MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

SACRAMENTO, CALIFORNIA

FRIDAY, JANUARY 25, 2013

10:05 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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APPEARANCES

COMMITTEE MEMBERS

Thomas M. Mack, M.D., M.P.H., Chairperson

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. Melanie Marty, Assistant Deputy Director, Scientific Affairs

Dr. Jay Beaumont, Staff Toxicologist

Dr. Kate Li, Staff Toxicologist

Ms. Carol Monahan-Cummings, Chief Counsel

Ms. Cynthia Oshita, Proposition 65 Implementation

Dr. Karin Ricker, Staff Toxicologist

Dr. Martha Sandy, Chief, Cancer Toxicology & Epidemiology Section

Dr. Feng Tsai, Staff Toxicologist

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PROCEEDINGS

DIRECTOR ALEXEEFF: Good morning, everyone. If you could take your seats, we'll get started in a minute.

I want to welcome everyone here -- and is there on-line as well?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

DIRECTOR ALEXEEFF: -- on-line, to the meeting of the Carcinogen Identification Committee on January 25th, 2013.

Before we start, I'll just give information for the folks here. First of all, evacuation information. So please look around, see the exits that you have, and if there is an alarm that we have to leave the room, please leave through an exit and go down the stairs. And then there will be a stairwell. And then if we have to leave the building, we usually meet across the street in the park across the street.

And then in terms of restrooms and drinking water, if you go out the back door and -- you can't hear me?

If you go out the -- there we go. I'll speak up. See that was all testing of the mic. All right. In terms of -- this is more important, restroom and drinking water. So out the back door and to the left. And there's also some food downstairs in the cafeteria.

So, again, I want to welcome you all here, and I want to welcome the members of the Cancer Identification Committee. What I was planning on doing is just briefly introduce their names and titles, and then I was going to ask them all to introduce themselves and give just a couple minutes of background about them -- about themselves.

So directly to my left is Dr. Thomas Mack, who's the Chair. He's a professor of the Department Preventive Medicine and Pathology at the USC Keck School of Medicine and he's been our Chair for several years now.

Next to him is Dr. David Eastmond. He is a professor and Chair of Cell Biology and Neuroscience, and also a research toxicologist at UC Riverside.

And next to him is Dr. Luoping Zhang who is the 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 next to her is Dr. Duncan Thomas, who's a professor of biostatistics at the Verna R. Richter Chair in Cancer Research at the University of Southern California.

And next to him on the far -- my far left is Dr. Shanaz Dairkee. And she's a senior scientist at the California Pacific Medical Center, and a consulting

professor for the Stanford University School of Medicine.

Now, on my right is Dr. Joseph Landolph. And he's the associate professor for the Department of Molecular Microbiology and Immunology at the University of Southern California, Keck School of Medicine.

Next to him is Dr. Jason Bush, associate professor of cancer biology at the California State University in Fresno.

And on my far right is Dr. Peggy Reynolds, 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.

Also, I'll introduce myself. I'm Dr. George Alexeeff. I am Director the Office Of Environmental Health Hazard Assessment. And then we have a number of staff here. I'll just introduce them. We have almost directly in front of me is Carol Monahan-Cummings. She's our lead counsel. So if any legal questions come up, if any of the members of the Panel have a question or have a question about -- a legal question, feel free to ask to pause, so we can ask Carol if there's anything we have to be -- we have to think about.

And then next to Carol is Dr. Melanie Marty. She's the Assistant Deputy Director for Scientific Affairs

at OEHHA. And next to her is Dr. Martha Sandy. She's the Chief of our Cancer Toxicology and Epidemiology Section.

And then directly behind the court reporter is Dr. Feng Tsai. She is a toxicologist with OEHHA. And also next to her is Karin Ricker who is also a toxicologist here at OEHHA.

And then we'll have some additional staff members. We'll introduce them when they -- when their item comes up. And we also have Cynthia Oshita. If you'd raise your hand, Cynthia. So any questions about the particular organization of this meeting or public comments, feel free to talk to Cynthia. She'll be glad to help you.

All right. Now, I'd like to turn it over to Dr. Mack and have him introduce himself and the members of the Committee.

CHAIRPERSON MACK: Well, my name is Tom Mack, and I'm a --

DIRECTOR ALEXEEFF: You'll have to get closer.

CHAIRPERSON MACK: How's that?

It's on.

I'm basically a general epidemiologist and started out in infectious disease more decades ago than I'd like to think, and moved from there to cancer epidemiology and other chronic diseases, epidemiology, and

basic biology.

Do you want me to go through and --

DIRECTOR ALEXEEFF: No, I think each one should introduce themselves.

CHAIRPERSON MACK: Okay. David, why don't you go ahead.

COMMITTEE MEMBER EASTMOND: Hi. My name is David Eastmond. As indicated, I'm a professor at the University of California, Riverside. My area of expertise is kind of chemical carcinogenesis, genetic toxicology, with some interest in risk assessment. I've been on this Committee most of the time since 1999 with a short period in there when I was not on the Committee.

Anyway, Luoping.

COMMITTEE MEMBER ZHANG: So I'm Luoping Zhang, adjunct -- associate adjunct professor in toxicology. My research mostly focus on the study mechanism of chemical-induced cancers, particularly in leukemia and the lymphoma. And my specialty would be genetic toxicology.

COMMITTEE MEMBER THOMAS: I'm Duncan Thomas from the University of Southern California. I'm trained as a biostatistician, and have been primarily working in the area of statistical methods development and study designs for epidemiology, both environmental epidemiology and genetic epidemiology.

Of course, in the course of this, I've gotten involved in a broad range of environmental epidemiology, including cancer epidemiology studies. So I have fairly broad interests in epidemiology. I also served on this Committee for a period of about 3 years about 20 years ago. So it will be fun to be back.

COMMITTEE MEMBER DAIRKEE: I'm Shanaz Dairkee. I'm at the California Pacific Medical Center in San Francisco. I'm a new member on this Committee, and really looking forward to serving. I'm a cancer biologist. My main interest is in model development, so that we can have assays that apply to -- toxicology assays that apply to human disease. And that's where most of our focus is developing better translational models for chemical testing.

COMMITTEE MEMBER LANDOLPH: Hi. I'm Joe Landolph. I was originally trained as a chemist. I got my Ph.D. in physical and biophysical chemistry at UC Berkeley, and started doing toxicology then. Then I did a post-doc Charlie Heidelberger, and I've become a chemist, turned genetic toxicologist, turned molecular carcinogenesis researcher. And we've been interested for many years in polycyclic hydrocarbons and more recently in arsenic, nickel, and chromium and how they disrupt gene expression at a global level to result in transformed

cells.

COMMITTEE MEMBER BUSH: Good morning, everyone.

Good morning. I'm Jason Bush.

Thank you.

Good morning, everyone. I'm Jason Bush from California State University in Fresno. I'm an associate professor. I'm a cancer biologist as well. My background, I've got a Ph.D. in experimental medicine from the University of British Columbia in Vancouver, Canada. I run a research lab. Our areas of interest are the role of pesticides in breast and prostate, the hormone-related cancers.

I'm particularly interested in using proteomics as a way of getting to the cell biology and the mechanism of why normal cells become cancerous.

Thank you.

COMMITTEE MEMBER REYNOLDS: And I'm also a new member of the Committee. Peggy Reynolds. I am a cancer epidemiologist. And I head up the environmental research group for the Cancer Prevention Institute of California, where we conduct and have been conducting a number of human health studies of environmental influences in cancer, particularly cancers in children, and breast cancer in women.

