerPoint presentation that were not included in the HID document that was provided to you.

These studies represent important information that put the data into context, and support that DINP is not a human carcinogen. I would especially like to

highlight the last reference by Corton et al., the critical review, which was just posted on-line November 2013. This is of special importance, because it's a publication by a diverse panel of experts, one of which you heard from today, evaluating the PPAR alpha mode of action, which includes the Ito paper and other more recent information on that mode of action.

And it was published just last month and was unfortunately not available to the HID whenever they put together their paper for you guys to review. The main conclusions being that liver tumors are due to the PPAR alpha mode of action and are not relevant to humans.

I'd like to thank you for your time. Hopefully, I did not speak too quickly, but I was trying to get through it to stick with our 30 minutes.

And if you have any questions for the general panel, we'd be happy to address them for you.

CHAIRPERSON MACK: Thank you, Dr. Foreman.

Now, are there questions from the panel for any of the four presenters?

COMMITTEE MEMBER LANDOLPH: Yeah. Thank you all for your nice presentations. I have a number of questions. I guess for Dr. Cunningham, thank you for your presentation. In terms of plots of the cancer risk versus the dose with the PPAR compounds in rodents, how do the

curves look? Do they have thresholds in them or are they linear no threshold dose response curves?

DR. CUNNINGHAM: In rodent studies?

COMMITTEE MEMBER LANDOLPH: Yeah.

DR. CUNNINGHAM: They tend to be dose related.

COMMITTEE MEMBER LANDOLPH: But I understand that. That's fine. Now, I'm asking you specifically how dose related? Is there a threshold and then an upward trend or are they linear and do they extrapolate through zero dose?

DR. CUNNINGHAM: From the data I'm familiar with, there's certainly a threshold. And some studies that I'm familiar with they're actually reversible if you take the compound out of the diet, like six months before sacrifice, and the tumors regress.

COMMITTEE MEMBER LANDOLPH: And then another question on the hydrogen peroxide generation. Is that a leakage of active oxygen species that misses the substrate that generates the hydrogen peroxide? How is that formed?

DR. CUNNINGHAM: I think the common idea is that it's an overproduction of super oxide, because you've got an increase in substrate. And the first part of the metabolism is to activate molecular oxygen adding two electrons to cause the actual oxidation of the substrate, and that overwhelms the catalase and the peroxidases and

all the antioxidant defenses. And I have seen some papers where measuring things like vitamin E or vitamin C those actually fall after chronic exposure to peroxisome proliferators.

COMMITTEE MEMBER LANDOLPH: So then you're getting oxidative stress, so you should be getting 8-hydroxydeoxyguanosine in the DNA. That should be mutagenic. Is that the case, do you find that?

DR. CUNNINGHAM: There's been one or two papers where that has shown up as an increase, but there's several papers that have not demonstrated that as well. So I think that's probably based on the difficulty of accurately analyzing for 8-hydroxyguanosine in DNA. But it has -- there has been some reports where that has increased.

COMMITTEE MEMBER LANDOLPH: And has anybody looked at tumors generated in rodents, say in the liver, by the PPAR alpha agonists and sequenced oncogenes or sequenced tumor suppressor genes and asked whether there were mutations there consistent with 8-hydroxydeoxyguanosine induced mutations, has that been done?

DR. CUNNINGHAM: That's an excellent suggestion and nothing comes to mind that that's been done. Sorry.

COMMITTEE MEMBER LANDOLPH: Thank you.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: Yeah, I have a couple of questions. First of all, I'd like to thank the reviewers, the public for making the comments. I found them very helpful.

Dr. Hard, two questions for you. First of all, it's my impression there are two different types of tumors that were seen on the kidney in these various studies, right? So you're focusing mainly on the tubular ones exclusively.

DR. HARD: (Nods head.)

COMMITTEE MEMBER EASTMOND: And the other one, which was a rare one, doesn't fall into this same mechanism.

DR. HARD: No, it does not. Transitional cell carcinomas are indeed very uncommon, but I do -- would like to point out that they -- where they occurred, it was non-significant incidence. I personally would have liked to have had a look at them to be able to be assured that they were correctly diagnosed.

And the third thing is that in that Lington study. If you look at the data, the pathology data on that, there is a very -- quite a high incidence of transitional cell hyperplasia in all of the groups, controls included, and much higher than I would have

1 expected. So that suggests to me that maybe there's some
2 infection going on, and so I think those -- those
3 transitional cell tumors are not really -- not related to
4 DINP.
5 COMMITTEE MEMBER EASTMOND: Let me ask for
6 clarification. You had indicated that of the specific
7 changes that really form criteria for these alpha
8 2u-globulin mechanisms, that they weren't -- those
9 specific changes weren't seen in the female animals
10 correct?
11 DR. HARD: (Nods head.)
12 COMMITTEE MEMBER EASTMOND: Apparently, in the
13 report in the document, I think Rajpal mentioned there
14 were some kidney effects seen in the -- in those studies.
15 Can you contrast those or give them a little more
16 background on it.
17 DR. HARD: One thing we haven't discussed here is
18 the spontaneous entity that is very common in rat strains
19 called chronic progressive nephropathy, CPN, I'll call it.
20 And CPN is exacerbated by, in my experience, all chemicals
21 that induce alpha 2u-globulin. So it's a co-partner of
22 the alpha 2u response. Pathologists describe the early
23 lesions of chronic progressive nephropathy as regenerative
24 tubules or regenerative basophilic tubules. And in the
25 female instance that you're referring to, it was the

1 description of that change was regenerative tubule.
2 Again, that is telling me that this is CPN not
3 related to the actual alpha 2u-globulin sequence of
4 events. And spontaneous CPN was recorded in some of the
5 other studies.
6 COMMITTEE MEMBER EASTMOND: Thank you very much.
7 I have another question for Dr. Foreman, if
8 that's...
9 DR. FOREMAN: Yes.
10 COMMITTEE MEMBER EASTMOND: Towards the end of
11 your presentation, you had mentioned the issue about there
12 was some strong peroxisome proliferating activating
13 agonists.
14 DR. FOREMAN: High affinity.
15 COMMITTEE MEMBER EASTMOND: High affinity, that
16 was it, okay. And can you describe kind of the effects
17 that are seen with those in humans and why you think
18 they're different than the rodent effects?
19 DR. FOREMAN: Well, I would say fibrate drugs
20 would be a good example of a higher affinity PPAR alpha
21 agonist. And this is used as treatment of hypolipidemic
22 aspects. And it's used in the clinical aspect, and so
23 follow up with these patients over 10 years, you see
24 decrease in cholesterol and blood anomalies. But after
25 liver biopsies and such, you don't see any effects in the

liver that you would see in the rodents after exposure to these same compounds which have a much higher affinity. And given the progression of the disease, even if you saw it earlier on in humans, you would still expect to see evidence of the progression, even if you weren't seeing the tumors exactly.

So these high affinity agonists, which are activating the receptor to a much higher extent than DINP, have been evaluated in a clinical setting and have not seen higher incidence rates from people who have been exposed or have been taking these. Does that answer the question?

COMMITTEE MEMBER EASTMOND: Yeah. Thank you very much.

DR. FOREMAN: I would just like to point out - I forgot to mention - that the other modes of action that were brought up as possible mechanisms, they're all part of the PPAR alpha mode of action. So the first step of activation is necessary but not sufficient. So it needs to be followed by these other steps like the NF kappa B activation, the gap junction. It's all part of the downstream processes that occurs.

So it's well known and has been considered within the PPAR alpha mode of action. So it's not a separate entity. It's part of that mode of action. And the first

step is the activation of the PPAR alpha, which has been classified in the human framework as necessary but not sufficient.

COMMITTEE MEMBER EASTMOND: Thank you.

COMMITTEE MEMBER THOMAS: While you're up therefore, Dr. Foreman, I have one more question for you. For the MNCL you highlighted the high background incidence in this -- in the Fischer rats, which are enormously variable, two and a half to four-fold almost. Can you give me any rationale why we should not favor the study controls, which show strong dose response in a presumably well controlled randomized assignment, as opposed to the -- you know, why we should give any greater weight to this historical control data?

DR. FOREMAN: So if you look at the information, there are multiple factors that affect this variability. You're looking at, in these animals, most likely a disease subset. And it's possible that you could have diseasing, which is secondary. So the MNCL is responding to a secondary event, which is not specific to the treatment.

Again, I'm going out and hypothesizing. This is not my area of expertise, but there's a good chance you may see the dose response related to the fact that these animals are responding to something else. If changing their food or giving them a gavage or their diet or

housing has the ability to accept the variability, it's not so much of a stretch to assume that a diseased animal might show a different variability in a background incident tumor.

I mean, also it's within the historical control range. There may just be incidence that occurs that's chance findings. It's not repeated across multiple studies. So other ones have been within the Sprague -- within the Fischer, you see multiple Fischer studies, which have the background incidence, but cancer studies with DINP done in other strains and done in mice do not show any occurrence of this.

So that is, I think, probably the key reason why you wouldn't consider that is because it's unique to that strain, and that strain is known to have problems. So you can look to the other studies. And in those other studies, in the Sprague-Dawley in the mice, you don't see that effect or any indication of that effect. So I'd say that was the strongest piece of evidence.

CHAIRPERSON MACK: Thank you, Dr. Foreman.

Jason.

COMMITTEE MEMBER BUSH: Thank you. I, too, want to thank the presenters for the data that they put forth. It was informative. I do have a specific question for you, Dr. Foreman. You had mentioned about the MNCL

equivalent disease was -- and that's a point of clarification, was that -- you said it was something like a natural killer?

DR. FOREMAN: Natural killer cell derived malignancy.

COMMITTEE MEMBER BUSH: More prevalent in children.

DR. FOREMAN: It's the closest analog.

COMMITTEE MEMBER BUSH: Okay.

DR. FOREMAN: So I wouldn't say it's equivalent, but it's the closest analog that people have tried to find that may potentially be related. So there's a lot of caveats whenever you're looking at the equivalency of this. And again, this has been considered previously in a lot of the expert's reviews and other organizations that have dismissed these as being of relevance to humans.

COMMITTEE MEMBER BUSH: Okay. Thank you. The reason I ask is some of the data that we have in front of us about the exposure in biomonitoring suggests that the metabolites of DINP are higher in children and toddlers. Do you -- are you able to make any comment about that?

DR. FOREMAN: I would say that there is no increased risk -- I'm going to say increased hazard for children or toddlers. I mean, we have a well -- the uncertainty. We have a well good idea of the level of

exposure. It's well measured. And this is again, like I said, the closest analog in young adults not children or toddlers.

Dr. Hallmark is one of the experts here, would you like to add a comment to that? At the discretion of the Chair, if I may.

DR. HALLMARK: My name is Nina Hallmark. I'm a toxicologist with ExxonMobil. My research background is in testicular cancer. What I just wanted to take the liberty to share is while we didn't expand on authoritative bodies today at the request of the Chair, I would just like to highlight that in Europe, the European Chemicals Agency has just done a detailed evaluation of DINP with children in mind, and they did not have a concern for DINP with children.

CHAIRPERSON MACK: Thank you.

Joe.

COMMITTEE MEMBER LANDOLPH: For Dr. Cunningham. I don't think Jim Felton can answer us. Jim mentioned that there was no evidence of mutagenic potential. And he said all Ames tester strains were used. Did they use the one TA102 which specifically detects oxygen radicals, induced damage?

DR. CUNNINGHAM: Do you know?

DR. FOREMAN: I'm sorry, which one?

DR. CUNNINGHAM: TA102?

I think that's one of the standard strains, so I would assume, but I didn't review the mutagenicity data.

COMMITTEE MEMBER LANDOLPH: Okay.

DR. FOREMAN: Can you repeat the question?

DR. CUNNINGHAM: TA102?

COMMITTEE MEMBER LANDOLPH: Was TA102 used as a tester strain for DINP?

DR. FOREMAN: I don't see any indication in Felton's comments, but I'd be happy to -- you have them in front of you. You should -- they've been submitted and be happy to go over them. His overall conclusions was that genotoxicity was not an issue for phthalates in general and DINP specifically.

COMMITTEE MEMBER LANDOLPH: Yeah, just that question still not answered. I read his comments. Thank you.

Could I ask Dr. Hard a question. Thank you for your nice presentation. In female rats and mice is alpha 2u-globulin not present? Is it not synthesized?

DR. HARD: Alpha 2u is not present in mice. It's present in -- mainly in male rats and where it's synthesized in the liver, but also present in some of the secondary sex glands. And in female rats, it's present in salivary gland and some secondary sex glands. But in

terms of excretion of alpha 2u, the difference between males and females is something between 100 and 300 times more prevalent in the males.

So that's coming mainly from the liver synthesis, but it would not be correct to say that there's no alpha 2u. And it's probably different -- this is jet lag garble -- probably different isomers.

COMMITTEE MEMBER LANDOLPH: And does the mineralization lead to a scoring of the kidney epithelial cells? Does it lead to a compensatory hyperplasia? Is that how tumors are generated?

DR. HARD: Not really. We think that the -- well, I think we're pretty sure that the mineralized cell debris is actually in the descending limbs of Henle, and probably blocks them, but there doesn't appear to be any morphological consequence of that.

COMMITTEE MEMBER LANDOLPH: So the mineralization is not leading to tumors is what I think I hear you saying, is that correct?

DR. HARD: No, it's not leading to tumors, but I think -- again in my experience, I think that the presence of that lesion is a marker in a sense that there might be tumors. In other words, if a very weak alpha 2u inducer may not produce mineralization in the papilla and may not

1 produce renal tumors.
2 COMMITTEE MEMBER LANDOLPH: Thank you.
3 CHAIRPERSON MACK: If there are no questions --
4 if there are no more questions, then Joe, would you like
5 to provide your summaries, views.
6 COMMITTEE MEMBER LANDOLPH: Sure, Tom. Thank you
7 ver much. I read this material pretty extensively on
8 DINP.
9 CHAIRPERSON MACK: Joe, I'm sorry. Would you
10 like to make some remarks?
11 DR. SANDY: Yes. Thank you, Dr. Mack. I think
12 we'd like to respond to a few things, if we may. Dr.
13 Landolph asked a question about which salmonella strains
14 had been tested. And if you turn to page 31 of the hazard
15 identification document, that's where we review the
16 information we have. And DINP has been tested in TA
17 strains TA 98, 100, 1535, 1537, and 1538. But we're not
18 aware of any testing done in the strains that are
19 sensitive to oxidative DNA damage such as TA100 and 104.
20 COMMITTEE MEMBER LANDOLPH: Thank you. Yeah, and
21 I asked that question, because of the possibility that the
22 tumors might be mediated through hy --
23 8-hydroxydeoxyguanosine from the peroxide. Thank you.
24 That's very interesting.
25 DR. SANDY: I also, if I may, would like to

discuss the issue of controls. We've heard a lot about that. And it's the general principle which is espoused in the most recent IARC preamble, for example, is that the most appropriate control is the concurrent control, and that's what we should look at. When you have some variability in the level of spontaneous incidence seen in animals, then you sometimes turn to historical control data to get some additional information. And so now I'd like to talk about historical controls, and what the ideal historical control would be.

That would be data on untreated animals from the same laboratory and animals from the same supplier, as the study of interest. You'd want to use -- look at the untreated animals that had the same route of exposure. So if it was an inhalation study, you'd want chamber controls. In this case, it's a feeding study, so you'd want to look at controls in feeding studies, diet studies. You'd also want to look at, within the same point in time, and usually it's plus or minus three years. Sometimes plus or minus five years from the date of the start of the study that you're concerned about and the end of that study.

So for the studies we're talking about here with DINP, we don't have historical control data from the same laboratory. We don't have -- we only have one set of

1 studies that's published in the literature. There's no
2 historical control data from those laboratories that's
3 been provided to us. So what we have done is look in the
4 literature to find what information we can about other
5 studies in the same strain and sex of animal, but we can't
6 say that that's optimal data. It's just what we could
7 find
8 If you would like, we can elaborate a little more
9 on the specific sites, tumor sites. So I see some nods
10 that that would be helpful.
11 COMMITTEE MEMBER THOMAS: Can I just follow up
12 with your comments on historical controls though. I agree
13 with the principles that you've described, and just wonder
14 if you could respond specifically to the comment about NTP
15 having discontinued use of the Fischer rats, and whether
16 that is relevant for us to consider, in terms of the
17 credibility of those findings for the leukemias.
18 DR. BUDROE: Well, NTP hasn't exactly
19 discontinued the use of Fischer 344 rats. They've
20 discontinued the use of the N substrain, which is the NIH
21 derived substrain. They are now using, for example, Han
22 Wistar rats in some studies, but they're also using
23 Fischer 344 NCTR substrain. And the F344/NTac substrain,
24 which is Taconic Farms derived. So they've gone away,
25 more or less, from using the N strain, but they are still

using Fischer substrains.

COMMITTEE MEMBER THOMAS: Thank you.

CHAIRPERSON MACK: Okay. Joe.

COMMITTEE MEMBER LANDOLPH: So -- oh, go ahead.

CHAIRPERSON MACK: Who wants to speak?

DR. SANDY: I'm sorry. We did see some -- I did see some nods from some Committee members on, yes, they would like to see some more information on the historical control data we found in the literature. And we have it summarized. So I'll ask John Budroe to present that.

We'll just present a little bit on the MNCL first.

DR. BUDROE: Okay. On the slide, the first quote is by a publication by Thomas 2007. F344 LGLL, and that's the author's term for mononuclear cell leukemia or MNCL, is quite comparable to the aggressive human natural killer cell LGL leukemia on morphological, functional, and clinical basis.

U.S. EPA in a toxicological review of trichloroethylene in 2012 noted that the analysis by Thomas found that Fischer MNCL induction was more often than not confined to one sex.

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DR. BUDROE: And it's -- in light of that, it's relevant to note that a significant increase in MNCL

1 incidence was reported in both male and female DINP
2 exposed Fischer rats by both Lington in '97 and Moore in
3 1998.
4 CPSC in the 2001 CHAP review stated that, "Also
5 while the lesion rarely occurs in untreated rats less than
6 20 months of age, DINP animals were first observed with
7 this tumor at considerably younger ages. It is therefore
8 highly unlikely that these findings were unrelated to
9 treatment".
10 And in a technical review by U.S. EPA in 2005,
11 and I'll note that this was a review of toxicity, but was
12 not a cancer classification review, that to quote from the
13 document, "The increases mortality due to MNCL in DINP
14 treated rats suggests that DINP is associated with the
15 elevated incidence, progression, and severity of MNCL.
16 The tumor findings may be biologically significant because
17 the time to onset of tumor was shorter, and the disease
18 was more severe in treated than in control animals. The
19 agency believes that the data for MNCL are indicative of a
20 carcinogenic response to DINP".
21 COMMITTEE MEMBER EASTMOND: Tom, can I ask a
22 question?
23 Now is that an EPA -- the 2005, is that one of
24 their draft documents? Because I understand they never
25 finalized their review on --

DR. BUDROE: That was a technical review document. I'm not -- yeah, probably for TSCA, so it wasn't done, for example, for the IRIS Program.

DR. SANDY: And if I can add. As I said before, that was just a review of data submitted to EPA under TSCA. It was not an overall review of the carcinogenicity of DINP.

--o0o--

DR. BUDROE: Okay. Discuss some of the male rat renal tubular cell carcinoma data. The IARC 1999 relevance criteria for male rat kidney tumors produced by chemicals that also induce renal alpha 2u production.

The IARC criteria are newer and they're more detailed than the corresponding U.S. EPA 1991 criteria. And as noted in the HID, several IARC criteria were not met. Now, the Schoonhoven 2001 abstract says conclusions which could support -- would potentially support IARC criteria number 2. Acute exposure exacerbates hyaline droplet formation, and supporting evidence number 1 reversible binding of chemical or metabolites alpha 2u-globulin.

However, the abstract does not provide details of study design, methodology, or detailed data. And this study was never published in a peer-reviewed journal.

And with regard to the Caldwell 1999 study, there

were some parameters like, for example, increased cell proliferation in male rat cortex. Caldwell reported increased cell proliferation, but it wasn't statistically significant. In fact, the percentage of proliferation in the male rats were relatively close to that seen in female rats. So there wasn't a great deal of difference between the sexes.

--o0o--

DR. BUDROE: And in 2007, published in-house it's the NTP studies, which indicated the lack of correlation between male rat kidney tumor response and renal alpha 2u-globulin concentrations, or micro histopathological evidence of alpha 2u-globulin associated nephropathy. So this suggests that alpha 2u-globulin induction may not adequately explain male rat kidney tumors.

DR. SANDY: And just to add, we don't have any data on the bioassays -- on what the effects. We heard some presentations from the public commenters that there were -- there was accumulation of hyaline droplets. We don't have even a description of that in any of the secondary reviews done by the EC or CPSC. So we were looking at the data we had, and wrote that up in the document.

Cindy, if we could have one of the other slides next.

--o0o--

DR. BUDROE: Okay. Regarding the pancreatic islet cell carcinoma incidence in the DINP treated male Sprague-Dawley rats and the available historical control data. In the Bio\Dynamics 1986 study, control incidence was 1.4 percent, and the 10,000 ppm treated DINP group was 5.7 percent. The historical control data available over four studies essentially indicates that the incidence is generally low enough. The mean incidence in the historical control group is available to us that pancreatic islet cell carcinomas are rare in male Sprague-Dawley rats.

--o0o--

DR. BUDROE: And endometrial adenocarcinoma incidence in DINP treated female Sprague-Dawley rats compared to the available historical control data Bio\Dynamics 1986 controls zero percent 0 to 70, 10,000 ppm DINP, 2.9 percent. As you can see from the five historical control data groups that we had available, the range -- one range given was 0 to 1.4 percent. Most of the mean incidences were well under one percent. The 10,000 ppm DINP incidence falls outside of the one historical control range we have available. And the incidence -- the historical control incidences are generally below one percent, in some cases well below one

1 percent.
2 And we believe this historical control data
3 indicates that endometrial adenocarcinomas are rare in
4 female Sprague-Dawley rats.
5 --o0o--
6 DR. BUDROE: And for pancreatic islet cell
7 carcinomas in female B6C3F1 mice and historical control
8 data. Moore 1998, 0 of 70, zero percent. And controls,
9 8,000 ppm DINP, 2.9 percent, two of 70. The incidence in
10 available from Haseman 1998, which is -- essentially
11 covers a span of NTP studies of controls, the incidence
12 there was 0.2 percent, the range was 0 to 2. And more
13 recent NTP data using the Haseman data would have use NIH
14 '07 data. NTP switched their diets. So more recent
15 evidence -- more recent historical control data we have
16 from NTP uses the NTP 2000 diet. Zero to 494 animals with
17 pancreatic islet cell carcinomas.
18 So essentially, the historical control data that
19 we have available indicated that pancreatic islet cell
20 carcinomas are rare in female B6C3F1 mice. And the tumor
21 incidence that was noted in the Moore study falls above
22 the historical control range published by Haseman in '98.
23 DR. SANDY: So that may be more historical
24 control data than you wanted to know. If I could indulge
25 in one more point?

CHAIRPERSON MACK: Always can be indulged to a point.

(Laughter.)

DR. SANDY: Thank you. Okay. So the last thing I wanted to say was we've heard a lot about the PPAR alpha mode of action hypothesis. And I wanted to point you to the page numbers in the hazard identification document where we address this specifically with the data on DINP. And so that's page 53 through 56, where we discuss the data from studies with DINP related -- so related to PPAR alpha. And it is clear that DINP does activate PPAR alpha. And that's reviewed on the first two pages, 53 through 54. And then we look at the information that suggests that it may be relevant to the induction of the liver tumors that are seen.

And our conclusion is that there's inconsistency in the hepatocellular proliferation in the short term in these studies, in the DINP-exposed rats and mice, and there's also a lack of sustained, long-term hepatocellular proliferation in the DINP-exposed rats that suggests that PPAR alpha activation may not be involved. And you've heard in the document reviews other things that DINP does. It activates other nuclear receptors and does a whole host of other things. I just wanted to point you to that.

Thank you.

CHAIRPERSON MACK: All right. Now, Joe.

COMMITTEE MEMBER LANDOLPH: I want to thank Dr. Budroe, Dr. Sandy and all your team for putting together the hazard ID document, and the public for all your comments.

I thought about this quite a lot. And Dr. Luoping and I were on an EPA panel, and we dealt with perchloroethylene, and a lot of same issues came up. The issue of the MCL as an endpoint. We thought it's a little bit of wonky endpoint, because the background is always high, but you do see dose responses against that.

And there's arguments as to whether it's relevant to human tumors. One author claims it is, other authors claims it's not. And we went through the same arguments about the liver tumors, and we had one of Jim Klaunig's very competent colleagues from Indiana University discuss that.

And I would take the same approach here as I did there. We've got four tumor sites. They're all positive. There's induction at every site, so it's difficult for me to throw that positive data out the window. I think that's intellectually dishonest, so I can't do that.

So I have to respect that, particularly when a lot of the data, not all of it, but a lot of it is very dose responsive. And for much of it, the trends -- not

all of it, but for much of it, the trends are statistically significant, and the fact that the other PPAR agonists cause it.

So I respect that data. It's clear that these compounds are not much in a way of genotoxins. They're still an open hypothesis, in my mind, that maybe they're generating oxygen radicals through the hydrogen peroxide leakage, but that's not been followed up. It's not substantiated yet.

So I think it's easy for me to say this next sentence, but I'm going to need a legal consult for the following sentence. So I think this stuff causes cancer in rodents and rats and mice. Now, the question is what do we do about the extrapolation question?

And so can you tell me, Fran, what does the law tell us we have to vote on?

STAFF COUNSEL KAMMERER: Well, Dr. Landolph, the law is pretty clear -- well, rather unclear as far as the animal and human, but if you look at your criteria, you do discuss that in the criteria.

So if the weight of scientific evidence clearly shows that certain chemicals causes invasive cancer in humans or that it causes invasive cancer in animals, unless a mechanism of action has been shown not to be relevant to humans, the Committee will normally identify

the chemical for listing.

Does that address your question?

COMMITTEE MEMBER LANDOLPH: Yeah, I think so, because Tom and I and the rest of the Committee wrote those criteria. So I just wanted to --

(Laughter.)

COMMITTEE MEMBER LANDOLPH: I just wanted to see what you had to say from a legal perspective. And I guess the answer is it's unclear, right?

STAFF COUNSEL KAMMERER: Not as far as the statute is. I mean, the criteria in the statute I read to you early in the meeting, and it doesn't really define that. It's been discussed in some cases, but as far as this, no.

COMMITTEE MEMBER LANDOLPH: So, yeah, that was the answer to my question. Okay.

STAFF COUNSEL KAMMERER: It's up to the Committee's judgment. That's why you debated it in the criteria when you came up with those criteria. I know this was discussed amongst many things. So it's your decision. It's your scientific judgment.

COMMITTEE MEMBER LANDOLPH: Right. Okay. Thank you. So I have no trouble saying that this compound is a carcinogen and that it causes cancer.

CHAIRPERSON MACK: We're talking now among the

Committee members.

DR. FOREMAN: Is it possible before you go into the discussion to address some of the issues that were brought up?

CHAIRPERSON MACK: No, I think we've heard you address it already.

DR. FOREMAN: We weren't -- didn't have a chance to address their follow-up considerations to what we said. I just thought a couple of key points on the historical control ranges was that they were from the data -- the laboratory data that the tests were done in, and they were not statistically different from controls. So they provided a lot of historical ranges from literature.

I would just like to point out that the ones that we provided in our submission was from the control -- from the laboratories that ran the experiments based on the evidence that they gave, and --

CHAIRPERSON MACK: Thank you very much.

DR. FOREMAN: Okay. Thank you for your consideration.

COMMITTEE MEMBER LANDOLPH: And then my next sentence was I struggle with the issue of the relevance to human tumors. I respect Jim Klaunig, and I respect Jim Felton's comments, and all the comments that were given by the industrial firms. So I still struggle with that

issue. And I certainly respect the comments that Martha brought up that maybe this issue is not quite so settled is that these are acting by PPAR mechanisms or by the hyaline droplet mechanism. There's still a little bit of wiggle-room there. So that's about all I can say.

CHAIRPERSON MACK: Dr. Zhang, do you have anything to add?

COMMITTEE MEMBER ZHANG: Dr. Landolph already -- Sorry. Yeah -- seems expressed the most things I needed to say. But again, with -- I'm just going to talk a little bit more on the MNCL, as Joe just explained. And a few years ago we did -- and I actually quite remember the Thomas 2007 paper, but I want to make sure I just want to get it out.

So the thing is the -- you know, our Committee member too was questioning about high background level on the mononucleated cell leukemia. But the Thomas 2007 basically reviewed all the chemicals NTP screened on this Fischer 344 rats. But if you look at all the 34 compounds, which do not include the DINP, but if you look at all the compounds, it's only five of the 34 become positive, both in male and the female.

So that point is even though -- even though the background is high, but if we see dose response, number one; number two, if we see the similar results from two

1 different studies, two different laboratories, so which
2 seem to me, you know, mostly I'm doing the leukemia
3 research, cannot -- I'm still convinced this model still
4 work somewhat regarding what he was saying.
5 But also again on this same rats, it's not only
6 the MNCL, you also see the liver -- other type of the
7 cancer. So I totally agree with Dr. Landolph, you know,
8 at least, you know, is animal carcinogen.
9 CHAIRPERSON MACK: Thank you.
10 Peggy.
11 COMMITTEE MEMBER REYNOLDS: So I'd also like to
12 express my thanks actually to all of the presenters for
13 educating me on this particular chemical. As an
14 epidemiologist, and given the complete lack of epi
15 evidence on this, I'm a little bit pressed about what to
16 say. I really would like to hear more as we sort of go
17 down the line in terms of Committee members who are in
18 other disciplines about this issue that seems very key,
19 which is really whether the mechanism of action has been
20 shown to be relevant in humans.
21 And since we have no human health evidence, I'd
22 really like to hear more about that if anybody else has
23 comments on it on the panel.
24 CHAIRPERSON MACK: David.
25 COMMITTEE MEMBER EASTMOND: Sure. Let me bring

this forward and make it a little easier for me.

I've spent actually quite a bit of time reviewing both this compound and the other one and thinking about them and kind of wrestling with this. And I'll just go through kind of my thought process, and go through these descriptions.