DIRECTOR ALEXEEFF: All right. Now, I'd actually

like all of the members to stand and I'll administer the oath of office here. And since we're doing them all together, just so we understand what's happening, when we say I, and then -- say I then your name.

(Laughter.)

DIRECTOR ALEXEEFF: Okay. And then just -- Okay. I'll hold it up here.

So this is the oath for the Office of Member of the Carcinogen Identification Committee. So let's begin.

I --

(Thereupon each Committee member stated their name.)

DIRECTOR ALEXEEFF: -- do solemnly swear or affirm --

COMMITTEE MEMBERS: -- do solemnly swear or affirm --

DIRECTOR ALEXEEFF: -- that I will support and defend the Constitution --

COMMITTEE MEMBERS: -- that I will support and defend the Constitution --

DIRECTOR ALEXEEFF: -- of the United States and the Constitution of the State of California --

COMMITTEE MEMBERS: -- of the United States and the Constitution of the State of California --

DIRECTOR ALEXEEFF: -- against all enemies

foreign and domestic --

COMMITTEE MEMBERS: -- against all enemies foreign and domestic --

DIRECTOR ALEXEEFF: -- that I will bear true faith and allegiance --

COMMITTEE MEMBERS: -- that I will bear true faith and allegiance --

DIRECTOR ALEXEEFF: -- to the Constitution of the United States --

COMMITTEE MEMBERS: -- to the Constitution of the United States --

DIRECTOR ALEXEEFF: -- and the Constitution of the State of California --

COMMITTEE MEMBERS: -- and the Constitution of THE State of California --

DIRECTOR ALEXEEFF: -- that I take this obligation freely --

COMMITTEE MEMBERS: -- that I take this obligation freely --

DIRECTOR ALEXEEFF: -- without any mental reservation or purpose of evasion --

COMMITTEE MEMBERS: -- without any mental reservation or purpose of evasion --

DIRECTOR ALEXEEFF: -- and that I will well and faithfully discharge --

COMMITTEE MEMBERS: -- and that I will well and faithfully discharge --

DIRECTOR ALEXEEFF: -- the duties upon which I am about to enter.

COMMITTEE MEMBERS: -- the duties upon which I am about to enter.

DIRECTOR ALEXEEFF: Thank you.

So I'll now turn it over to Dr. Mack.

CHAIRPERSON MACK: Well, I have one initial comment. I think we should be concerned that at least 3 members of the Committee have deep Canadian roots, and that we should want to make absolutely sure that we're taking these oaths seriously.

(Laughter.)

CHAIRPERSON MACK: So, Martha, are we ready to begin?

DR. SANDY: I think we are, and I think Carol Monahan-Cummings is up.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. My name is Carol Monahan-Cummings. I'm Chief Counsel for the Office of Environmental Health Hazard Assessment. I've been with the Office for 10 years. And I'm also counsel for this Committee, in terms of your work on the

Committee.

And I just need to give you a quick overview on some legal requirements for the Committee, and then we'll go into a discussion -- a general discussion about Proposition 65, what happens when chemicals get listed, how they get listed, and some basic information.

And then Dr. Sandy will go over a little more specific information on the scientific issues that you'll be looking at today.

DIRECTOR ALEXEEFF: Can you speak closer to the mic.

CHIEF COUNSEL MONAHAN-CUMMINGS: Sorry. And I also have to apologize. I'm getting over a cold myself, so hopefully the voice will hang in there till I'm done.

All right. So you can see the slide up on the screen right now talks about the Bagley-Keene Open Meeting Act. Are your computers on?

CHAIRPERSON MACK: Yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Cool. I sent you some information earlier on this, a little package from the Attorney General's Office, so that you could get some background on it. But I just want to go through a few things generally, and also remind you, since I am counsel for each of you as a member of the Committee, if you have individual questions, you're always welcome to

talk to me. You don't have to do it -- do that kind of discussion in the meeting here.

Okay. Let's see if this works.

Okay. So the purpose of the Bagley-Keene Open Meeting Act is to allow the public to be informed about the proceedings of public agencies. And even though you're not exactly a public agency, you have been appointed by the Governor to do -- advise the Governor and our office in regard to the listing of chemicals under Prop 65, so the Act does apply to this group.

It's also intended to make sure that the deliberations and actions that committees like yourselves make are open to the public, and that the public has the opportunity to have input in that decision making.

So the main requirements of the Act are that the public must be provided with a reasonable notice of the location and timing of the meeting, and what's going to be discussed there. We're, at a minimum, required to get our agendas out 10 minutes -- 10 days prior to a meeting. And we generally try and publish them much more before that.

But the Committee Chair, Dr. Mack, is the one that helps us put together the agenda for the meeting. And then we go ahead and publish it in the -- on our website and in the notice register.

We have to have all of our discussions of this

Committee need to be public, and in a public location like the meeting here today. Some of you may participate in teleconference meetings or things like that on other committees that you're on. And we actually are able to do that, but the logistics are so difficult, we usually just try and have you all meet in the same room.

So it also -- the main thing that you should keep in mind is that conversations or discussions between yourselves and any discussions you have with third parties about the subjects that you're making decisions on in the meeting should be done in the public meeting, and where the public can hear those.

If, for some reason, you have discussions off line, you know, at lunch or in the hallway or something, it's best to disclose those when you come back to the meeting, and let people -- the members of the public know that you talked to someone and the basic content of that discussion.

Okay. So what is a meeting?

One would think that that would be fairly obvious, but actually it can be a congregation of the majority of any of the members of the Committee. That's called a quorum, and it can be any place. You might be at lunch, like I said, or you might be emailing each other, or talking on the telephone, or talking through a third

party. For example, if you talked to me, and then I talked to each one of you separately about that same thing, then that was a meeting of the Committee, and that would be a violation of the Bagley-Keene Act, unless we disclosed that.

So you do need to keep in mind that it isn't just a meeting when you're all in one room together. It can be emails. Sometimes, if you -- for example, if you get an email from Cindy or someone else from our office, people have a tendency to want to hit, "Reply All", on things that you get. And it's much better if you do not do that. You just hit, "Reply", or pick up a telephone, and then you don't have concerns about accidentally having a meeting.

Okay. What's a remedy if you violate the Act?

Nobody goes to jail, but you do have to do it over, basically. Any prior action that you took or decisions that you made without those being done in public would have to be taken over, and the prior one would have no legal effect.

There's a lot more to the Bagley-Keene Open Meeting Act, but I don't want to go into that level of detail for you today. If you have specific questions, I'm always available to answer those.

I did want to touch on a couple of other things.

One of them is that there's also a law called the Public Records Act that applies to our agency and this Committee. And that means that under that law that virtually everything that you create, either hard copy or electronic, is open to the public upon their request.

And so that means your emails, instant text messages, for example, if they happen to be kept, meeting notes, things like that can be requested by the public. And there's very few exceptions that we can use to keep those from being provided to any member of the public that requests them.