Basically, you have a compound that, from all evidence, is nongenotoxic. So you would say, okay, that indicates it's very likely some -- through some sort of nongenotoxic receptor-mediated mechanism, and you have some very good plausible mechanisms. We'll come back to that in a minute.

As far as there's no human epi data that we can rely upon, we go to animal studies and there's a wide -- a large number of animal studies, which have shown increases or significant increases.

However, when I start boiling it down to those, and it was kind of pointed out, many of these were not significantly elevated. They're elevated in relationship to sort of historical controls, but it was not significant in those studies themselves. And, for me, that -- I don't consider that significant -- sufficient information to -- basically for a listing. So I would drop out most of those.

So it really boils down to three main tumors.

All of these are -- have been controversial. There's large discussions over them. And I'll go through one by one essentially.

The other thing to realize we've got 12 dietary cancer studies. And given the number of tissues that are evaluated in every one of these studies, typically on the order of 40 or 50, you're bound to find significant increases in, you know, animal cancer studies. The real issue goes into sort of historical control incidence, dose relationships, et cetera using a higher level sort of evaluation on it.

So let me just parse away. The mononuclear cell leukemia, this is one that has a highly variable incidence. It's been a challenge to try and make sense of, you indicated, Rose, in one of your earlier evaluations. I've watched this from a distance. People just don't know what to do with this type of leukemia, because, again, it doesn't have a clear, clear relationship to any sort of common leukemia in humans.

Apparently, it's related to a very, very rare natural clear cell leukemia, which frankly I've never even heard of before. And chemically-induced leukemias is one of my areas of expertise. But the high variability in the Fischer 344 rats is one that makes me very cautious about going forward with a listing based upon this particular

1 tumor type.
2 The kidney tumors, again, the presentation that
3 this appears to fit most, possibly not all, of those due
4 to the mechanism -- due to this alpha 2u-globulin related
5 mechanism. And, for me, the evidence is sufficiently
6 strong. Most of those actually were not significantly
7 increased in the study, so it really boils down to one
8 study or two.
9 And if I look through this, that doesn't -- I
10 think the evidence is not ideal, and particularly since
11 some of the key evidence was only published as an abstract
12 and you don't have the data to go back to. It makes me a
13 little cautious about that one. But again, that one -- I
14 think the explanation as presented is such that I -- you
15 know, I don't feel confident listing based upon the renal
16 tumors. The real key element for me comes down to the
17 liver, and there's lots and lots of evidence in liver
18 tumors. So it clearly causes liver tumors in rodents.
19 The key question now becomes, are those relevant
20 to humans? And this is one that's really a judgment call.
21 I've followed this story. This is not my area of
22 expertise, but I followed this story for many years.
23 Watched as more data has accumulated, and was very
24 interested in this latest results of this NIEHS convened
25 panel that just published the results, the Corton et al.

study.

They weren't entirely unanimous on it, but a majority indicated these types of tumors that were induced by PPAR alpha were not relevant to humans or not likely to be relevant to humans. And so, you know, for me, that's another one that I feel -- I don't feel real confident listing on that given the human relevance that there's real questions about. I mean, these are very significant questions about whether this data is relevant to humans.

So that's my kind of longer explanation. But going through these, usually, I would list this, because there are just so many tumor types that are positive. And as Joe said, you know, you can explain maybe one, possibly two. When you get this many, it really is very difficult not to list it.

But this goes against my usual nature, but I'm right now not convinced to list, just simply because I see enough weaknesses on each of these that I don't feel real confident.

CHAIRPERSON MACK: Dr. Dairkee.

COMMITTEE MEMBER DAIRKEE: As a cell biologist, I must say when I see receptors, nuclear receptors, being activated, it concerns me. And there seems to be evidence for that, especially the estrogen receptors, so the possibility of endocrine disruption and other tumor types

that we have not seen in the animal models simply because they may be very slow growing tumors that do not work well with animal models, but they may have human relevance, that is my major concern. The nuclear receptor activation is something that really concerns me, and yes, tumors in animals of such a vary diverse kind also concern me.

And I would just stop right there.

CHAIRPERSON MACK: Duncan.

COMMITTEE MEMBER THOMAS: Could I get clarification about the kidney tumors. The only significant finding that I find is in the recovery studies, is there anything -- is there another one that I missed that maybe not appeared in one of the tables?

That's it. Right.

CHAIRPERSON MACK: Jason.

COMMITTEE MEMBER BUSH: So listening to panel members and trying to sift through the data, I find myself wrestling with the decision as well. And, for me, it comes down to this dose response. A lot of the animal based studies at, you know, 10,000 ppm or 12,000 ppm, I mean, those are high.

And the biomonitoring data suggests that, you know, a normal human exposure is around 0.85 micrograms per kilogram per day.

So it comes down to this dose response. I mean,

I think there are clear biological effects here, but you know, at high doses, of course, you can find a lot of different biological effects. And I guess what I'm wrestling with is whether this is meaningful for humans?

I think it is clear that it does form tumors and thus ought to be a carcinogen, but at what dosage level, and is something to consider for the panel.

CHAIRPERSON MACK: Thank you. My own view is that I wish the proposition had been worded a little bit better. I wish it had said in humans, but it didn't say in humans. And that means that we're left either pretending that we're the Supreme Court, and we can interpret and make law, or we can simply be technologists and apply the rules that we're given. And I think we're -- my own position is we're stuck with the latter.

So the question to me is does this stuff cause cancer? And I have to rely upon the dose response relationships. And I actually am moved by the number of cancers which pop up, in an unusual circumstance, including the kidney, the pancreatic islet cell and the leukemia. I understand completely the points that David has made about -- and that the regulated community has made about the mechanism issue.

And I wouldn't be a bit surprised to find in the long run that each of these tumor frequencies can be

explained by mechanisms that are not pertinent in humans.

But my gut response right now is that that can't be an assumption I can make. And so my inclination is to make the judgment on the basis of whether or not the cancers that are caused in mice are invasive and truly malignant. And I presume that that's -- not presume. I know that that's the case. So that's my attitude.

And I guess now we're ready to take a vote.

Is that right, George?

COMMITTEE MEMBER ZHANG: But I still have a question. I thought I heard the law or criteria we do not -- do we require it for human data? That's not a known, right, which means by law we could vote or list based on animal data, right?

CHAIRPERSON MACK: That's correct.

STAFF COUNSEL KAMMERER: That's correct, yes.

CHAIRPERSON MACK: The only point about humans that Fay mentioned I think was in the criteria document that we produced, which discusses the pertinence to humans.

But, of course, in the absence of epidemiologic information, we're stuck making decisions about animal data. And the inference I don't think we can go on, but Joe, go ahead.

COMMITTEE MEMBER LANDOLPH: Actually, Tom, we

1 already have once. And we already have made that decision
2 once. It was on the retraction of cyclamate, because I
3 was the primary reviewer on that.
4 CHAIRPERSON MACK: We've made it a couple of
5 times.
6 COMMITTEE MEMBER LANDOLPH: Saccharin, yeah,
7 sorry -- where that mechanism didn't exist in humans who
8 didn't get that precipitate.
9 CHAIRPERSON MACK: We did it with that and
10 gasoline additive a couple of years ago. So I think --
11 and I think we're stuck with it.
12 So are ready to call for a vote?
13 COMMITTEE MEMBER THOMAS: Well, I still would
14 like clarification on this relevance question. As I read
15 the guidelines that says that if it causes invasive cancer
16 in animals parenthesis, unless the mechanism of action has
17 been shown not to be relevant in humans. Now, as I
18 understand, I think it was Mandy's comment, the -- we
19 clearly show that the PPAR alpha mechanism is not relevant
20 in humans, but that's not the only possible mechanism,
21 that there are others about which we are simply unsure.
22 And so the possibility that it's relevant still stands, as
23 I read your comments, or whichever of you it was.
24 CHAIRPERSON MACK: Can I make comment first.
25 Having -- being the person who wrote those guidelines, I

1 have to try and describe to you the reason why that
2 verbiage was put in there. Can you picture a circumstance
3 where there's extremely good epidemiologic data suggesting
4 that there is no effect on humans, a carcinogenic effect?
5 And, at the same time, there is one or two animal studies
6 with liver cancers in rats, in which there is a marginally
7 increased effect.
8 And I think the point of that mechanistic
9 inclusion in the criteria document is thinking about that
10 rather than this. Here we're in a situation where there
11 is no epidemiologic data. We have to go solely on the
12 animal data.
13 Am I wrong about that? Does anybody have an
14 alternative point?
15 MR. LANDFAIR: Mr. Chairman, since you asked?
16 CHAIRPERSON MACK: Pardon me? I didn't mean you.
17 (Laughter.)
18 MR. LANDFAIR: You didn't mean me. I would just
19 like to add that we're certainly addressing the right
20 issue, because there are animal data, and everyone
21 concedes from this side of the aisle that the animal data
22 do show different cancers in different animals. And the
23 question before the Committee is whether those data are
24 relevant to humans?
25 And if for all the reasons --

CHAIRPERSON MACK: That's not the question. That's the whole problem. The question is not whether or they're relevant to humans. That's not what the law says. The law says that the regulation, which comes from the Proposition 65, says does it cause cancer? It does not say does it cause cancer in humans?

So we're not the same as IARC, and we're not the same as the Supreme Court. We have to make a technical decision based on the question as put to us. So you're mistaken about that allegation.

MR. LANDFAIR: Well, with all respect, these criteria that the Panel has authored and adopted --

CHAIRPERSON MACK: Did you just hear what I said about why the panel -- why we wrote those criteria? We wrote them for the circumstance in which there was a conflict between human epidemiologic data and information from animals. And, in any case, I don't think we can discuss it any further. We have to take a vote now.

So if you'll permit me, we'll go ahead and do that.

MR. LANDFAIR: I'll always permit you to go ahead and vote.

CHAIRPERSON MACK: Thank you.

MR. LANDFAIR: I think we have a very valid question under your criteria, and which have been

interpreted and applied by the courts and been accepted.

CHAIRPERSON MACK: Well, maybe they'll have to be again. We'll see.

MR. LANDFAIR: Well, we hope that's not the case.

CHAIRPERSON MACK: Peggy.

COMMITTEE MEMBER REYNOLDS: I just wanted to ask an informational question. And that's, one of the challenges we have is that a lot -- not all of this information is published in the peer review literature. And so you've been -- in reviewing it, there's been a little bit of a disadvantage in having all of the detailed information. Is there -- for a -- for an agent that is in such high production and high use, is there any reason that we know of that we're not really seeing more in the peer-reviewed literature?

I sort of ask that of OEHHA staff. It just seems a little odd.

DR. SANDY: And you're addressing that to me, Dr. Reynolds.

COMMITTEE MEMBER REYNOLDS: I'm kind of looking at you, yeah.

DR. SANDY: I cannot tell you why it's not in the published peer-reviewed literature.

DR. HALLMARK: Dr. Mack, if I may?

My name is Nina Hallmark. I'm with ExxonMobil

Chemical, the manufacturer of DINP.

I have to say that all the hazard identification studies that we've conducted are in the published literature. I can't speak to other organizations that may have done research on this chemical. But what I would also offer is that the biomonitoring data that has been conducted here in the U.S. by CDC, absolutely in the public domain.

So if -- I have to say I'm struggling to conceive a hazard identification gap that isn't available to this committee.

CHAIRPERSON MACK: So can we go now with the vote?

I would read the -- has diisononyl phthalate been clearly shown, through scientifically valid testing, according to generally accepted principles to cause cancer?

All those voting yes, please raise your hand?

(Hands raised.)

CHAIRPERSON MACK: So I count one, two, three, four, five, six. Six yeses.

All those voting no, please raise their hand?

(Hand raised.)

CHAIRPERSON MACK: One.

All those abstaining, please raise their hand?

(Hand raised.)

CHAIRPERSON MACK: One.

We have at least five yes votes, and therefore we will recommend that this chemical be added to the list.

Now, I think we should take a break.

DIRECTOR ALEXEEFF: Dr. Mack requested that we take a lunch break till 1:45.

(Off record: 12:56 PM)

(Thereupon a lunch break was taken.)

A F T E R N O O N S E S S I O N

(On record: 1:51 PM)

DIRECTOR ALEXEEFF: Good afternoon, everybody. Let's bring the meeting back to order. All the Panel members are present. And I'll turn it over to Chairman Mack.

CHAIRPERSON MACK: Martha, would you like to say a few words.

DR. SANDY: I would. Thank you very much. And I'll be short. Good afternoon. Butyl benzyl phthalate has a lot of additional types of evidence coming from studies conducted in a variety of in vivo and in vitro experimental model systems. Many of these studies have utilized molecular methodologies to examine changes in gene expression and protein expression, and some have investigated the links between altered gene expression or protein expression with phenotypic changes indicative of cancer progression using model systems.

This evidence has been summarized at some length in the hazard identification document. Today, we're only going to present a simple overview of that information, and I'll now turn it over to Dr. Budroe.

DR. BUDROE: Good afternoon, Dr. Mack, members of the committee. I'd like to present to you Dr. Jennifer Hsieh and Dr. Meng Sun. And they will be presenting

evidence in the carcinogenicity of butyl benzyl phthalate.

(Thereupon an overhead presentation was presented as follows.)

DR. SUN: Good afternoon. My name is Meng Sun. So we are going to start with an overview of the presentation. We will start with the use and biomonitoring of this chemical butyl benzyl phthalate, or BBP, followed by the evidence regarding the carcinogenicity of BBP, including human epidemiological studies, BBP carcinogenicity studies in animals followed by other relevant data.

We will also present possible mechanisms of action and reviews by authoritative agencies. And we will finish with a summary of the evidence.

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DR. SUN: The figure on the left shows the chemical structure of butyl benzyl phthalate. It is a diester of phthalic acid with a butyl chain and a benzyl chain. The major use of BBP is a plasticizer in polyvinyl chloride, or PVC products, such as flooring tiles and carpet backing. It also used as an additive in a variety of products.

Since 2009, the use of BBP in toys and child care articles has been restricted by U.S. and California laws to be at levels no more than 0.1 percent.

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DR. SUN: This slide shows the biomonitoring studies of BBP. Monobenzyl phthalate, or MBzP, is the major and specific a BBP metabolite in humans. BBP biomonitoring studies have used MBzP as a biomarker. This table shows the geometric means of urinary levels of MBzP in the U.S. population in two samples from California.

Data for the U.S. population is from the National Health and Nutrition Examination Survey, or NHANES. And the California data is from Biomonitoring California.

From the U.S. data, you can see that BBP exposure is present in different age groups of the U.S. population. From the California data, you can see BBP exposure is present in firefighters and pregnant women in California.

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DR. SUN: Next, we will be presenting the BBP carcinogenicity evidence, including human epidemiological evidence, carcinogenicity studies in animals and other relevant data.

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DR. SUN: For the human studies, I'm going to hand over to Dr. Hsieh.

DR. HSIEH: Thanks, Dr. Sun. My name is Jennifer Hsieh. I will present BBP's human carcinogenicity evidence. So far, two case control studies were

identified as having cancer epidemiological results for BBP.