I also wanted to let you know that in particular as it applies to this Committee, there's something called a litigation hold that can be put on your records. And, in fact, there is a litigation hold for the members of this Committee. Surprise, all of you new folks didn't know that you'd been sued, but you have.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: And so essentially there's been a lawsuit that's been going on since the end of 2007. That's primarily an action against the Governor and our agency, but also named the CIC members. And we've diligently been trying to resolve that case. But in the meantime, I need to require all of you to keep your materials that you have for the meetings, and

1 particularly keep those things that you've written on or
2 that you have specific, you know, notes or whatever.
3 And as soon as I'm able to let you destroy those,
4 I'd be more than happy to, but I can't let you do that
5 now. So just note up here that the litigation hold does
6 not expire until you hear from me in writing that you
7 can -- that I'm releasing those documents. And just keep
8 in mind that if you use your home computers or your own
9 hand-held devices, the records that you have on those can
10 also be subject to the litigation hold.
11 Lastly, I just want to mention, and I know you
12 all are aware of this, because you've filed your Form
13 700s, is that there are laws that affect this Committee,
14 along with all of us who work for the State, that require
15 you to disclose your monetary interests that may cause you
16 a conflict of interest on this Committee.
17 You have already done this, and I just want to
18 remind you that those documents are public, and anybody
19 from the public can request those. And it doesn't mean
20 that when you're putting those on the form that you, in
21 fact, have a conflict of interest. It just means that
22 there's a potential for that in certain circumstances. If
23 you believe that you have a conflict or are uncomfortable
24 making a decision or discussing any item on our agenda at
25 this meeting or any others, you're always welcome to

recuse yourself from the discussion and the decision, and we don't ask you why that is. Just let me know.

Any questions about those items?

Yes, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Hi, Carol. Do we have to keep things like notes we wrote and the hard copies that you gave us -- that OEHHA gave us?

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

COMMITTEE MEMBER LANDOLPH: So keep everything?

CHIEF COUNSEL MONAHAN-CUMMINGS: Pretty much keep everything, and then we don't have to worry about whether or not somebody discarded something. Now, if you -- I know all of you got the same set of materials. And so if for some reason you're not writing on those, you have separate notes or something, you can keep your separate notes. We don't need duplicates of everything in the world, but what we're trying to do is keep those materials that are specific to your work here, you know, of your own -- you know, if you write something down in particular.

COMMITTEE MEMBER LANDOLPH: So a follow-on question. Before my understanding was it was just materials related to the prioritization process. Now, it's much broader than that.

CHIEF COUNSEL MONAHAN-CUMMINGS: It's pretty much

everything that's related to this Committee at this point.

COMMITTEE MEMBER LANDOLPH: Thank you.

COMMITTEE MEMBER EASTMOND: Carol, let me just --

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

COMMITTEE MEMBER EASTMOND: So basically we can throw away things that are -- we haven't marked up that are just generic for everyone --

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

COMMITTEE MEMBER EASTMOND: -- everyone else got it? I mean, I literally have boxes and boxes of things.

CHIEF COUNSEL MONAHAN-CUMMINGS: I understand that. So do we.

COMMITTEE MEMBER EASTMOND: Because we have over 10 years worth of stuff we've had to hold. And the prioritization gave us a lot of paperwork.

CHIEF COUNSEL MONAHAN-CUMMINGS: It did.

Can you put up the next set of slides, please.

Okay. Here I am again. This part of the orientation we just wanted to give you some background on what your Committee does and how it fits into the overall Proposition 65 program.

You may have heard of the name Proposition 65, hopefully. But the Act itself is called the Safe Drinking Water and Toxic Enforcement Act of 1986. And it was passed, as the name implies, in 1986. And it was a voter

initiative, not something that was established by the Legislature.

Okay. So what I want to do is just give you a very quick kind of a general outline for what Prop 65 is and how the Committee fits into that. And if you have any specific questions after that, just let me know.

Prop 65 is only focused on specific types of chemicals. It doesn't include the whole chemical universe. It has to do with carcinogens and reproductive toxicants only. If a chemical causes some other effect, that isn't something that's covered by Proposition 65.

There is 4 different ways that chemicals can be listed under the Act, and we'll go through each one of these separately. And there are overlaps between the 4 different mechanisms, although the criteria for each one is slightly different.

The first way that the chemicals can be listed are when they're identified by the CIC or DARTIC Committees. And, of course, that's you here in the room. That this is the only part of our listing procedures that actually has experts -- our own experts looking at all of the data and making a decision. The other 3 mechanisms are all administrative and rely on other groups' decisions -- scientific decisions.

Okay. There's another listing mechanism called

the Findings by Authoritative Bodies. You may have heard of it as the Authoritative Bodies or AB mechanism. Authoritative Bodies are those scientific agencies that have been identified by your group, the CIC, and the DARTIC, as experts in the identification of carcinogens and reproductive toxicants.

I should go back just briefly here. I had mentioned before that there's a slightly different criteria for each of the listing processes. And I just want to mention for yours, and you'll hear this again, that the criteria for listing by this Committee is that a chemical is clearly shown, through scientifically valid testing, based on generally accepted principles, to cause cancer.

And you'll note that that doesn't say human cancer. It can include just studies that show that a chemical causes cancer in animals.

Okay. So in terms of the Authoritative Bodies listing mechanism, some of the groups that have been identified as Authoritative Bodies include the U.S. EPA, the National Toxicology Program, and the International Agency for Research on Cancer.

And we have developed regulations that provide the structure for whether or not a chemical can be listed under this mechanism. And those regulations were

established with input from the CIC Committee.

There's another listing mechanism that we call, "Formally Required", and that really means that there's a requirement, by generally it's FDA, that a chemical be identified as causing cancer or reproductive toxicity. And I say it's FDA, because it's been primarily used for the listing of prescription drugs, because of the labeling requirements -- labeling inserts for drugs.

And if there's a requirement that the drug be identified as causing cancer, then the chemical is listed under Prop 65.

And lastly, there's a listing process that we call the Labor Code listing process, but I mention it up here as an occupational warning requirement, because essentially chemicals that are listed because they are incorporated by reference in the California Labor Code, which is why we call it Labor Code, but they are chemicals that are identified under California or federal law as chemicals that require warnings in the occupational settings.

So, for example, if federal OSHA requires a chemical manufacturer to label or provide an MSDS for their product that says its causes cancer, then we need to list those chemicals under Prop 65.

Okay. We have used all 4 of these listing

mechanisms for the last 25 years or so. And the chemical list now contains over 800 chemicals of 1 of the 3 endpoints, or all 3, of cancer, reproductive, or developmental effects.

So what happens once a chemical is listed?

Well, there's 2 things, and a whole bunch of things that don't happen. The 2 things that can happen are that depending on the situation, a person who causes an exposure to a chemical listed under Prop 65 can be required to provide a warning to the individuals who are exposed to that chemical. It's not always required. There is a threshold level where a warning is required and where it's not.

But for purposes of this Committee, the general idea is that once a chemical is listed there's a potential for a warning requirement. There's also a requirement under the statute that any chemical that's listed cannot be discharged into a source of drinking water.

One thing that doesn't happen, and sometimes you get the impression it does, is that a chemical is not banned from use just by virtue of it being listed under Prop 65. A business can still use the chemical and expose individuals to whatever level of the chemical, as long as they provide a warning to that individual.

Okay. So what are your duties in particular for

this Committee?

I mentioned before that you are required under the statute to determine whether a chemical has been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause cancer.

That is not a legal standard. That's a scientific standard that -- you have been chosen because you have scientific expertise and can apply your scientific knowledge to the information that you receive and determine whether or not a chemical is known to cause cancer.

I mentioned already that it can be -- your decisions can be based on either animal or human evidence. It's not necessary that you find that a chemical is a known human carcinogen in order for it to be listed.