The first study is a population-based case-control study conducted in Massachusetts from 1983 to '86 to study the association of occupational BBP exposure and breast cancer risk. The results show no significant association with breast cancer risk and probable past occupational BBP exposure as determined by questionnaire.

However, the study has limitations, including a lack of information of non-occupational exposures, and the use of cases of deceased individuals based on next-of-kin interviews with no mention of a number or percentage. This often increases inaccuracy.

Another hospital-based case-control study that examined the association between urinary metabolite monobenzyl phthalate level in the breast cancer incidence in northern Mexican women from 2007 to 2008 that found a significant inverse association. However, the study is limited, in that only a single urine sample was collected after cancer diagnosis. And this data allowed evaluation of past exposures.

Both studies has limitations. Therefore, currently, there is inadequate evidence of human cancer caused by BBP exposure available.

Next, Dr. Sun will continue the presentation on

the evidence of animal cancer data.

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DR. SUN: Thank you, Dr. Hsieh. So this slide is an overview of the BBP carcinogenicity studies in laboratory animals. Nine animal bioassays were identified and reviewed, including six feed studies in male and female F344 rats by the National Toxicology Program, or NTP, two feed studies in male and female B6C3F1 mice by the NTP, and one short-term study with IP injection of BBP in male strain A mice by Theiss et al. published in 1977.

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DR. SUN: We will start with rat studies. There were six NTP bioassays in male and female Fischer rats, all feed studies. Of NTP 1982, the male rat study was terminated early because the animals died prematurely from internal hemorrhaging. Therefore, we will only be discussing the female rat study of NTP 1982.

NTP 1997a and b were carried out at the same time in the same lab. The differences are that 1997a were regular cancer bioassays with every group of animals getting feed ad libitum while 1997b used 1997a as the ad libitum-fed part of the study and added new groups, which are weight-matched control groups, and feed-restriction groups. We will give you detailed information on study design later.

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DR. SUN: This slide shows the tumor incidence in female Fischer rats, NTP 1982. In the female rats, there were statistically significant increases of mononuclear cell leukemia, abbreviated as MNCL, in the high dose group with significant dose-related trend. Looking at combined leukemia and lymphoma, the increases were also significant.

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DR. SUN: Moving on to NTP 1997a male rat study. There were significant increases of pancreatic acinar cell adenoma and combined adenoma and carcinoma in the high dose BBP-treated male rats with significant dose-related trend. There was one carcinoma in the high dose group, and no pancreatic acinar cell carcinoma had ever been observed in untreated male Fischer rats in NTP feed studies.

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DR. SUN: Now, we're looking at NTP 1997a female rat studies. Two animals in the high-dose group had pancreatic acinar cell adenomas. Pancreatic acinar cell adenoma is rare in untreated female Fischer rats with a historical incidence rate of 0.2 percent.

Two animals in the high-dose group had urinary bladder transitional cell papillomas. While there was no

significant increase of the tumor, there was increase of the hyperplasia which is a pre-neoplastic lesion. Bladder transitional epithelium papilloma is a rare tumor in untreated female Fischer rats.

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DR. SUN: Here's a diagram showing you the design of the male and female studies of NTP 1997b. Overall, there were four comparisons made for each gender. The first comparison is essentially NTP 1997a. The second comparison was made between the weight-matched control and the high dose of NTP 1997a. The weight-matched control group of rats were given a restricted amount of food, so their weight matches the high dose group.

The third comparison was made between two groups that were both given restricted amount of food for two years, one control, and one treated with high dose BBP.

The fourth comparison was made similar to the third, only the animals were tested for three years or when the survival rate was decreased to 20 percent.

So in these studies in the male rats, increases of pancreatic acinar cell tumors were observed from NTP 1997a, as we mentioned, from comparison with the weight-match control, and from the three-year feed restriction comparison. In the comparison with the weight-match controls, we also saw increases of

mononuclear cell leukemia and adrenal medulla tumors.

In the female rats, increases of urinary bladder transitional cell tumors were observed in the feed restriction comparisons.

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DR. SUN: This table shows the tumor incidences in male rats in the first two comparisons of NTP 1997b. The P values are indicated in the columns of the controls. I have highlighted these two columns in purple to re-emphasize that of the three groups shown here, these two are from NTP 1997a. And we already showed you the significant increase of pancreatic acinar cell tumors on slide number 10.

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DR. SUN: This is the same table here. Only these two highlighted columns show the comparison between the high-dose group and the weight-matched control group. Again, the P values are indicated in the column of the weight-match controls. We saw increases of pancreatic acinar cell adenoma and combined adenoma and carcinoma, combined benign and malignant pheochromocytoma and mononuclear cell leukemia.

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DR. SUN: Here are the findings from the male rat study comparison number four, where the animals were kept

on a restricted diet for three years, or 20 percent survival rate, which was 30 months here.

A high percentage of animals in the BBP-treated group had pancreatic acinar cell adenomas compared to zero in the control.

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DR. SUN: This slide shows you the findings from the female rat feed restriction studies for three years. Four animals in the treated group had urinary bladder transitional epithelium carcinomas and two had papillomas. The carcinomas had never been observed in untreated female Fischer rats in NTP feed studies. And NTP considered this to be biologically relevant, because these are both rare tumors in female rats and because of the consistency of the neoplasm and the hyperplasia responses.

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DR. SUN: So far, we have presented the regular cancer bioassays in rats. There were also two co-carcinogenicity studies in rats, where the animals were given BBP and a known carcinogen. In the first study by Singletary at al., BBP was given by gavage to female SD rats. The animals were also given the carcinogen DMBA. The endpoints were mammary tumors.

In the second study by Kohno et al., BBP was given in feed to male Fischer rats. The animals were also

given the carcinogen DMAB. And the endpoints were prostate adenocarcinomas. In both studies, BBP did not increase the tumor incidence.

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DR. SUN: Now moving on from rat studies to mouse studies. Two NTP cancer bioassays and one short-term bioassay were identified. The NTP 1982 studies were two-year feed studies conducted in male and female B6C3F1 mice. And BBP was not associated with statistically significant increases of any type of tumor in male or female mice.

Another study was by Theiss et al. 1977, a 24-week study in male strain A mice, only looking at pulmonary adenomas. No increase in the number of lung tumors per mouse were seen with BBP.

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DR. SUN: Next, we will be talking about other relevant data regarding BBP carcinogenicity. The evidence includes data on genotoxicity, in vitro transformation studies, pharmacokinetics and metabolism, effects on breast tumor susceptibility and development, effects on cancer-related protein expression in the human live cancer cell line HepG2 and structure activity comparisons with two other phthalates.

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DR. SUN: First, we will start with in vitro genotoxicity findings. In mammalian species, BBP was positive in inducing DNA-based lesions in mouse osteoblast cells; inducing DNA single strand breaks in human HepG2 cell line; and inducing DNA protein crosslink in rat liver homogenate.

BBP was negative in assays testing for forward mutations in mouse lymphoma cells, sister chromatid exchanges, or chromosomal aberrations in Chinese hamster ovary, or CHO, cells.

BBP was tested in several mutation assays in bacterial species, and the results were negative.

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DR. SUN: Now, we're looking at in vivo genotoxicity evidence. In vivo BBP-induced sister chromatid exchanges and chromosomal aberrations in male B6C3F1 mice. BBP also induced DNA protein crosslinks in mouse hepatic cells. BBP was negative in the micronucleus assay and dominant lethal assay in mice.

In the in vitro transformation study, BBP tested positive in inducing morphological transformation of Syrian hamster embryonic, or SHE, cells.

Dr. Hsieh will take over from here.

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DR. HSIEH: Thanks, Dr. Sun. I will continue the

presentation on BBP's pharmacokinetics and metabolism. The evidence summarized here are similar in humans and rats. First, BBP was rapidly absorbed, distributed, metabolized, and eliminated within 24 hours following by oral exposure.

Next, the majority of BBP are excreted in urine or feces within 24 hours after treatment. Lastly, there is no long-term tissue accumulation of BBP occurred.

Next.

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DR. HSIEH: The scheme of BBP's metabolic pathways, which are adapted from the Wistar rat study is proposed here. Again, it is expected to be similar in human and rats. First step, BBP diester phthalate is hydrolyzed by lipases or esterase in GI tracts to two main ester monoester phthalate metabolite, monobenzyl phthalate, MBzP, and monobutyl phthalate, MBuP.

In human, MBzP is the major BBP metabolite. And the ratio of MBzP and MBuP is about 3 to 1. However, in rats, MBuP is the major metabolite.

Next step, these two monoester phthalate either goes through phase II metabolic conjugation or breakdown to the small molecule metabolite, which are indicated here in purple.

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DR. HSIEH: Now, I would like to move onto the topic of BBP's potential effect on mammary gland development and breast tumor formation using the following two slides. Before we start the discussion, it is worth noting that in the NTP animal bioassays and co-carcinogenesis animal study introduced in the previous slide, BBP was given to animal at around six to seven weeks, at the age when animal's mammary glands had already developed. The results show no increase in BBP-treatment related breast cancer incidence.

Here, we show the carcinogenicity evidence in mammary gland of female Spargue-Dawley rats offspring conducted by Moral et al., 2007 and 2011 on different BBP exposure window, including in utero and neonatal exposure prior to mammary gland maturation in molecular, cellular, and organelle levels.

First at the molecule level, BBP neonatal/prepubertal exposure elevate expression of gene involved in breast cell proliferation, communication and signal transduction. In general, BBP in utero exposure tended to reduce expression of genes involved in breast cell differentiation, gland lactation, immune-related responses, and apoptosis.

Next at the cellular level, the data show that BBP increases cell proliferation index of mammary gland

structure, such as terminal ductal structure, TD, and terminal end bud, TEB.

Finally, in the organelle structure -- level, BBP can also alter mammary gland morphology, increasing the number of terminal end buds. For example, these terminal end buds are sensitive to carcinogenic insults. Therefore, increasing the number of terminal end buds and alteration of cancer-related gene expression and gland structure in mammary gland of BBP-treated animals or their offspring could potentially elevate breast cancer susceptibility later in their life.

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DR. HSIEH: A number of studies, using experimental model systems, have shown that BBP can effect multiple stages of neoplastic transformation. Many of these studies have been conducted with human breast cell lines in vitro. Others have been conducted with human breast cell lines treated in culture and then injected into nude mice, and still others have involved use of a xenografted mouse model. BBP-induced alterations in micro-array gene expression profiles linked to these various stages of neoplastic transformation have also been reported in many of these studies.

The schematic figure here demonstrates the multiple stages of neoplastic transformation. In general,

the process begins with inducing cell proliferation and/or suppressing apoptosis, proceeds to tumor growth and progression stages, then angiogenesis, epithelial-mesenchymal transition, invasion, migration and eventually metastasis.

The studies reported by Hsieh et al., 2012 were done with a human breast epithelial stem cell line, known as R2d cells, and are indicated here with the black check-mark. These studies in R2d cells demonstrate BBP's ability to induce multiple stages of neoplastic transformation in vitro, including inducing cell proliferation, angiogenesis, epithelial-mesenchymal transition, invasion & migration. And in vitro/in vivo angiogenesis was measured by matrigel plug assay in BBP-pretreated R2d cell on xenograft mouse model. In vivo metastasis was demonstrated by R2d in athymic nude mice with BBP treatment to the mice.

Studies performed with the human breast cancer cell lines, MCF-7 and MDA-MB-231 cells are indicated here with the purple check-mark. Also, demonstrate BBP's ability to induce cell proliferation, angiogenesis, and invasion, migration in vitro. The ability of MCF-7 and MDA-MB-231 cells to induce angiogenesis in vivo was also demonstrated.

The alteration of micro-array gene expression

profiles also correlated with all the cellular neoplastic transformation in vitro and in vivo, in both non-cancer and cancer human epithelial cell lines.

In conclusion, these studies in human breast cell lines suggests that BBP has the potential to effect tumor growth, promotion, progression, and metastasis.

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DR. HSIEH: Now, moving on to the effects of BBP on the pattern of protein expression in a human liver cancer cell line, namely HepG2 cells, reported by Choi et al., 2010.

The results of this proteomic analysis shows the expression pattern of some proteins involved in tumor progression, metastasis, and oxidative stress were altered by BBP treatment. These changes in protein expression was validated by the authors using western blot analysis. In this same set of experiments, Choi et al., 2010 also assessed the level of DNA single strand breaks in HepG2 cells treated with BBP, reporting an increase. This was reported in an earlier slide summarizing the positive genotoxicity findings of DNA single strand breaks in HepG2 cells in vitro.

The table here lists some of the proteins involved in tumor progression, metastasis, or oxidative stress, for which the expression levels were altered with

BBP treatment. The table represents the brief version of Table 21 in our HID.

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DR. HSIEH: Now, moving on to the structure activity comparison of BBP and its two other phthalate analogs, diethyl hexyl phthalate, also known as DEHP, and diisononyl phthalate, also known as DINP. The chemical structures of these chemicals are illustrated in the bottom of the slide.

Among them, DEHP has been listed as a carcinogen in Proposition 65, and also be classified by IARC as a 2B carcinogen, and U.S. EPA as group B2 carcinogen. And DINP is the first chemical candidate on today's meeting agenda.

To sum up, the overall evidences indicates they do share some common tumor sites. The increase mononuclear cell leukemia and pancreatic tumors were observed in BBP, DEHP, and DINP-treated rats.

In addition, the elevated same cell type tumor, transitional epithelial tumors in renal and bladder were observed in both BBP and DINP-treated rats.

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DR. HSIEH: This slide concludes and summarized the overall evidence on BBP and its two other phthalate analogs, DEHP and DINP, share a lot of common mechanisms from left to right, such as genotoxicity, in vitro cell

transformation, and several nuclear receptor mediated pathways, including peroxisome proliferator activated receptor, PPAR alpha, and gamma, estrogen receptor, ER, aryl hydrocarbon receptor, AhR, pregnane X receptor, PXR, mediated mechanisms and anti-androgenic and anti-steroidogenesis mechanisms.

To sum up, the section here, it is worth noting that most of the receptors, genes, and proteins discussed in our presentation are existing in each of the target tumor sites induced by BBP exposure in animals.

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DR. HSIEH: Moving on to next section, BBP's possible mechanism of actions:

First, BBP could promote tumor formation through a genotoxic mechanism, such as inducing DNA and chromosome damage. Next BBP's possible mechanism is the AhR-mediated mechanism. For example, BBP's effects on tumor progression has been shown in MDA-MB-231 cells, which are mediated by the non-genomic AhR receptor type pathway through signal transduction cascade to induce target gene expression, then tumor progression occurs.

Another BBP's possible mechanism is the ER-mediated mechanism. For example, BBP's effects on increasing human breast cell proliferation are mediated by classic genomic ER-mediated mechanism to induce ER target

gene expression, such as progesterone receptor and cyclinD3, then cell proliferation occurs. BBP's effects on causing angiogenesis in MCF-7 derived cells are mediated by non-genomic signal transduction ER-mediated pathway to activate several kinases then to increase vascular endothelial growth factor expression, then induce angiogenesis.

BBP's effects on causing epithelial-mesenchymal transition in R2d cells were also mediated by non-genomic ER-mediated pathway to activate growth factor receptor and kinase signal transduction cascade, to increase vimentin gene expression, then the epithelial-mesenchymal transition occurs.

Next mechanism PPAR alpha- and gamma-mediated mechanism has been proposed as BBP's possible mechanism for pancreatic acinar cell and urinary bladder transitional epithelial tumor formation in rats.

BBP's anti-androgenic effect. Some evidence indicates that BBP can work as androgen receptor antagonist. For example, Androgen receptor activity induced by dihydrotestosterone can be reduced by BBP in both yeast and mammalian cells. And also, evidence has been shown that BBP has an effect on steroidogenesis disruption. For example, a number of studies reported that in utero BBP exposure could decrease the level of

testosterone in male rats offspring.

Next, the epigenetic mechanisms of BBP has been shown as a study reported that MCF-7 cells treated with BBP can decrease the methylation of CpG islands in the promoter region of ER alpha gene.

Again, the receptors, genes, and proteins discussed in our presentation here are existing in each of the target tumor sites induced by BBP exposure in animals.

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DR. HSIEH: Okay. Data on the carcinogenicity of BBP has also been reviewed by some authoritative bodies and its classifications are summarized here.

First, U.S. EPA classified BBP as a class C chemical, which we represent as a “possible human carcinogen” in 1993. However, currently, BBP is still under re-assessment by U.S. EPA.

Second, IARC classified BBP in Group 3 chemical, which stands for “not classifiable as to its carcinogenicity to human” in 1999, based on the evidence of the carcinogenicity of BBP in human was inadequate, and the evidence in experimental animals was limited.

Last, BBP has not been classified as to its carcinogenicity by either U.S. FDA or NIOSH.

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DR. HSIEH: In the following two slides, I would

like to briefly summarize BBP's carcinogenicity evidence that we compiled in our HID.

First, two case-control studies of breast cancer, both with limitations in study design. No positive associations between BBP and breast cancer risk has been found in these two studies.

Next, in our review of animal carcinogenesis data, BBP was reported to statistically significant increase in tumor incidence in Fisher rats at mononuclear cell leukemia in male and female; adrenal medulla tumors in male; pancreatic acinar cell in males; and, the pancreatic acinar cell carcinomas are also considered rare in male rats.

In addition, BBP was reported to increase two tumor sites, which tumor incidence increased not statistically significant, but tumor types considered to be rare.

First, bladder transitional epithelium papilloma and carcinoma in female rats are considered rare, and also bladder transitional epithelium hyperplasia.

Second, pancreatic acinar cell carcinomas in male and carcinomas and adenomas in female rats are considered rare.

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DR. HSIEH: Continuing on the summary conclusion

from the other relevant data. BBP induced multiple positive genotoxicity in mammalian cells, also induced morphological cell transformation in SHE cells in vitro, and alter expression of carcinogenesis associate genes and proteins.

Next, BBP demonstrated the ability to induce multiple stage neoplastic transformation in human breast cell lines. The effects are intermediated through AhR, ER-mediated mechanisms. Finally, BBP shares common tumor sites with its phthalate analogs, DINP and the known carcinogen, DEHP.

That concludes today's presentation on the evidence on the carcinogenicity of butyl benzyl phthalate.

Next, we will take questions and comments.

Thank you.

CHAIRPERSON MACK: Thank you, Dr. Hsieh.

Does anybody on the Committee have any questions about clarification of the presentation?

It must have been really clear.

COMMITTEE MEMBER THOMAS: Just one. I wonder whether you could comment the Upson paper that was distributed to us just shortly before this meeting, the one on endometriosis?

DR. HSIEH: Upson paper. Okay, we have a back-up slide. So can we show you?

1 That Upson paper shows -- we have an
2 epidemiologist in our branch. She will be the better
3 person to answer that question.
4 DR. KAUFMAN: Hi. I'm Dr. Farla Kaufman.
5 So this study is a recent study. It's a case
6 control study. And it was one of the few studies that
7 looked at this and saw an increased risk. But according
8 to the statistics, it wasn't significant as it included
9 one in the odds ratios confidence intervals. I don't
10 know. What would you like to know about this study?
11 COMMITTEE MEMBER THOMAS: Well, first of all, I
12 mean, it's not obviously relevant to us in terms of cancer
13 risk. The focus being endometriosis. But the general
14 disruption of hormone balances I think is a concern, and
15 it seemed to -- you know, different elements of this
16 family of chemicals had a variety of effects, some
17 positive and some negative.
18 Should we be concerned that -- in your view,
19 should we be concerned even though it's not direct
20 evidence about cancer, about the potential implications of
21 these hormonal changes?
22 DR. KAUFMAN: Dr. Sandy will answer, but I think
23 it's been shown that there is a connection between --
24 there's an increased risk of ovarian cancer in women who
25 have experienced endometriosis or have that condition. So

I think that link is pretty strong and relevant here. If these studies did show a significant risk of endometriosis with exposure to BBP, I think that would be important.

However, I don't think the epidemiology studies are as significant to indicate that.

DR. SANDY: Thank you, Dr. Kaufman. And I just wanted to add, the reason those -- I believe we may have sent two new studies, is because -- well, maybe just one. We sent any studies that had been published since the HID was sent to you. And that was just one study. As Dr. Kaufman mentions, we do discuss in the hazard identification document, there's a section on endometriosis and studies looking at the relationship between BBP, endometriosis. And then we also discuss the endometriosis link with ovarian cancer. So we are just providing it to you as addition -- one additional study to walk through.

CHAIRPERSON MACK: Dr. Dairkee.

COMMITTEE MEMBER DAIRKEE: I have a question about the two other epidemiology studies that were negative correlations with breast cancer that were in the HID. And in your opinion, are these studies better designed or -- because there was some comment about weaknesses in design. I'm not an epidemiologist, that's why I'm asking this question.

DR. KAUFMAN: I think that those were the epidemiology studies looking at breast cancer?

COMMITTEE MEMBER DAIRKEE: Correct.

DR. KAUFMAN: I'm sorry, I didn't look at them. I just reviewed these recently. I think Dr. Beaumont has reviewed those studies, and he can address your questions.

COMMITTEE MEMBER DAIRKEE: Thank you.

DR. KAUFMAN: Thank you.

DR. BEAUMONT: Hi. I'm Dr. Jay Beaumont, and I didn't quite understand your question.

COMMITTEE MEMBER DAIRKEE: Okay. So in the breast cancer studies, they're showing a negative correlation with BBP. They're saying there's less --

DR. BEAUMONT: Well, one did.

COMMITTEE MEMBER DAIRKEE: Yes.

DR. BEAUMONT: But in that one study that found a negative correlation was the study that had only one urine sample after case -- cancer case diagnosis, and no historical data.

COMMITTEE MEMBER DAIRKEE: Correct. And the other studied show no correlation, I believe.

DR. BEAUMONT: Of any kind, right.

COMMITTEE MEMBER DAIRKEE: Right. So my question really is, is the endometriosis study better designed than the breast cancer studies?

DR. BEAUMONT: Oh, I couldn't speak to better or worse. They're different studies, but some have shown an association between BBP exposure and endometriosis. And there is an association in the literature between endometriosis and ovarian cancer, but the causality of that is not settled at all. It could be that the same thing is causing both endometriosis and ovarian cancer, but there is an association.

CHAIRPERSON MACK: Does anybody else have any clarifying -- sorry, yeah.

Sorry about that. Does anybody else have any clarifications?

No, it seems not. So let's proceed to the presentations by Alan Olson to be followed by Ann Claassen.

(Thereupon an overhead presentation was presented as follows.)

MR. OLSON: Good afternoon, Mr. Chairman and Committee members. Thank you for the time this afternoon.

I'm the corporate product stewardship director for Ferro Corporation. We're headquartered in Cleveland. We're the only manufacturer of BBP in the U.S. today. BBP has been on the market for about 50 years now, having been brought on the market by Monsanto in the seventies -- or the sixties.

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MR. OLSON: Basically we sell this as a polymer additive for several types of plastic. It winds up primarily in the built environment. We don't sell BBP to consumers today.

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MR. OLSON: Again, I mean I've been a regulator myself in Ohio for probably eight years, so I understand, you know, going through the process. And part of the process here is the relevant weight of evidence from all the available test data. And we recognize -- you know, I again recognize the process, but point out, you know, IARC looked at the NTP studies, put it in Group 3 as not classifiable for cancer.

The European Chemical Bureau, which is the precursor to ECHA, the REACH agency, spent probably several years, maybe five years, in its risk assessment of BBP and found it to be not genotoxic and not carcinogenic.

And I think we've discussed the three NTP studies. But when EPA did look at BBP under IRIS, I think it only had the 1982 study. So when it relooks at it, it will have the benefit of the other two NTP studies and others published since then.

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MR. OLSON: And then finally, we had submitted

comments in January of this year, and again more comments after the HID document was published. In our submissions and on our comments today, we'll speak to a number of studies not necessarily reviewed or listed in the HID that we think -- that are important, and that also complement the HID document, insofar as adding to the body that you need to consider for weight of evidence.

So Ann Claassen, who will follow me, is our outside counsel on this issue, and then John Butala is the person who will follow Ann. He's conducted toxicology studies on phthalates. He's worked in the area for probably at least 20 years. And he had put most of our technical comments together. But within there, there are comments from Errol Zeiger who had worked at FDA, and then NTP. And also Eugene McConnell, who had worked at NTP.

So when we've looked at the sum of the studies and the weight of evidence, we see that BBP should not be listed as known to the State to cause cancer.

But thank you, you know, for your time. I'll introduce Ann Claassen from Latham and Watkins.

CHAIRPERSON MACK: Thank you, Mr. Olson.

MS. CLAASSEN: Thank you, Alan.

Thank you, Dr. Mack and members of the CIC. I am Ann Claassen with Latham and Watkins, counsel to Ferro -- and I can't make this work.

Am I using the wrong one?

Yes.

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MS. CLAASSEN: Okay. You had quite a bit of discussion about criteria for DINP, and I'd like to revisit those again for a moment in the context of BBP, which is a different situation. We're not looking at whether tumors seen in animals are relevant to humans. We are looking at whether the weight of the evidence in the animals is sufficient to say that BBP is known to the State to cause cancer. And that is defined for you in the statute. It is within the meaning of this chapter of Prop 65. It's its own standard, not EPA's or anybody else's.

And it is a "clearly shown" standard, and also is to be shown through scientifically valid testing, not any speculation about what may be happening, but what you've actually seen in testing.

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MS. CLAASSEN: Under your own criteria, again as Alan said, it is a weight of the evidence evaluation, based on all evidence, the complete database that -- of scientifically valid testing and relevant to the issue of carcinogenicity.

You are allowed to look at in vitro data definitely. However, your criteria state that whole

mammals are the most pertinent, so are move heavily weighted, whole animal studies.

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MS. CLAASSEN: And with regards to those, the general presumption is that you want to see the tumors in two genders of a species, or in two distinct species, or two different experiments in different laboratories with different protocols.

You can use lesser evidence than that, if there's some supportive evidence, but there's a fairly high bar for how supportive that has to be. And, of course, you want the tumors to be statistically significant not something that can be explained by chance.

We believe that the data for DINP -- excuse me, last chemical -- the data for BBP do not rise to this level. And Mr. Butala is going to address the data on that. But before he goes up, I just would like to say for a moment on the biomonitoring, because Dr. Bush asked about this with DINP, the data that you've been shown are the levels in micrograms per liter in the urine. If you could convert those with creatinine excretion, and convert to what the actual exposure was, which we do have the data to do, the differences largely disappear between adults and children between the various categories.

Thank you very much.

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DR. BUTALA: It's a pleasure to be here today and an honor. Thank you for allowing us to comment.

I will be going over a fair bit of the toxicology information again with --

DIRECTOR ALEXEEFF: Could you pull the microphone a little bit closer, please?

DR. BUTALA: Of course. Is that better?

DIRECTOR ALEXEEFF: Yes.

DR. BUTALA: And on overview, we do believe, as you've heard, that the weight of evidence is not sufficient for determination that BBP has been clearly demonstrated to cause cancer. There are three reports, three bioassay reports, from the National Toxicology Program, that -- the three reports, of course, are reports we've been hearing about, and we have a bit more to say about those. I think we're fortunate to have that much information from -- in bioassays.

There are the two limited epidemiology studies, and then the last that were negative, we heard about those. And in addition to my comments here today, we have submitted comments from Dr. Errol Zeiger and Dr. Gene McConnell. And I will introduce you to those people.

Dr. McConnell has a 40-plus year career as a pathologist, as an animal pathologist. He was the former

head of the pathology branch at the NTP. And, at that -- in that position, he directed the NTP toxicology research program and testing program, again as well as heading up their path branch.

We asked Dr. McConnell to take a look at the HID that you've given us, and the three 3 NTP reports on BBP. And he has commented on those. And it's his comments that I'm going to be referring to here. And the tables in this report are largely -- and the tables I'm going to present today are largely from his reports.

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DR. BUTALA: And you will be able to find details that support those tables in his report. His conclusion is that the weight of evidence does not support listing BBP as a carcinogen under Prop 65.

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DR. BUTALA: Now, although there was a statistically significant incidence increase in mononuclear cell leukemia in the female rats in the NTP 1982 study. And again, we're going to refer to these studies as 1982, 1997a, 1997b. There was no such increase in female rats in the other two studies. No such increase meaning statistically significant.

The increase incidence in mononuclear cell leukemia was not seen in male rats of any of the studies,

and I'll go into some detail on that. You've heard a few minutes ago that the 1997b study showed an increase incidence of mononuclear cell leukemia in both males and females, all right.

But the actual NTP report does not say that. The actual NTP report says that there are, I'm quoting now, "No treatment-related mononuclear cell leukemia effects", due to BBP in the 1982 studies.

And even though there was an increase, they lay that increase off, and this is in their report, to an artificially depressed incidence of mononuclear cell leukemia in the control values. Okay. And that is explained in some detail in the actual report.

That being the case, that means that MNCL only showed up in first study and only in females. And much of the criteria that we're all talking about here is a bit of a counting exercise, how many species, how many sexes, et cetera. Okay. So we don't have MNCL in more than one species.

The same thing, to save time, occurred -- occurs with the pancreatic tumors -- I'm sorry, the -- with the adrenal tumors. Turning our attention now to pancreatic tumors. Again there was a statistically significant increase of pancreatic cell tumors in the male rats in the '97a study.

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DR. BUTALA: But there was no increase, according to NTP, in the 1997b study, with the exception of the weight-restricted studies. That's where there was no increase. There was an increase in the non-weight-restricted animals. There was no increase in female rats of the studies. And I think the point this raises is there needs to be some consideration as to what is the relevance to human health of tumors that occur in ad libitum fed animals, but not in weight restricted when there is a body of information that says that in the case of pancreatic cell tumors, caloric restriction does have a suppressive effect, and that's one large area to consider.

And then overlaying that is what does that have to do with butyl benzyl phthalate in particular in the context of that. I don't have an answer for that, but I think that is a consideration. There was an observation of pancreatic tumors in mice.

A point of clarification. We heard that in these series of studies at NTP with butyl benzyl phthalate, there was an observation of pancreatic cell carcinoma, and that had never happened before. I don't know if that's the case, or at least not in controls. But I do know in these studies that in the follow-up study, the 1997b study, there was a carcinoma in the untreated controls,

and there was also in that study a carcinoma, one carcinoma, in the tested animals. So the incidence was the same.