Some things that you don't need to concern yourself about when you're making these decisions is whether or not the current dose to humans that may be received now or anticipated now, whether that particular dose causes cancer, since that determination really is done at a later part in the process when it's determined whether a warning is required.

I also mentioned earlier that this group, the Committee, has identified these Authoritative Bodies that

we use for administrative listings, and that's an open process. You can designate more Authoritative Bodies or you can remove Authoritative Bodies. That's entirely up to your Committee.

Dr. Sandy is going to go into this idea of helping us prioritize chemicals for presentation to your Committee in more detail, but I just wanted to mention it here, that you also are involved in the prioritization of chemicals.

We also ask you to review some of our procedures and other materials from time to time. One of them that is related to the prior note is that we have a process for prioritizing chemicals. And this Committee, as well as the DART Committee, were involved in our development of that document. And Dr. Sandy will go over what that process is, but you can have input into that if you think it needs to be changed in some way.

You've also developed -- or this Committee has developed a guidance document on how to make your decision -- your scientific decisions here. You should have that in your materials. There was guidance for a listing, and that was developed by this Committee, and again it can be changed by this Committee if you think that it needs updating or changing.

We also ask you to provide peer review for safe

harbor numbers that we develop under Prop 65 for chemicals that have been listed. And the safe harbor numbers are what I was mentioning when I said that once a chemical is listed, there's a certain level that requires a warning, and a certain level that doesn't. And we establish those levels for many of the chemicals that are on the list. And when we do that, we send those documents, and particularly the risk assessment part of those documents, to your Committee for review and comment.

And lastly, I wanted to mention that you also, and you're going to get to do this today, are asked to identified chemicals that haven't been adequately tested for their potential to cause cancer. It's a very little known provision of Prop 65, and we'll go through it later on this afternoon, but it is one of the duties for your Committee.

All right. This is my last slide. I just wanted to let you know there's 3 different options that you can choose today. Once you have heard all the evidence on the chemical that's being put in front of you today, Dr. Mack is going to read off a little script. And he's going to ask you whether or not a chemical -- the chemical you're considering has been clearly shown, by scientifically valid evidence, according to generally accepted principles, to cause cancer. You're going to be able to

say that in your sleep pretty soon, because we're going to keep saying it over and over.

So you can find that it has been. You can find that it has not been, and we usually do that by a hand vote. And you can also defer your decision to another meeting. That doesn't come up very often, but sometimes if someone raises an issue that you hadn't thought about, there's a brand new study that we didn't know about, or you just feel like you don't have -- haven't had enough time to really deliberate together, then we can -- you can ask us to defer to another meeting. We can set the chemical for discussion at another meeting.

Okay. Any questions on that stuff in general?

Yes, Dr. Thomas.

COMMITTEE MEMBER THOMAS: Are we required to use only published literature in making this decision? If we're -- if things in the gray literature has come out that we're not aware of previously, can that be brought before the Committee?

DIRECTOR ALEXEEFF: Yeah. George Alexeeff. I can answer that. I mean, I would just go to what it states. It says that, "by scientifically valid testing, according to generally accepted principles". So that is really up to the members to decide. That's your determination that it was scientifically valid and that it

was by generally accepted principles. So there are different sort of principles out there by different organizations.

And as Carol mentioned, there is a guidance document that this Committee had developed and could -- you know, it can revise over time. So that does provide some guidance as to what level of evidence might lead one to a decision. But in terms of the types of methods, like whether or not there was a study that was done and it was, you know, published in one journal versus another journal, that's really up to the Committee member to decide whether it was scientifically valid and by generally accepted principles.

CHAIRPERSON MACK: I would think though that if somebody was going to use something that was not published and not reviewed carefully by staff and summarized for the Committee, that it would be incumbent upon somebody who wants to consider something else to be able to lay out the circumstances of his study, and the circumstances of his passage through the scientific community, in order that we can evaluate the credibility of the findings.

So normally if you're going to accept non-published studies, then we have to know enough about them to be able to evaluate them.

COMMITTEE MEMBER THOMAS: I was thinking, for

example, of papers that we become aware of that are in press, but not yet published by the time -- the date that we're making this decision.

CHAIRPERSON MACK: I think if you found such a study, the first thing you would do is call Martha and call it to her attention. She would respond with an embarrassed, "Okay, I'll look at it". But I sincerely doubt you'll find one.

(Laughter.)

COMMITTEE MEMBER EASTMOND: If I can weigh in. It's not common, but we have periodically reviewed studies which have not been published in the general peer-reviewed literature. Oftentimes, you have GLP studies or studies sponsored by U.S. government agencies, which have been conducted under contract, and we've reviewed those, and actually been one of the major things that have been used to make decisions.

So we're -- the idea is to just make a judgment based on the information we have. And if we think that's a valid study, then we can go forward.

COMMITTEE MEMBER THOMAS: Thank you.

DR. SANDY: Okay. Carol, would you mind going to the next slide. I just have a few slides, and click on, and let's show the whole -- I'm going to go through the process. Why don't you go ahead and show them the slide

in its glory here

This lays out the process by which we develop hazard identification materials and bring them to your committee. And in orange you see the opportunities for public comment at these various stages.

So with the first stage, the prioritization process, we go through -- we track chemicals for carcinogenicity concern. We evaluate them through a prioritization process. Dr. Mack had asked me to give a little more detail. So we have some screening procedures and then we bring those chemicals to your Committee for consultation and advice.

So OEHHA will select chemicals for preparation of hazard identification materials. We identify those chemicals through the prioritization process with public input and consultation advice from you, the CIC.

And then the second step, OEHHA will issue a request for relevant information, otherwise known as a data call-in, on selected chemicals, during which time data submissions may be received from the public.

And then the third step up there, OEHHA then prepares the hazard identification materials taking into account all relevant information. And then the completed hazard identification materials are sent to you and released to the public for public comment.

The Committee then reviews the materials we've sent and any public submissions. And finally, in a public meeting, which is an open meeting, the Committee discusses the evidence, takes public comment, deliberates, and renders a decision.

Next slide, please.

So here I've outlined that the hazard identification materials are prepared by OEHHA to support Committee deliberation. The topics covered in the hazard identification materials include a section on chemical identity occurrence and use. Then we review all the evidence available from human studies, all the evidence available from animal studies, and then all the mechanistic evidence and other relevant data that are available. And that may include pharmacokinetic information, information on metabolism, genotoxicity pathology, structure activity comparisons, and so on.

And next slide, please.

There are various formats that can be used to prepare these hazard identification materials. The format used for the 2 chemicals on today's agenda consists of a document written by OEHHA summarizing and reviewing available evidence.

And when we sent these documents to you, we also sent copies of all the references that were cited in the

1 documents. So you actually have the basis for the
2 summaries.
3 Another format that we've used in the past has
4 been -- for example, we've used this for fluoride and its
5 salts and vinclozolin. It will consist of a brief summary
6 by OEHHA, along with summaries from other entities, such
7 as, for example, the National Academy of Sciences, as well
8 as individual study reports, and other scientific
9 publications.
10 Next slide, please.
11 So to aid Committee determinations on whether a
12 chemical has been clearly shown, through scientifically
13 valid testing, according to generally accepted principles
14 to cause cancer, your Committee receives hazard
15 identification materials, all public comments on the
16 above, and studies and other information that the
17 Committee members request from OEHHA to obtain for them.
18 Are there any questions?
19 DIRECTOR ALEXEEFF: Yeah. Martha, could you --
20 thank you very much. Could you elaborate more on the
21 prioritization process, just explaining -- just -- so for
22 the new members so they understand when we do that, what
23 it will be like.
24 CHAIRPERSON MACK: Let me just specifically say
25 what I think the difficulty always is that there's a whole

bunch of chemicals. And when we consider the extent of public exposure, and the magnitude of the potential danger from what little information we often know, before you've actually gone into the literature in detail, there has to be some prioritization within these subsets.