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DR. BUTALA: Now, to the adrenal tumors, the HID states that there was an increase in adrenal medulla pheochromocytomas in females in a 1982 study. But this again was not the finding that was reported by NTP. In the actual statistical analyses table in the 1982 report, there is no statistically significant increase indication with that particular lesion. In fact, the dose response data are actually negative for the administration. The control animals had a higher incidence than the dosed animals.

There was in the 1997a and b studies no statistically significant increase in tumors laid onto the test compound, BBP. And again that is for the same reason I gave a few minutes ago. There was a suppressed incidence in control animals, that according to the NTP scientists accounted for an artificial and artifactual statistical elevation.

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DR. BUTALA: We come now to urinary bladder tumors. And this one is -- it's a bit of a story to listen to. And that is that in the initial study, the

1982 study, there were no urinary bladder tumor findings of significance. In the 1997a study, there was an increase in -- there was an increase in urinary transitional tumors in female rats that was not statistically significant, and the NTP did not consider this a positive finding.

Now, what I wanted to say about that is that, once again, in the actual NTP report, the description of the increased incidence of these bladder tumors in the female animals was considered not a neoplastic finding, because they list that in the report separately and it did not appear there. It was classified as equivocal in meaning and not a positive response. That's really the only thing that can be said about it there. It was -- if anything, it was not positive for bladder tumors in that study.

McConnell -- Dr. McConnell incidentally considered the bladder changers -- bladder changes likely due to chronic irritation in the 32-month study via physical damage to the epithelium, so a mechanical irritation of the epithelium.

I would ask you to ponder that for a moment. The animals -- the females that developed this condition were receiving 24,000 ppm butyl benzyl phthalate daily for 32 months. And 32,000 ppm is about 1,200 milligrams per

kilogram per day, and that is a massive dose for 32 months.

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DR. BUTALA: Turn my attention now to the genetic toxicology. And Dr. Zeiger wrote a report, and I would leave it to you to consider what you -- what that report -- what the impressions of that report were on your studying of it. I would tell you this though, that when Dr. Zeiger made his evaluation of all of the studies, I think he ran into the same thing that I've heard described here earlier today, and that is that full reports on each of the studies were not available.

And what he did -- and that will help understand this table. What he did in that situation is that in those circumstances where there was not enough information available to support or sustain a finding of a positive mutagenicity finding, he did not count that report as a positive finding, and that is how these tallies are run. I want to be very clear, that's how the tallies are made.

For instance, there are several studies for which only an abstract was made available. And I think that's all you all had to work with as well. In that case, and I think this situation came up earlier this morning in one of the comments from your OEHHA staff on availability and clarity and completeness of data, when only an abstract

was available, Dr. Zeiger did not know anything about the dose response, he did not know anything about the actual methodology, or whatever data calculations and statistical analysis were performed. So he would not sustain that report as positive, if that's what it actually said in the abstract.

Here we have seven positive studies and 21 studies that are not positive.

CHAIRPERSON MACK: Dr. Butala, it's me. You're kind of running a long time over the 15-minute mark, so if you could try and be as succinct as you can.

DR. BUTALA: I will try to do that. Thank you.

I think we need to consider just two more points here. One again is on the weight of evidence, and that is there's no consistency in the tumor findings. I mean, that's the main thing I see here. The tumor findings in the suite of NTP studies were not able to be replicated from one study to the next, to the next. And I believe that does factor into your considerations.

The weight of evidence is that butyl benzyl phthalate, based on that and details of course are in Zeiger's report, is that it's not genotoxic. We had the two published epidemiology studies you heard about. And we believe taken together that the weight of evidence suggests that BBP is not carcinogenic.

I would also like to add two more quick comment sentences. One is that on this business of exposure, you heard Ann Claassen talk about the ability to transform urinary levels into actual, you know, body doses, and from the biomonitoring study. I did that calculation, and, you know, many of the studies that were done here by the NTP were done at 1,200 parts per million. And that turns out to be about 500 milligrams per kilogram per day. That's the dose the animals got. The urinary levels that we saw in the HID report are anywhere from a half a million to 1.1 million-fold below that.

I guess on mode of action I would say that, yes, you know, there was an array of in vitro assays that talked about activations of genes and proteins that might be associated with some forms of cancer, particularly mammary cancers or estrogen-influenced cancers. I would point out that in all of the NTP assays, the apical assays for those kinds of cancers, none were positive. In fact, and this is from the NTP reports, there was a negative association in the NTP assays in cancers in preputial cancers, in pituitary cancers, and cancers of the clitoris. And in the case of mammary cancers, there was no elevation of mammary cancers in any study.

And the context of that is that the mammary cancer incidence in the Fischer rat is about 51 percent in

1 untreated controls. I considered that to be a hair
2 trigger for the development of mammary tumors.
3 If butyl benzyl phthalate could produce mammary
4 tumors, administering it to rats who already enter this
5 study with a 50/50 chance of developing it and not having
6 it developed, I think is a strong indication that BBP does
7 not have the potential to produce mammary tumors.
8 My final comment is to draw your attention to the
9 report we gave you from Dr. Timothy Zacharewski. This has
10 relevance to comments that the staff just made a few
11 minutes ago. Dr. Zacharewski, you should be familiar with
12 him. He is coming off of an assignment with the EPA to
13 advise them on the suitability of high throughput in vitro
14 assays in omics data for predicting long-term effects,
15 particularly these studies. And he said, and it's the one
16 sentence I will read to you. He specifically talked about
17 the studies that were under consideration here for duct --
18 breast duct formation.
19 And that is the authors of the study concluded
20 that, "The modest increases butyl benzene -- that BBP
21 produced did not include the formation of duct-like
22 structures and solid masses in response to BBP". Those
23 did not form, as opposed to something like bisphenol A,
24 which did cause that formation.
25 And with that, Dr. Zacharewski concluded that

these type of studies have substantial limitations. And I will end with that, and thank you very much for your presence -- for your patience.

CHAIRPERSON MACK: Thank you, Mr. Butala.

I'll ask the members of the committee if they have any questions for any of the speakers?

Hearing none. May I ask Martha or John, do you have anything to say in response?

DR. SANDY: I think we do.

CHAIRPERSON MACK: Not surprised.

DR. SANDY: I believe the presentation we just heard with the table on the MNCL female rat calls for the -- it was Technical Report 231, which is, what we called NTP 1982, it looks to me like it says the female findings -- OEHHA called them positive and NTP called them negative on the slide we just were presented.

Yet, the conclusion in that NTP report was that BBP was probably carcinogenic for female F344 in rats causing an increased incidence of mononuclear cell leukemias.

You can tell that this is an early report by NTP, so they're not using the levels of evidence we're used to hearing clear, some, equivocal, et cetera. They call this probably carcinogenic.

And then on that same chart for the males, NTP

did not evaluate the male study in 1992, because of excessive toxicity.

And I believe we have a few other things, but I'll ask the chair if we may go on.

CHAIRPERSON MACK: Yes, go ahead.

DR. BUDROE: I would just like to note that in the HID Tables 12, 13, and 14, where most of the -- where the genotoxicity results are displayed, most, if not all, of the positive studies were either published in the peer-reviewed literature or they are in NTP reports.

CHAIRPERSON MACK: Does that conclude your collective thoughts?

DR. BUTALA: Are you addressing me?

CHAIRPERSON MACK: I'm not addressing you, Mr. Butala. Actually, you've had your shot.

DR. BUTALA: I thought so. I just thought that perhaps there were questions for me.

CHAIRPERSON MACK: No. Thank you very much.

Is there a point to be made.

DR. SANDY: I don't know if it's -- yeah. We're -- if you have any questions of us, we'll be happy to answer.

CHAIRPERSON MACK: Then let's proceed, yes.

Thank you. You should be in front of me.

Okay. Let's go ahead with the Committee and

we'll start with David.

COMMITTEE MEMBER EASTMOND: Okay. Well, thank you. And I actually appreciate the presentation but Dr. Butala, in that there was quite a difference in -- in the document, it appears that there's a lot of consistency, but as he showed when you really dig into the data there's tremendous inconsistency between studies.

And that ends up being -- so let me go through and I'll just go through them one by one kind of as highlighted. But from my reading, there was a significant dose related increase in the female rats in the NTP study 1982 for mononuclear cell leukemia. That increase was not seen in the 1997a study, the first one, which was ad libitum feeding. It was seen in the b study, but only because the control levels had decreased substantially.

Now, depending on how you want to interpret that -- so as we talked about in the last one, this is a tumor type that's highly variable. The incidence here is well within the middle part of the range we talked about in the last group. Remember the range went up to like 60 percent. We're now at 27 on this one. So I didn't put a lot of stock in the mononuclear cell leukemias because of the variability that's seen in that tumor type.

The adrenal medulla tumors, there was a significant increase seen in the weight-match controls

when compared to the high dose, but this increase was not seen in the treated animals when they're compared to the ad libitum control. So again, it's one of these where the control values decreased. Now, that's one of the advantages of doing a weight matching is you will reduce your spontaneous, but it wasn't seen in other studies as well, so there's a lot of inconsistency on that point.

The urinary bladder tumors are actually more interesting. They're non-significant increase is seen in the female rats at the 32-month study, but you see a dose-related increase in hyperplasia, and bladder tumors are rare in untreated female rats. A does-related increase in hyperplasia was seen in the NTP 1997a study. Only a minor increase in papillomas was seen in the study. These are likely treatment related but not -- in my view, not significant -- sufficient to list this as a con basically.

The pancreatic acinar cell tumors are more challenging in some ways. Basically, there was no increase seen in the 1982 study in the female rats. There was an increase seen in the male rats in the 1997a study. This was entirely due to adenomas, one carcinoma, and this was only seen at the high dose -- increases only at the high dose.

As it says in the NTP study and indicated by the

presenters, there was a -- they've never -- basically, a carcinoma had never been seen to that point in a control rat. Except in the next study the 1997b study, there was a carcinoma in the control. So it's a little misleading, in that these parallel studies one of them they emphasize how important it is they've never seen a carcinoma. And the next hand, they actually see one in their controls.

So basically, you've got this -- this is considered a rare type of tumor in general, but not in this particular study. The control values were six percent. Three of the 50 animals had this particular pancreatic tumor, which for me suggested something is unusual about the particular animals or treatment or, et cetera.

I actually did a little more background in looking about this into this tumor type. It's not often induced by basically chemicals in the NTP studies, but they -- it is one that's heavily influenced by diet. Okay. And so although this was seen in the NTP 1997a where the animals were allowed ad libitum to eat feed, in the weight-restriction study, which was the parallel study where they restricted 24 months no increase in this tumor was seen.

So the parallel studies one has a significant increase at the high dose. The next one at 24 months

1 doesn't see any increase at all. When you go out to 32
2 months, there were, I believe it was, three animals
3 developed this type of tumor, but it was not statistically
4 significant. So my take on this is that there's a lot of
5 inconsistency in this particular tumor type. I might also
6 add that this tumor type is the one that's induced by corn
7 oil in Fischer 344 rats. So this is the one. So it's
8 very influenced by diet. Both dietary restriction drops
9 it down, corn oil and safflower oil actually induce this
10 particular type of tumor.
11 So this one, I think, is interesting and
12 suggestive, but I don't think it's sufficient to list.
13 One thing I might mention that the conclusions of the NTP
14 1997a I thought are important. And they refer to this --
15 NTP has these specific sort of definitions. So clear
16 evidence is their highest evidence of association. Some
17 evidence is the next one. And these pancreatic tumors
18 they considered to fit into the some evidence category,
19 which -- anyway. In the female rats they considered
20 equivocal evidence for that particular tumor type. And
21 some evidence, because of the transitional epithelial
22 papilloma in the urinary bladder.
23 So basically, as indicated by the presenter, for
24 me there's enough variability in this that makes me quite
25 concerned about listing, just because of the different

studies don't see the same consistent results. And so, you know, in my mind, certainly the results weren't clear enough for me to consider it clearly shown to cause cancer.

CHAIRPERSON MACK: All right. Dr. Dairkee.

COMMITTEE MEMBER DAIRKEE: I'm going to address the mammary gland issue a little bit. Although, there were no tumors detected there, but I feel the in utero induction of cell proliferation in the mammary gland is a concern. The fact that it is positive in the E-screen, which is an endocrine disruption screen, indicates that that might be something to be related to cancer.

There's chromosomal aberrations that have been observed in vivo again in the bone marrow of mice. So it may not be genotoxic to bacteria, to salmonella, but it does affect the chromosomal integrity of mammalian cells. And, of course, there's a lot of data on gene expression changes, which have been confirmed by proteomics showing that many of the hallmarks of cancer are induced by BBP.

And again, the fact that it induces angiogenesis, which promotes tumor growth is also a concern. And this is kind of what my take is on this chemical.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: Can I make one more comment on the genotoxicity. There is evidence for

genotoxicity. Although, it's not overwhelming. The doses where you saw the chromosomal aberrations in the NTP bioassay was at 5,000 milligram per kilogram dose, given IP, by intraperitoneal injection. The LD 50 in mice is somewhere about between 3,000 to 6,000 milligrams per kilogram, so you're really close to that LD 50 range where you see the chromosomal aberrations.

So, you know, it certainly was reproducible and it's there, but it's about roughly nine times higher than the dose that was given -- a dietary dose than was given in the bioassay. So it's quite a high dose in that particular study.

CHAIRPERSON MACK: Can I just ask you, David, to tell me again what your opinion is about the two-year 1998b feeding study, which both male and females showed hepatocellular carcinoma increases?

COMMITTEE MEMBER EASTMOND: I don't think we've got hepatocellular carcinomas in this case. Are we -- that's acinar. That's the kidney --

CHAIRPERSON MACK: It says seven at 4,000 ppm concentration in seven out of 67.

COMMITTEE MEMBER EASTMOND: Let me see if I've got --

CHAIRPERSON MACK: I'm sorry. I'm sorry. I screwed up. No. Did I screw up? This is DINP or I'm

still looking at --

COMMITTEE MEMBER EASTMOND: Which page are you on?

CHAIRPERSON MACK: Oh, I'm sorry. My mistake.

COMMITTEE MEMBER EASTMOND: Yeah, this one didn't have a liver.

CHAIRPERSON MACK: I've got the wrong page. Excuse me.

So, Duncan.

COMMITTEE MEMBER THOMAS: I'm afraid I don't have a whole lot to add. I'm not about to comment on the biology, that being far out of my expertise. And the only comment I would like to make about the toxicology, the animal carcinogenicity, is that as I sit here I worry about the multiple comparisons problem. This is, of course, a recurring theme any time we look at these kinds of data.

What I don't think we want to do is take the single strongest finding and do a Bonferroni correction for it, because we're not here to ask whether liver tumors in rats are significantly associated in this study. What we're asking is, is there a general pattern of association of any cancer with this chemical that is minimally consistent, meaning that we see it in multiple studies. We see it in multiple species. We see it in both sexes.

1 That sort of thing. Now, if that were a well defined
2 criterion, then we could compute the test statistic and we
3 could do some sort of a permutation test or something like
4 this to address the significance of that pattern of
5 cancer.
6 Now, there are near infinite number of such
7 criteria that we could come up with to formalize this
8 notion, so I'm not suggesting that as a practical thing
9 that staff should do. Instead, we're falling back on our
10 judgment, each of us as individuals, to decide whether or
11 not the pattern that we're seeing here is -- has
12 sufficient degree of consistency and biological
13 plausibility to rise to the standard that's written down.
14 And I'm having a hard time figuring that out, in
15 this case. I don't see a clear pattern of the same cancer
16 being represented in both sexes consistently. We have one
17 cancer that appears the -- I guess it's the MNCL that we
18 see in both sexes, but not in the same study, and others
19 that we see in one gender but not the other gender, or in
20 one -- or anyway, broadly inconsistently, but there's
21 enough of it to be worrisome. So I'm still undecided and
22 look forward to further discussion amongst the Committee
23 to help educate me about this.
24 So to the extent that I have any expertise to
25 offer, it would be about the epidemiology and there just

isn't any epidemiology, so that makes my job easy. Or at least there's almost no epidemiology. We have two very weak studies that were amongst those that were discussed in the HID, both of them with many limitations, neither of them with any significant positive associations, and indeed generally negative.

And then the endometriosis study, which was just published, shows again a pattern of inconsistent findings across about a dozen different related chemicals of which, if I have it right, there is one chemical that is the same as the one we're talking about, although it's not spelled the same way.

And that one shows a null association, neither positive nor negative. The one which was mentioned by the staff earlier this afternoon shows a non-significant positive association, so that's a little worrisome. But all of the two or three significant findings are all in the other direction.

Nevertheless, that creates, in my mind, an image of a class of chemicals that are doing something to the endocrine system that worries me, given how much we know about its association generally with various cancers. But that's not direct evidence that I think this committee should give very much weight to.

So all in all, I'm conflicted. At this point,

though, I would be hard pressed to make a strong statement that this chemical is known to the State clearly to cause cancer, and even if I don't say in humans.

CHAIRPERSON MACK: Jason.

COMMITTEE MEMBER BUSH: I really don't have anything to add, other than perhaps one query for the HID report. And following up with some of the concerns earlier about the estrogenic potential of these chemicals. In Table 22, you've got a partial list of MCF7 and ZR75 cell proliferative studies. ZR75, as you indicated, is known to be more estrogenic, but are you able to comment on how to break those out a little bit. I mean, was ZR75 more responsive in these studies? You're merging the data there, and it's hard to figure out what's actually going on with that table.

And if you can't make comment, that's all right, too.

DR. HSIEH: Yeah, it's mentioned in the original paper. I take the original statement from the paper in Jobling et al. 1995. In their lab they tested two different cell lines, ZR75 and MCF7 cell, and they found out it's a more response to estrogen treatment in the ZR75 cell line compared to MCF7 cell. They didn't provide a clear explanation in their paper, so I cannot answer. But they did have -- they do have evidence and it's not

published.

COMMITTEE MEMBER BUSH: Okay. Thank you.

CHAIRPERSON MACK: Dr. Zhang.

COMMITTEE MEMBER ZHANG: I have a question for Dave. My understanding is for the mononucleated cell leukemia never reported in male rats, right, no matter in NTP maybe '82 study or 1997a and b, is that the case? I was trying to find it.

COMMITTEE MEMBER EASTMOND: In male rats?

COMMITTEE MEMBER ZHANG: In male rats.

COMMITTEE MEMBER EASTMOND: I'm not familiar with the specifics on this. In this particular case, the significant increase in the mononuclear cell leukemia was in the weight match controls, because the controls went down. The ad libitum controls, the frequency --

COMMITTEE MEMBER ZHANG: But are you talking about the female?

COMMITTEE MEMBER EASTMOND: -- is likely higher.

COMMITTEE MEMBER ZHANG: Are you talking the female?

COMMITTEE MEMBER EASTMOND: No, this is in males. In males, the ad libitum control is 62 percent, and the treated high dose is 60 percent, but in the weight-restricted ones it goes down to 30 percent. And that's where the significance comes from is in the weight

reduction. Now, that -- presumably that's valid, but that's the -- that's why the significance is seen there is actually is in the weight-restricted controls, not the ab libitum feed controls.

COMMITTEE MEMBER ZHANG: Okay. So I look at the Thomas 2007 paper again, that's how they conclude for BBP is positive in female rats, but inadequate in the male. So I was trying to update on that.

See, so compare with the first chemical, DINP, we discussed for the MNCL at least for DINP we found for both genders, but here is only one. And human data is clearly negative, but I also have one other notice is dose response. Even though the P value, if you look, is like mostly 0.01, but if you look at the low dose or medium dose it's always the same as the control. So to me, it's not -- I don't see the real dose response. It's only like a high dose.

And also, I noticed for the animal study, quite many animal studies didn't have the highest, so -- or sometimes it's just a medium dose. So if I look at the issue study only, you have whatever the highest dose in that study really had an effect. So that's also I feel is different from DINP. It's no -- to me there's no clear dose response.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree with Luoping. I was looking at the dose responses. It's mostly high end. There's not a clear dose response. I don't know why the statistics say that the trend test is positive, because it doesn't look like it is to me. But nevertheless, there is data in the hematopoietic system, the liver, the pituitary, the pancreas that there is positivity. And some of these, like the urinary bladder, it goes up reasonably well.

So there are high-end dose responses. There also is genetox data that's positive here, and it's more positive than the DINP. And I was looking you got DNA protein cross-links, DNA base lesions --

CHAIRPERSON MACK: Joe, get a littler closer to the mic, please.

COMMITTEE MEMBER LANDOLPH: Yeah, sorry. You've got DNA protein cross-links, DNA base lesions, DNA single strand breaks by comet, and -- yeah, so there is genetox data here. It's not negative. And you have to be very careful how you look at genetox data. It doesn't have to be positive across the board. It can be positive in specific assays.

So I would say there is data for carcinogenesis and there is data genetic toxicology. It's not as nice as I would like to see. It's not dose responsive. They

1 didn't do enough doses, but there is positivity in this
2 database. The data here is not as strong, the
3 carcinogenesis data, as for the DINP for sure, which was
4 much more dose responsive.
5 CHAIRPERSON MACK: Peggy.
6 COMMITTEE MEMBER REYNOLDS: Well, finally, we
7 have some human health data. I have to say that I'm
8 neither dissuaded by the two small breast cancer study --
9 null studies nor persuaded by the several endometrial
10 cancer studies. It's interesting that this new study
11 found an association with a urinary metabolite and the
12 other studies only found it with blood levels of BBP.
13 I agree with Dr. Dairkee, I was intrigued by a
14 number of other lines of evidence, the genotoxicity
15 issues, the estrogen receptor mediated affects in breast
16 cancer lines, the effects on mammary gland development,
17 even though the actual point estimates in those few epi
18 studies tended to be below one, which isn't entirely
19 consistent.
20 And I would have been particularly intrigued by
21 some of these lines of evidence, except that the animal
22 evidence seems so mixed and inconsistent. And given our
23 criteria, it is a little less convincing.
24 CHAIRPERSON MACK: Well, I have just as much
25 difficulty as anybody else with this one. I keep looking

at the pancreas and the liver and these two-year feeding studies. And, yes, it's true that it's only the highest dose.

DR. SANDY: Could you speak in the mic, please.

CHAIRPERSON MACK: Yes, it's only the highest dose, and, yes, it's -- I'm convinced by David that there's a lot of inconsistency. But when I put that together with the analogy to the related compounds, which are much more convincing, at least one of them is, that that bothers me a lot, and that pushes me no more toward listing, but I'm still on the cusp.

David.

COMMITTEE MEMBER EASTMOND: Well, let me comment. The pancreatic acinar cell tumors are actually -- for me, they're inconsistent in this, but they are probably caused because lots of PPAR agonists cause this type of tumor. But in my mind, this issue is has it been clearly shown through scientifically valid testing. And for me, there's too much variability here across studies for me to feel like that standard has been met. If I were to be a betting person and say what do I think?

Sure, I think these are probably caused by -- and I think the bladder cancer probably are too, but I don't think the evidence is sufficient, in my mind, to list it, but that's where I come in on it. So I do see multiple --

and I can argue biologically why I think the pancreatic -- why these pancreatic tumors are relevant. But, you know for me, based upon the statute, it's clearly shown, and for me it hasn't been clearly shown, but that's my personal perspective.

CHAIRPERSON MACK: And you think that the things that are in the back of your mind that convince you that it's really true are not science.

COMMITTEE MEMBER EASTMOND: No, I think they're science. I mean, I could go either way on this. I mean, honestly, but I have to -- you know, the problem is is that I think these are probably due to a PPAR alpha related mechanism, which probably is not relevant to humans. So then you've got this interesting dilemma, but since we're not going into the relevance to humans, then I go strictly does the data show it that's in front of me?

And then I say there's too many inconsistencies for me to feel comfortable. But if I were going to say -- if I were doing a hypothesis or putting forward a proposal to study, I would propose it, because I think it's certainly interesting there's some evidence there.

CHAIRPERSON MACK: Oh, dear.

Dr. Zhang.

COMMITTEE MEMBER ZHANG: I have a question for Peggy. You know, epi study, although the -- although the

kind of negative study and also OEHHA scientists represent and analyze the inadequate part of the design or -- what's your -- you know, before I can make my own decision, I'd like to hear your comment on the, you know, particular two studies and the process of the new one.

COMMITTEE MEMBER REYNOLDS: On the two studies?

COMMITTEE MEMBER ZHANG: Yeah. So what do you think from the study design or the weakness the OEHHA scientists represent and --

COMMITTEE MEMBER REYNOLDS: I think that OEHHA did a very nice job of outlining those studies and the issues around those studies. And obviously, human health studies are always challenging. We can't do a perfect study. We can never make it perfect. The one study was a population based study in which they were looking at probable exposure from occupation. That's difficult and has its own challenges. The Mexico hospital-based study was based on a metabolite in the urine. And it was a pretty small study with hospital controls, and has always got the problem when you're looking at a metabolite or a body burden of having post-diagnosis measurements, which are hard to interpret.

So I think there are lots of very legitimate reasons that were given by the reviewers of why those human health studies, even though they were null, and

neither one of -- they both had point estimates that were within the null. A lot of good compelling reasons why they might have been null based on design, even though, you know, maybe -- if we could do a perfect study, maybe you'd see a risk association, but it's only the two studies and they each had a different kind of a measurement of the exposure.

CHAIRPERSON MACK: I didn't mention the two epidemiologic studies. So given that you've asked her the question, I'm going to weigh in.

I think they're completely useless. And the reason I do is different for the two studies. The first one was a study of dead people, which compared dead people with other dead people. And that's just like having a hospital control. It's a matter of what's associated with the reasons why the controls died. And I just think -- and in addition, they did information gathering by asking spouses about occupational exposures. And I just don't think that's very useful.

On the other study, the Mexican study, which I was really excited to see that there was a big Mexican study, but unfortunately they were basing their conclusions on a sample of blood that was drawn after diagnosis. And so I don't really think you can make any conclusions at all from that one either. And it was being

compared to non-comparable controls.

So I think the two studies are totally meaningless, and we have to depend on the animal information.

COMMITTEE MEMBER REYNOLDS: So I think we agree with OEHHA and the limitations.

CHAIRPERSON MACK: Pardon me?

COMMITTEE MEMBER REYNOLDS: I think we both agree with OEHHA that they're very limited.

COMMITTEE MEMBER ZHANG: So then one more question. So if now we have to heavily rely on animal studies, so the following question would be if we only see the high-dose effect, not a clear dose response, by law, how should we respond?

CHAIRPERSON MACK: There's no law.

COMMITTEE MEMBER ZHANG: So yeah, that's another question I wanted to --

CHAIRPERSON MACK: Can I respond before you?

STAFF COUNSEL KAMMERER: Oh, certainly.

CHAIRPERSON MACK: Not evening going into law. I mean, you can have causal relationships which don't have dose responses, especially when it's very crude measurements of dose, which they are inevitably. There can be thresholds. There can be all kinds of differences in the dose response curve, so that I don't think you have

to have the dose response. And certainly a threshold is a perfectly reasonable possibility. And maybe Duncan would disagree with that.

COMMITTEE MEMBER THOMAS: No, I wouldn't.

CHAIRPERSON MACK: You agree. So I think the absence of a dose response is not very helpful. And I'm concerned that when you give a lot of the stuff it increases the risk of pancreas cancer, even though that's inconsistent, as David has said.

So I'm really stuck, so I think we better take a vote and see what everybody is -- which side they're stuck on. Anybody want to make any -- here we go, guys.

COMMITTEE MEMBER ZHANG: I have one more question.

CHAIRPERSON MACK: Oh, Dr. Zhang has something.

COMMITTEE MEMBER ZHANG: At the beginning I heard you were saying as Committee members we also could defer our decision, but is that different from abstain? Is that a case --

STAFF COUNSEL KAMMERER: It's different. You can defer the decision for a later meeting if you need more information. If you feel like you don't have enough information, you can defer for a later date.

COMMITTEE MEMBER ZHANG: I see. Okay.

CHAIRPERSON MACK: But, of course, you'd only do

that if you think you're going to get better information --

(Laughter.)

CHAIRPERSON MACK: -- sometime in the recent future.

COMMITTEE MEMBER ZHANG: There is no good human data.

COMMITTEE MEMBER REYNOLDS: So I would presume the process is such though, should there be a bunch of studies that come out in the next several years, this is something that could be brought back to the table and rediscussed?

DR. SANDY: Yes.

DR. ZEISE: Yes.

CHAIRPERSON MACK: Do you see any sign of that?

DR. SANDY: The answer is yes, if there were new studies we could bring it back.

DIRECTOR ALEXEEFF: The sign is --

CHAIRPERSON MACK: What did you say?

DR. SANDY: I said that yes we could bring a chemical back if there were significant new data, and you so wished.

CHAIRPERSON MACK: And the contingency is unlikely?

DR. SANDY: (Nods head.)

CHAIRPERSON MACK: Yes.

DIRECTOR ALEXEEFF: The reason -- there was the newer data that was emerging regarding breast -- looking into the breast cancer issue. That seems to be an active area of research, so I think there's going to be more research in that area. Maybe it will stimulate another epidemiologic study that's better designed.

COMMITTEE MEMBER REYNOLDS: I would just add that I do think the phthalates in general are of considerable public health interest, and it's not unlikely that in the next several years there might be some human health studies.

CHAIRPERSON MACK: Okay. I think we've had enough speculation about both causality and the future. So let's go ahead and do the -- make the -- do the deed.

Based on the information you have been -- wait a minute.

DIRECTOR ALEXEEFF: Yes, let's not do that one.

CHAIRPERSON MACK: Sorry about that. Where did that come from?

DIRECTOR ALEXEEFF: That's the next item.

CHAIRPERSON MACK: Has butyl benzyl phthalate been clearly shown through statistically valid testing, according to generally accepted principles to cause cancer? All those voting yes, please raise their hand.

(Hand raised.)

CHAIRPERSON MACK: One. My goodness gracious.

All those voting no, please raise their hand.

(Hands raised.)

CHAIRPERSON MACK: One, two, three, four, five. Five it is.

All those abstaining, please raise their hand.

(Hands raised.)

CHAIRPERSON MACK: One, two.

Well, we did it. We definitely decided against listing butyl benzyl phthalate.

All right. Next agenda item.