And in the past, sometimes you've asked us to help prioritize, knowing what little we know in addition to what you know, to try and help you do that. And I think the Committee members would like to hear that that happens from time to time.

DR. SANDY: Sure. Yes. The last 3 meetings of this Committee, in fact, the Committee has had to look at anywhere from 20 to 30 to 35 chemicals at a meeting, where we've asked you for your advice and consultation on ranking of these chemicals.

And how did we -- dow did those chemicals arrive here? It's through, what we call, the prioritization process. There's a document that was developed with the input from your Committee and the DART Identification Committee, and it was released in 2004. And so we're following that process. OEHHA tracks chemicals that seem to have some evidence that's related to possible carcinogenicity. And so those number in the hundreds.

And then we look at that, and we look for chemicals that we believe have apparent exposure in

California, some potential for exposure. So that's the first cutoff. We'll only look at those chemicals.

And then we applied some data screens. We looked to see if there are any positive studies in humans indicating an association between exposure to the chemical and increased risk of cancer. And if we think there's enough information, it passes that human data screen.

We have an animal data screen. The first one we've applied for the last 3 years. We look to see are there any animal bioassays that suggest that treatment -- exposure to the chemical causes an increase in cancer treatment related tumors in the animals.

And we had some criteria. We needed either 2 studies or 1 study with multiple tumors, or at an unusual site or type or age of onset, or 1 study with malignant and combined tumors and a second study with benign tumors. So we had a screen laid out in the document. So we'd look through these chemicals and we would screen them in a very preliminary manner quickly doing a literature search and deciding, yes, this bunch of chemicals passes this screen, an animal screen, or a human screen.

If it did, that meant it went into another pool of chemicals. And those we tried to look at the overall evidence in a very preliminary manner, because again it's a screening process.

So we identified chemicals we thought had a sufficient amount of evidence to bring to you and have -- and we summarize that evidence. We tabulate it or compiled it, I should say, not summarize. And we actually gave you the studies -- the publications. And we asked you in batches of, as I said, you know, 20 something to 30 something chemicals per meeting to look at these and rank them for priority ranking as high, medium, low, or no priority for development of hazard identification materials.

And you took a look at that. We gave you information on the scientific data. We also gave you information on what we knew about the exposure, but it was -- this process is a screening level process. It's not a comprehensive literature review of every single chemical.

Did I leave anything out?

CHAIRPERSON MACK: Thank you for indulging me.

COMMITTEE MEMBER THOMAS: This Committee has now listed something like 800 chemicals, I think you told us. That may include reproductive and developmental. And presumably some additional number that have been considered by this Committee and not listed.

Has anybody ever tried to do a statistical analysis of those data to see what are the most

interesting predictors?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm not sure anybody has done that, but I did want to clarify that the 800 chemicals that we were talking -- that I mentioned were listed under all 4 of the listing mechanisms. And at different times in the history of Prop 65, a lot of them were listed under different, you know, authorities, maybe by this Committee or other times through the Authoritative Bodies or the Labor Code. And so -- and then the 800 includes chemicals that are listed for more than 1 endpoint also. But I can't really speak to the statistical analysis.

COMMITTEE MEMBER THOMAS: But there's other listing mechanisms that potentially are also relevant for the purposes of prioritization.

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, in terms of prioritization, if a chemical qualifies for the other listing mechanism, we'll use that one rather than bring it to the Committee.

COMMITTEE MEMBER THOMAS: No, I understand that, but as a statistical exercise it might be a fun thing to try one time, because you have well-defined metrics. Now, you may not have actually bothered to extract that information for the ones that were not brought before this prioritization scheme got established, but it seems to me

a relatively simple thing to do.

DR. SANDY: If you would like, we do have some data. We didn't do a statistical analysis, but right now, there are 554 chemicals listed as causing cancer under Proposition 65. And we've used all 4 mechanisms, as Carol said. So we have 246 have been listed by the State's qualified experts, and then the rest have been listed by other mechanisms.

And in our prioritization process, if we knew a chemical or thought a chemical was a candidate for listing via another -- an administrative listing process, we did not bring it to your Committee.

COMMITTEE MEMBER THOMAS: Understood.

COMMITTEE MEMBER DAIRKEE: Is there any prioritization based on its presence in drinking water?

DR. SANDY: We include that when we're considering possible exposure to the chemical, drinking water and other routes, but we're not limiting the exposure concern to drinking water.

COMMITTEE MEMBER DAIRKEE: Would that not be a priority though, that chemicals that are high in content in drinking water should be considered first, because exposure is much higher there?

DR. SANDY: That's a very good idea that you, as a Committee, can discuss and decide when we're

prioritizing chemicals, because Dr. Mack maybe wants to say something, but each Committee member participated in making their proposals for ranking.

CHAIRPERSON MACK: Yeah. I think, in general, we have tended to favor prioritizing things which are either very much in the news or very much controversial in the community, and things which have a substantial number of people, or especially highly sensitive people being exposed to it, for example, drugs that are given to kids, or a good example of one that we selected early was fluoride, because fluoride was such a controversial issue, and because the evidence existed, and we felt it was worthwhile upping it to -- upping its priority.

And so the Committee gets an opportunity to do that from the group of chemicals that are in roughly the same basket. Is that fair?

DR. SANDY: (Nods head.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. Dr. Mack, if you could keep the microphone right up by your mouth, that would help, because we've got the people on the webcast that are probably having a hard time hearing you.

So put it right up there.

CHAIRPERSON MACK: I said that the Committee gets an opportunity on the basis of both the degree of controversialness of a chemical and what we know about the

magnitude of the exposure, and especially whether it's targeted to especially sensitive subgroups of the population, like kids. And so each person has to use his own judgment about whether or not he wants to push for upgrade of that particular chemical, while we get the change to put our 2 bits in when the time comes. Is that clear?

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. That helped very much. Thank you, Dr. Mack.

CHAIRPERSON MACK: George.

DIRECTOR ALEXEEFF: Yes. I just wanted to comment a little bit on the materials we provide the Committee. So our intent is to provide the Committee all the information we can that would be relevant to your decisions.

So as noted by Martha, sometimes we -- or many times we actually develop a document. So we try to synthesize the material, if we feel it's very sort of disparate and there isn't really a good sort of base document to look at. And under those circumstances, we try to bring to your attention the most relevant materials.

But in those documents, we do not make a decision. So we don't provide like a straw decision that the Committee either approves or disapproves. But we do

try to let you know those types of data or articles or publications that seem to be most relevant for consideration.

And also, when we send the information to you, we do provide a lot of articles, but there may be other articles that you would like us to get. So feel free to come back to us, either through Cynthia or Martha, to ask us for some additional information if you don't have access to it. It could be a report or government report, or something like that that we may have access to.

And so that's something that we will not be -- we do not -- we can't create a meeting, so we won't be polling all the members for additional materials, but if there is some information you would like, feel free to ask us for it, if we can provide it.

CHAIRPERSON MACK: So are we finished with that component, and shall we proceed to the first chemical?

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Sorry. I think we have to allow just a couple minutes for public comment, in case somebody wanted to make a comment?

Did anybody put in a card?

Okay.

CHAIRPERSON MACK: Thank you, Carol.

DR. SANDY: So we will be discussing this 2,6-Dimethyl-N-Nitrosomorpholine. And Dr. Karin Ricker and Dr. Feng Tsai will be presenting.

But before they start, I wanted to mention how this chemical got to the Committee, so that the new members would understand that. So OEHHA briefed the CIC on this chemical in May of 2009. And the Committee recommended that the chemical be placed in the high priority group for preparation of hazard identification materials.

So OEHHA issued a request for relevant information in February of 2011. No information was received. And we completed the document and released it in August of 2012. And it was open for public comment and again no comments were received. So I'll turn it over to Dr. Ricker.

DR. RICKER: Good morning. My name is Karin Ricker. As Martha said, I'm a staff toxicologist.

DIRECTOR ALEXEEFF: Pull it closer.

DR. RICKER: Okay. I'll try not to eat it.

My name is Karin Ricker. I'm a staff toxicologist with OEHHA. And this is my colleague, Dr. Feng Tsai. We're here to present evidence today on the carcinogenicity of 2,6-Dimethyl-N-Nitrosomorpholine. The presentation this morning is a shortened version of the

data that we presented in the hazard ID document, which you received.

We'll start out with a little bit of chemistry. 2,6-Dimethyl-N-Nitrosomorpholine is a heterocyclic nitrosamine. You can see the chemical structure here. It has a morpholine ring with 2 methyl groups attached, and a nitroso group attached here and circled in red. The chemical exists as a cis- and a trans-stereoisomer.

It typically forms in industrial environments. For example, it is found in the rubber industry, and it also has been used as a model compound in cancer research.

We would like to start out here with cancer studies that were identified in our literature search. So we did not find any human cancer studies. However, we identified many positive animal bioassays, and we've compiled a little table here for you to see.

Primarily, DMNM has been tested for carcinogenicity in 3 rodent species, particularly the rat, hamster, and guinea pig, as well as in one fish species, the trout. Studies were mostly conducted in male and female animals, and investigators used various routes of exposure.

We started with the studies in rats. And I forgot to mention, we will abbreviate the chemical as DMNM, because it's such a mouthful to say its full name

every time.

So DMNM has been tested in 3 strains of rats, the Sprague-Dawley, Fischer Rat and the Wistar rat. Studies were conducted in male and female animals. And the routes of exposure included oral route, like drinking water and gavage, subcutaneous injection, intraperitoneal, and intravesicular bladder injection.

Typically, in these studies, authors used a smaller number of animals, you know, ranging from 9 to 20 animals per dose. And we had one study that used 50 animals.

Four of these studies used concurrent controls, and some other studies compared the results to a continuous series of untreated animals, which the investigators maintained at their facility during the same time frame.

Here's a brief overview of the tumor findings that were observed in the rats. Tumors were observed at multiple sites in rats. They also occurred in multiple strains in both male and female animals, and through multiple routes of exposure. Almost all the tumors that were observed are rare. We have listed them here on this slide.

The next slide will present some examples of these studies. We will not be presenting all the studies

that were reviewed in the HID document. Rather, we present a few selected examples showing results by different routes of exposure.

Here's our first example. The species is Sprague-Dawley rat, and the table here summarizes the results of 2 experiments, one in male, one in female rats. The exposure was via subcutaneous injection given weekly for life of the rat. The treated animals had a shortened lifespan compared to the controls.

In male rats, full length tumors were observed. Again, it was multiple tumor sites and included the esophagus, lung, and livers. These tumors were statistically significant.

I would like to point out that esophageal and lung tumors are rare. And that the observed incidence here is nearly 100 percent for the esophagus tumor, and over 50 percent for tumors in lung.

No tumors were observed in the controls. All treated animals died of esophageal tumors. And very similar findings were observed in the study of the female rat, which is also shown here.

DIRECTOR ALEXEEFF: Can we try switching the mic to see if that works. We're going to try another mic just to see if it helps.

DR. RICKER: Okay. Better. Sorry.

COMMITTEE MEMBER THOMAS: One other question. Do you mind interruptions as you go along or do you want us to hold questions till the end.

DR. RICKER: It's up to you.

Do you have a question?

COMMITTEE MEMBER THOMAS: Yeah, I would just like one of the -- yourself or one of the staff -- one of the Committee members to enlighten me about how we are to interpret gross effects on survival when taking into account the carcinogenicity data?

You pointed out that all treated groups, including the lowest dose group, had shortened survival, which indicates to me toxic effects through a noncancer mechanism, which may reflect -- may cause us to question whether or not the carcinogenic effect would be present at lower doses.

DR. RICKER: Well, the lower dose animals, you know, showed tumors, and in the higher dose they just didn't survive long enough to develop tumors.

COMMITTEE MEMBER THOMAS: But I thought you said all exposed groups had shorter survival?

DR. RICKER: Yes, I think it was --

DR. SANDY: If I can --

COMMITTEE MEMBER THOMAS: That's what it says in the footnote to the picture.

DR. SANDY: Yes. So if you look at the -- there's 2 dose groups here and you look at -- every single animal that was treated had a tumor of one type or another. And I believe the authors indicated the animals were dying of a tumor.

But the larger question that you've asked is probably better addressed by -- you know, discussed among you as a Committee. And you're going to see this happen a lot in almost every study that we're presenting on these chemicals. So perhaps it's best to hold that discussion for the Panel.

COMMITTEE MEMBER THOMAS: Yeah, that's fine. Go ahead.

DR. RICKER: Sorry.

Okay. So I may just start over again with just this slide.

CHAIRPERSON MACK: Excuse me a second. Just a second. I think it would be preferable if we let them finish, then let the community make their points, and then we'll come to the Committee and let people who have been assigned to review the things, state it, and then you go after.

COMMITTEE MEMBER THOMAS: That's fine.

CHAIRPERSON MACK: Thank you. Go ahead.

DR. RICKER: So I continue then. Our next study

is female a Fischer rat study. The route of exposure was drinking water. In this case, the authors did not use a concurrent control, but they compared the treated animals to a continued series of untreated controls, which were maintained at the facility.

Tumor findings here included again multiple tumor sites, such as nasal cavity, tongue, esophagus and forestomach. These tumors are rare. And again, we see high incidence of these rare tumors in the treated animals.

None of the control animals had tumors. And again, animals used in this experiment had a shortened lifespan compared to control animals, and close to 100 percent of animal died of tumors at 20 weeks.

Here, we present the results of 2 gavage studies. One in male and one in female Fischer rats. No concurrent controls were included here. The treated animals had a shortened survival of less than 40 weeks, and, again, all animals died of tumors.

In the female rat, multiple tumor sites were observed. And the sites with tumors included the esophagus, nasal cavity, forestomach, and the lung adenocarcinoma. Again, these are rare tumors.

Similar findings were reported in the males, with the exception of forestomach tumors. And the authors note

that no tumors have been reported at these sites in untreated control animals in other studies conducted by these authors.

DR. TSAI: Good morning. And I'm going to present the results from the Hamster studies. There are 13 Hamster bioassays reviewed in detail in the HID. And here's an overview.