DIRECTOR ALEXEEFF: Update of section --

CHAIRPERSON MACK: Ah-ha. Is that going to be -- that's going to be Fran?

DIRECTOR ALEXEEFF: Yes.

CHAIRPERSON MACK: Madam.

(Thereupon an overhead presentation was presented as follows.)

STAFF COUNSEL KAMMERER: Thank you. Okay. Now, we go to the not-so-famous Proposition 65 list that you hear about every meeting.

Yes. By the mandate -- or mandated by Proposition 65 we are to look at state and federal agencies that have determined that more tests are needed

on certain carcinogens, and then we bring that to the state experts and you confirm that.

So Dr. Mack has language. I've -- Cindy has the slides up of the chemicals that were added, and some were actually removed, I guess. They were determined that there was sufficient evidence -- sufficient studies, but -- so there's a list. And I'm not going to try to read them out. I'm sorry. I'm not very good at chemical names, but they're in your book.

And Dr. Mack has the language he'll read to you to see if you will confirm these determinations, as long as you don't have any questions for me first.

COMMITTEE MEMBER REYNOLDS: So these are for reproductive toxicity, not carcinogenicity?

STAFF COUNSEL KAMMERER: Do we not have carcinogens?

COMMITTEE MEMBER REYNOLDS: So that wouldn't be us.

CHAIRPERSON MACK: I'll say what he just said to me, both Committees vote on both lists, okay, even though we don't know anything about reproductive toxicity testing.

All right. Now, I will read this statement. Based upon the information you've been provided from the U.S. EPA, should the chemicals as identified on the first

and second sections 27000 slides be added to the list of chemicals required by state or federal law to be tested, but which have not been adequately tested as required?

All of those voting yes, please raise their hand.

COMMITTEE MEMBER EASTMOND: Are we --

CHAIRPERSON MACK: You're supposed to make a decision here.

George.

DIRECTOR ALEXEEFF: I guess we need to clarify the process a little bit. Prior to each meeting or each year, according to the law, we ask the U.S. EPA, Department of Pesticide Regulation, and some other federal or state agencies what chemicals need additional testing. And then those -- they come back -- or which ones have the testing been adequately completed.

And based upon their responses, we provide that information to you, and we ask that you affirm, yes, they should be tested or they should be taken off the list as suggested by U.S. EPA or FDA in this -- U.S. EPA or Department of Pesticide Regulation in this case. So we realize it's an odd request, but it is what's required in the statute.

COMMITTEE MEMBER EASTMOND: George, we're being asked to vote that these should be added to the list of things needing testing?

DIRECTOR ALEXEEFF: Yes.

COMMITTEE MEMBER EASTMOND: Okay. I think that's a pretty easy vote.

CHAIRPERSON MACK: Can I ask a question, George? If we were not to vote positively on this, what would happen?

DIRECTOR ALEXEEFF: If you did not vote positively, we would bring it back to the next meeting probably.

(Laughter.)

CHAIRPERSON MACK: That's what I was afraid of. Does that answer your question?

COMMITTEE MEMBER ZHANG: George I have a question, so which means that all these chemicals lists which are currently not on the --

CHAIRPERSON MACK: Well, they would go onto their list of things to be looked at in the future.

COMMITTEE MEMBER ZHANG: I got it.

CHAIRPERSON MACK: All right. I'll now start again. Based upon the information you have now been provided --

DIRECTOR ALEXEEFF: Let's try the microphone and sit closer.

CHAIRPERSON MACK: Based on the information you have been provided from the U.S. EPA and from the various

members here, should the chemicals as identified on the first and second section 27000 slides be added to the list of chemicals required by state or federal law do be tested, but which have not been adequately tested as required? All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON MACK: Okay. That's unanimous.

All those voting no, please raise your hand?

(No hands raised.)

CHAIRPERSON MACK: All those abstaining, please your hand?

(No hands raised.)

CHAIRPERSON MACK: Okay. Now, we go to the other one. Based upon the information you've been provided from the Department of Pesticide Regulation and the U.S. EPA, should the chemicals as identified on the third section 27000 slide be removed from the list of chemicals required by state for federal law to be tested, but which have not been adequately tested as required? This is weird. All those voting yes, please raise your hand.

(Hands raised.)

CHAIRPERSON MACK: All those voting no, please raise your hand.

(No hands raised.)

CHAIRPERSON MACK: All those abstaining, please

raise your hand?

(Hands raised.)

COMMITTEE MEMBER REYNOLDS: I'm not sure about Maneb. I'd want more information

CHAIRPERSON MACK: Two abstainers, so at least we don't have to see it again.

Next item.

DIRECTOR ALEXEEFF: Okay. Staff updates.

CHAIRPERSON MACK: Ah-ha. Cynthia, your floor.

(Thereupon an overhead presentation was presented as follows.)

MS. OSHITA: Good afternoon. Just very quickly here, I'd like to update you on the administrative listings that OEHHA has been working on since the Committee last met earlier this year in January. OEHHA has administratively added nine chemicals to the list, seven as chemicals known to cause cancer, and two as chemicals known to cause reproductive toxicity.

And additions to the list, along with the effective dates, are shown on this slide here. You'll note that on the slide that bisphenol A was delisted on April 19th, 2013. And Fran will discuss the status of BPA further in her litigation update.

There are yet some other chemicals that are under consideration for administrative listing, and they include

beta-myrcene, and pulegone, and emissions of high temperature unrefined rapeseed oil as causing cancer. And then also trichloroethylene, methyl isobutyl ketone are under consideration for listing as causing reproductive toxicity.

We received comments on beta-myrcene, pulegone, and methyl isobutyl ketone, which are under review. And then the comment periods for the emissions of high temperature unrefined rapeseed oil will close on December 16th, 2013, and for trichloroethylene it will close on January 13th, 2014.

In addition to the listing considerations, we continue efforts to adopt safe harbor levels. Since you last met, we have not adopted any no significant risk levels, but we have adopted several maximum allowable dose levels. And those are shown here with their effective levels on this slide. That's it.

CHAIRPERSON MACK: Thank you, Cindy.

COMMITTEE MEMBER EASTMOND: I have a question.

CHAIRPERSON MACK: Yes, David.

COMMITTEE MEMBER EASTMOND: This is more -- I don't know if it deals with this. This might be regulatory in nature, but I find it interesting that this Committee met and reviewed trichloroacetic acid and decided not to list it. And then through an authoritative

body listing, it was listed independently. And I'm surprised that that would preempt or overturn the decision of this Committee. Is that considered a standard thing?

CHAIRPERSON MACK: That's the law.

STAFF COUNSEL KAMMERER: If I could answer that. There are different methods of listing. And it's not a matter of preemption, it's just that we have a ministerial duty to do it. So if it is determined by another method to cause cancer, we follow that too.

COMMITTEE MEMBER EASTMOND: Even though this Committee has met, reviewed it, and determined it did not -- was not relevant to humans? Is that to be meant specifically on that? And that was the conclusion.

CHAIRPERSON MACK: You should think of is that we did not see the evidence that convinced us to list at that time.

STAFF COUNSEL KAMMERER: Exactly. There might have been more evidence later that the authoritative body looked at.

COMMITTEE MEMBER EASTMOND: Well, I remember this quite well. There were six positive animals studies, and we concluded that they were not relevant to humans. So we actually specifically addressed that issue on relevance. So unless there's some other evidence that indicates these are relevant, it seems to me that it should not have been

listed.

STAFF COUNSEL KAMMERER: Well, as I mentioned, there are other methods. There are four methods of listing. And I think they were developed because the Committee can't look at all chemicals. So the law does not say whether one preempts or not, but we do have the duty to list under other methods. So OEHHA has followed that duty. It has not been -- this has not been argued under the law, so it hasn't been decided, but so we do have the obligation to follow the other methods.

CHAIRPERSON MACK: Remember that the authoritative bodies -- the other authoritative bodies don't have quite the same mandate that we have. In fact, it should have worked the other way around. In other words, they can consider human pertinence, whereas our law doesn't permit us to do that.

COMMITTEE MEMBER EASTMOND: Well, that's why it seems backwards to me.

CHAIRPERSON MACK: It is.

COMMITTEE MEMBER EASTMOND: Because we specifically looked and said this was not relevant to humans. And yet someone else, another committee, makes a decision, and it automatically trumps the decision of this body.

STAFF COUNSEL KAMMERER: But we're following

Proposition 65, which we do not have the authority to alter the statute itself, and that's the way the statute is written.

DIRECTOR ALEXEEFF: Well, yeah, just each of those methods have been determined to be independent. So it does seem -- it's not really a preemptive thing. It's simply an independent method. But staff may have some comments specifically on trichloroacetic acid. I don't know if they do or not.

COMMITTEE MEMBER REYNOLDS: Can I just ask a questions. I just had a question, and I wondered if we could know what authoritative body this was? You know, just -- it might be helpful, because different authoritative bodies use different criteria. So it might be just informative.

DR. ZEISE: So in this particular case, the International Agency for Research on Cancer reviewed the evidence for trichloroacetic acid, and we're under the requirement of listing it via this Labor Code mechanism. So as IARC identifies chemicals as having sufficient evidence in animals, we're required to place them on the list.

DIRECTOR ALEXEEFF: However, just to clarify, since we're discussing IARC, if IARC classifies it in group 3, which is not relevant to humans, which it did,

for example, for one of the phthalates --

COMMITTEE MEMBER EASTMOND: Group 4. Three's not classifiable.

DIRECTOR ALEXEEFF: So it's Group 4?

COMMITTEE MEMBER EASTMOND: Yes.

DIRECTOR ALEXEEFF: Okay. We would not -- is that correct?

DR. ZEISE: Yeah, so some chemicals IARC classifies in Group 3, they have sufficient evidence in animals, but then that evidence is determined to be not relevant to humans, and those -- in that case, they do not go on the Prop 65 list.

CHAIRPERSON MACK: Don't feel insulted, David. It isn't -- they didn't knock you.

COMMITTEE MEMBER REYNOLDS: So these would maybe have been 2Bs?

DR. ZEISE: Yes.

CHAIRPERSON MACK: Now, we come to the most exciting part --

COMMITTEE MEMBER LANDOLPH: Just a quick one. That last slide, could you flash that one again that just went off? It had the benzyl butyl phthalate 4, what was that listed under as? What was the toxicity endpoint?

DR. ZEISE: So that's listed as known to cause reproductive toxicity.

COMMITTEE MEMBER LANDOLPH: Repro tox. Um-hmm, Okay. Thank you.

CHAIRPERSON MACK: Can we now get to the most exciting part of the day. What's happened with the litigation?

STAFF COUNSEL KAMMERER: Litigation. All right. I can help you there. As Cindy mentioned, we do have a BPA case. We listed BPA based on a reproductive toxicity report from NTP. And we got promptly sued by the American Chemistry Council. And we were immediately ordered by the court to delist the chemical until the case is resolved.

Since then, the Natural Resources Defense Council has intervened as a co-defendant. This case is now at trial court level, and we don't expect the resolution until sometime late next year, and probably an appeal will follow. So BPA presently is not listed.

We have two more cases that we're involved in. The next one is a chlorothalonil case. In 2011, OEHHA changed the no significant risk level for chlorothalonil, and we were challenged by Syngenta. This case is also pending in the trial court level right now.

The third one is the one I think you're interested -- most interested in, is the Sierra Club case. In 2007, Sierra Club and some labor organizations sued us for not making timely decisions for listing under

Proposition 65. This case has been settled. And I think you've all heard that already.

The only part that's sill pending is the attorney fees. The CIC and the individual members have been dismissed. They were dismissed on October 15, 2013.

The changes that were affected -- that will affect this Committee that come from this settlement are the time frame for the listing decisions on certain chemicals. These were set out in the agreement. So some decisions have to be made in the next few months. Some listing decisions will be made next year, some not until 2015.

We have ongoing responsibilities to speed up some listing decisions, and we're on a tight schedule. If you have any questions on that, we can go further in detail.

It was also agreed to shorten some periods for public comments, including on the materials prepared for this Committee. The HID public comment period was shortened from 60 to 45 days. We eliminated the informal comment period for authoritative body listings.

And through the settlement, we also agreed to make some regulatory changes. One of those was adopting more specific regulations on the qualification for the members of the State's expert committees. Existing regulations are not clear on the level of the expertise

and how to measure that expertise. The new language will clarify that, and I'm sure you'll all be happy to know that you all satisfy those requirements.

Also, we agreed to initiate the process for the Labor Code regulations. We don't have currently regulations for that particular method of listing. And so we expect to propose one within hopefully the next three to four months.

We also have a project to adopt more specific regulations concerning warnings for chemicals listed under Proposition 65. These warnings would actually give more information to the consumers about endpoints and ways they can avoid diminished exposure -- they can avoid or diminish their exposure.

Currently, these warnings -- this detail of warning is not required by the statute or the regulations. All of these regulatory amendments or new regulations, they're all a public process. I think you're all on our listserv, so we welcome your comments on those, and you'll be maintained up to date to what's going on.

Any questions on that?

Yes, Dr. Reynolds.

COMMITTEE MEMBER REYNOLDS: So, if an agent is delisted pending the outcome of litigation, does that mean the court decides whether it should be listed or not?

STAFF COUNSEL KAMMERER: Well, the court will look at what -- if there is sufficient evidence, or I mean usually the courts don't look too much at the scientific aspect. They're look at this case in BPA -- see, I'm not the litigation attorney, so I'm trying to remember exactly what the facts were there. But the court, in this case, because we had listed it, the court wants to look at the listing process and what was involved in the listing of this. And they didn't tell us to delist it permanently yet. They're saying put it on hold until we can look at the facts of the matter.

COMMITTEE MEMBER REYNOLDS: Okay. That would be an interesting process for making regulatory decisions.

STAFF COUNSEL KAMMERER: It is. And a lot of proposition 65 is determined in the court room, because Proposition 65 is not that clear on certain details. So it has been, throughout the years, last 25 years a lot of things have been determined by case law.

DIRECTOR ALEXEEFF: Yeah. I think the simplest way of explaining it, at this point, I think the case is on the process that we listed it. And whether we followed the process correctly, so -- and not necessarily on the scientific merits.

All right, me again. All right. Well, first of all, I want to thank the Committee again for their work

today. And it's clear that the deliberations were, you know, very thoughtful, and that they were not straightforward. Required a lot of energy and thought on your part. There were four decisions that were made today.

The first one was on the chemical diisononyl phthalate, DINP. And the Committee voted to list the chemical as a chemical clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer.

The second decision was on butyl benzyl phthalate. And in this case, the Committee voted to not list this chemical. The other decision was to add a number of chemicals to the 27000 list, based upon U.S. EPA's recommendation that they require additional testing.

And then the last decision was to remove a number of chemicals from the 27000 list, indicating that adequate testing had already been conducted. So that's it for the conclusions.

So I do want to thank again the Committee, the staff, the members of the public who testified, those who have been viewing this on webcast.

And I'll ask Dr. Mack to close the meeting, unless there's something else he wants to bring up.

CHAIRPERSON MACK: If there's nothing else, thank

you. And I guess I hereby close the meeting. Thanks, everybody.

(Thereupon the Carcinogen Identification Committee adjourned at 3:51 p.m.)

C E R T I F I C A T E O F R E P O R T E R

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 17th day of December, 2013.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063