DMNM is tested in 2 different strains, Syrian Golden hamster and European hamsters by 2 different routes, gavage and subcutaneous injections in both males and females. And this study usually has small number of animals, ranging from 7 to 30 per dose group.

All studies, except 1, had concurrent controls. DMNM-induced tumors in hamster at multiple sites including 7 rare tumors and 5 other tumor types. In the first 2 rare tumors, nasal cavity and lung tumors, were also reported in the rats bioassay. And other rare tumor types are like pancreas and kidney tumors.

And I won't present all the results, but instead I'll just pick a few examples to show you results from different strains and different exposure routes.

This is a study done by weekly gavage for life in female Syrian Golden hamsters. And there are 4 dose groups. And the dosing range ranges from 1/40th to 1/5th of the lethal dose, 50. And there's dose response

survival seen in these 4 dose groups. It's ranging from 65 weeks, at low dose, and 24 weeks only in the high dose.

And no tumors were seen in the control. And dose animals often developed tumors at multiple sites. And treated related increased tumors were seen in these sites. And rare tumors are colored, so that it's easier to see.

For example, nasal cavity is a rare tumor that we're seeing as high as 7 out of 14 in the mid-dose. And lung tumors were seen in about 1/3 of the dose groups.

Other than these rare tumors, 3 additional tumor sites were seen. For example, for tracheal tumors, 8 out of 12 of the animals were observed with tracheal tumors. And the next slide is the result.

It's a study done on different strain of female European hamster by weekly gavage for life. And in this study, there are only 2 dose groups. And again, we see an increase in 2 rare tumors, nasal cavity and lung tumors.

For nasal cavity, you can see that over 1/3 of the dose animals had this rare tumor. And lung tumor was observed in about 50 percent of the high dose groups.

And tracheal and liver tumors were also observed in European hamsters treated with DMNM. And this study is done by a different route, weekly subcutaneous injection for life in Syrian Golden hamsters. Here, they have 3 dose groups. And again, we see dose response survival in

1 treated animal ranging from 32 to 40 weeks, as compared
2 with 50 weeks in control.
3 And you could see here almost all high dose
4 animals developed nasal tumors. And for pancreas -- for
5 lung tumors, it was found as high as 12 out of 30 in high
6 dose group.
7 And almost all tumor sites here show a
8 statistically significant increase, by both pairwise and
9 trend test. So the overall observation from this bioassay
10 as reviewed is that treatment-related tumor increases were
11 seen at multiple sites, including several rare tumors in
12 both Syrian Golden hamster and European hamsters by 2
13 different routes, gavage and subcutaneous injection.
14 And next, I'm going to present a study done in
15 guinea pigs. There are 2 strains being studies. Strain 2
16 and random-bred. And DMNM was gavaged in male animals
17 only. And in both studies, they had 18 to 20 animals per
18 group. And both had concurrent control. For guinea pig,
19 the target organ is liver, including hemangiosarcoma and
20 cholangioma.
21 So this is the first study done in male rats --
22 male Strain 2 guinea pig, and you can see that
23 hemangiosarcomas were observed in 2 dose groups. And in
24 addition to hemangiosarcoma, there are 4 other types of
25 malignant liver tumors seen in the lower dose.

Next slide.

And this is another study done in male random-bred guinea pigs. No tumor was seen in the control. And 14 out of 17 in high dose and 10 out of 15 developed hemangiosarcoma. And in addition, cholangiomas are observed in both dose group.

Next Karin will present the bioassay in trout.

DR. RICKER: Okay. So we're switching away from rodents. We're coming to the trout. It's depicted here in the slide. Trout actually have been used in cancer research for several decades. They show a high sensitivity to a variety of carcinogens, for example, some of the aflatoxins. And they also have a fairly well described tumor pathology.

We identified one study that was conducted in trout. It was a diet study. We showed the results here on this slide. The animals were sampled at 9 and 18 months. At 9 months, liver tumors were observed in 11 of 64 trout. And at 18 months, the number of liver tumors observed was 78 out of 113.

In addition, at 18 months, tumors of the glandular stomach and the swimbladder were also observed. No tumors were observed in the controls.

And I'd like to point out that liver tumors are rare in trout, but here observed at greater than 50

percent of the treated animals.

Okay. So we're now moving from cancer bioassay to present results from a genotoxicity study. Again, I'd like to point out that we present here an abbreviated version of the study findings. A complete and more detailed presentation of the data on genotoxicity is contained in your HID document.

We start out with findings for non-mammalian genotoxicity of the DMNM. DMNM was positive in multiple salmonella typhimurium reverse mutation assays. And it also tested positive in Drosophila melanogaster.

In salmonella, DMNM induced both base pair and frameshift mutation in various salmonella strains. And in Drosophila it induced X-linked recessive lethal mutations.

DMNM was also positive in mammalian test systems. In vitro, DMNM induced unscheduled DNA synthesis in rat hepatocytes and in hamster main pancreatic duct cells. And it formed DNA, RNA, and protein adducts in hamster pancreas cells.

In vivo, DMNM induced single-strand DNA breaks in hamsters, but not in rats, and also formed DNA adducts in hamster and rat.

DR. TSAI: The pharmacokinetics of DMNM is reviewed in detail in the HID document. Here are some short summaries. DMNM is rapidly absorbed and distributed

in vivo. In rats and hamster by one-time gavage of radioactive DMNM.

Within an hour, radioactivity was detected in many organs, such as liver, kidney, and pancreas. And there's no significant species difference of the DMNM concentration across tissues. And metabolism evidence comes from many in vivo and in vitro studies.

There are multiple metabolites identified in vivo in the blood, urine, liver, pancreas from different strains and different species. And I'll present more detail in the next slide.

There are multiple pathways alpha-hydroxylation involved in the metabolism, and various enzyme systems were involved for the DMNM metabolites. For example, in rabbits pre-treated with phenobarbital, an inducer of CYP2E1, showed increased metabolism of DMNM in vivo. In metabolism of DMNM in hamster liver microsome systems was inhibited by different cytochrome P450 inhibitors, such as alpha-benzoflavones.

As for the excretion, less than 2 percent of the parent compound was detected in the urine or feces after 24 hours of gavage. And this figure is compiled from many metabolism studies on DMNM, and its 5 identified metabolites.

And the 4 chemical names are shown here in the

legends. I won't try to say them all. There are 2 metabolic pathways. One is alpha-hydroxylation, the other is beta-hydroxylation. DMNM can be metabolized to reactive nitrosamine via alpha-hydroxylation, and then further degraded to diazonium or carbonium ions.

And alpha-hydroxylation is believed to be a major metabolic pathway for some cyclic nitrosamines, such as nitrosomorpholine, but for DMNM, beta-hydroxylation is as important.

As you can see that there are 2 tautomeric mixtures of HPOP. One is in the cyclic form. The other is in the open-chain form. And these 2 exist in equilibriums. And DMNM can be metabolized via beta-hydroxylation. And it is catalyzed by mixed-function oxidase, and require NADPH in oxygen to form HPOP. And then HPOP could be metabolized to BHP or BOP. But as you can see that HPOP is also the common metabolite of BHP, BOP, and DMNM.

And BOP could be further metabolized to MOP and MHP. Many of the DMNM metabolites are genotoxic and carcinogenic. Karin will talk more about these metabolites.

DR. RICKER: Okay. So on these next few slides, we are presenting information regarding the carcinogenicity and genotoxicity of some DMNM metabolites,

as Feng just said, as well as carcinogenicity and genotoxicity of some structurally related chemicals.

On this slide here, we are presenting a comparison of DMNM and 3 of its metabolites in terms of carcinogenicity. The 3 metabolites are listed here. They are HPOP, BHP, and BOP, and the structures are shown on the slide.

These chemicals were all tested in rodents, in the rat, the mouse, and the hamster. I would like to point out that DMNM was not tested in the mouse, and HPOP was only tested in the rat.

And as can be seen from this slide, all 3 metabolites cause tumors in rodents. They share common tumor sites with each other and with DMNM. For example, all 4 chemicals induce liver, nasal, and lung tumors in rats, and lung, liver, and pancreatic tumors in hamster.

In terms of genotoxicity, like the parent compound, DMNM and its metabolites were positive in a variety of tests. Some of this information, this table here, as you can see, all 4 were positive in salmonella mutagenicity assays, and they're also positive for DNA adduct formation.

We are now moving on to compare the carcinogenicity and genotoxicity of DMNM to 2 structurally related chemicals. One chemical, nitrosomorpholine, is

shown here, and the other is nitrosopiperidine. Each of these chemicals is already listed as a non-carcinogen under Proposition 65.

Like the metabolites, these chemicals were tested in rat, mouse, and hamster. And again, remember that DMNM was not tested in the mouse.

Like DMNM, nitrosomorpholine and nitrosopiperidine induced tumors in multiple species and at multiple sites, and they share common tumor sites with DMNM, for example, all induced liver, nasal, esophageal tumors in rats, which are rare tumors.

These chemicals were also tested for genotoxicity in these test systems shown here on this table. And we can see that all 3 chemicals are positive again in the salmonella mutagenicity tests, and all 3 induced unscheduled DNA synthesis in vitro.

What is a possible mechanism of action for DMNM?

DMNM is likely to induce tumors through a genotoxic mechanism. This is based on findings that DMNM was positive in multiple test systems like the salmonella and the Drosophila, and induced UDS in mammalian cells, as well as DNA single strand breaks. It also binds covalently to DNA and RNA and protein both in vitro and in vivo.

Furthermore, as reviewed under metabolism, DMNM,

like many other nitrosamines requires metabolic activation via cytochrome P450. And metabolic activation can occur at either the alpha- or beta-carbons of the molecule. And oxidation of DMNM likely results in the formation of multiple genotoxic and carcinogenic metabolites.

DR. TSAI: Okay. So to briefly summarize the carcinogenicity evidence we compiled in the 77-page long HID. From the review of more than 20 animal bioassays, DMNM induced multiple tumor sites from multiple species and strains in both males and females by multiple routes of exposures. And those tumors sites, a lot of them are rare tumors. And many of them showed statistically significant increase by both pairwise comparison and by trend test.

And this table summarized the shared tumor site among four species studied. And the rare tumors are marked in red, so that it's easier to see. There are 5 rare tumor sites shared by 4 species, such as nasal cavity and lung tumor.

And additional species-specific tumors are listed here. And again, the rare tumors are marked in red. As you can see that 2 additional rare tumors, tongue tumor and esophageal tumors are reported in red. And in hamsters, there are 5 additional rare tumors plus 2 other tumors sites. And in trout, there are 2 tumor sites

identified in the DMNM treated animal.

And in addition to the positive animal bioassays, DMNM is also genotoxic in both in vivo and in vitro systems. And moreover, the metabolites of DMNM, such as HPOP and BOP are also genotoxic and carcinogenic.

And 2 structurally related compounds nitrosomorpholine and nitrosopiperidines share similar tumor sites with DMNM, and both chemicals are listed as Proposition 65 carcinogens.

And this concludes our presentation on the DMNM carcinogenicity.

Thank you.

CHAIRPERSON MACK: Thank you very much. The 2 people on the Committee that have looked at this chemical, I think, are Dr. Eastmond and Dr. Zhang, is that correct?

COMMITTEE MEMBER ZHANG: Yes.

CHAIRPERSON MACK: Okay. Let's lead off with David.

COMMITTEE MEMBER EASTMOND: Well, thank you for the presentation, and putting together the materials. I should say for those who've just joined the Committee, you will probably never see a chemical with as many cancer studies as this one.

But it does bring up a bit of a challenge, because many of these studies were conducted early in the

days of carcinogen testing and using protocols that would not be widely accepted today. So you have this sort of interpretation, because the challenge of the Committee is to -- as I'll read it basically is to determine whether this chemical has been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer.

So it's a little different because you have to kind of weigh the studies. And so the way I did this was I kind of prioritized these studies by saying, which ones did I consider kind of primary studies, which ones would be supportive studies, and then other information that was useful for me.

And so I focused primarily on those which initially by the oral route, by gavage, rather than looking at those through subcutaneous or IP injection.

And the ones that I focused on primarily was, from my point of view, the tests that were conducted in the Syrian hamsters, in which DMNM was administered by gavage. I think it was clearly shown there are dose related increases in nasal cavity tumors, both benign and malignant, and you had significant height at individual doses as well.

Increase in tumors in nasal cavity in the liver and pancreas as well, and that was both in males and

1 females. There are also studies by other investigators
2 where they looked at European hamsters. And I don't know
3 if those are different strains or different species
4 actually, because some of the hamsters are dramatically
5 different than others.
6 But anyway, in that one both in male and female
7 European hamsters there were dose-related increases,
8 highly significant increase in nasal cavity and lung of
9 females, and to a lesser degree in the males, and
10 increases in other tumors. Again, this is combined
11 malignant and benign tumors.
12 And then the guinea pigs, 2 separate studies
13 showed significant increases in hemangiosarcomas and a
14 malignant tumor. Those, for me, were kind of the primary
15 studies conducted by oral gavage, pretty clear cut.
16 As far as other supporting studies, there were
17 these other studies in rats by other routes of
18 administration, which are clear increases. There were
19 also the other studies in which they didn't have
20 concurrent controls. Sometimes they used other controls
21 or independently, but the frequency of tumors was so high
22 of rare tumors, that for me that's sort of supportive
23 evidence, but it could not -- would not be the driving
24 piece of information.
25 And then there was certainly the significant

dose-related increases seen in the trout, which were very unusual, was supportive.

As you indicated, certainly mutagenic and short-term tests for mutagenicity, such as the Ames test, binds DNA in vivo. Induced unscheduled DNA synthesis in vitro, and single-strand breaks in pancreatic cells in vivo.

This is a, nitrosamine which belongs to a widely recognized mutagenic and carcinogenic group of agents. The metabolites are mutagenic and carcinogenic, and induced rare tumors.

So, in my opinion, that this particular chemical has been clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer and should therefore be listed.

CHAIRPERSON MACK: Thank you, David.

Dr. Zhang.

COMMITTEE MEMBER ZHANG: I fully agree what Dr. Eastmond just said.

Could I -- if I have some questions for staff, could I ask question before I --

COMMITTEE MEMBER EASTMOND: Go ahead.

COMMITTEE MEMBER ZHANG: I have to say this is really very well written, the documents. I enjoyed reading it. And whoever did the job I think is really

wonderful. You know, not only this, because I have been on a committee for -- I mean, other committees from, let's say, IOM or other. You know, so the documents I think are written very clearly and summarized very well, but I do have just a couple questions.

One of you mentioned the study never -- isn't -- I haven't seen that much animal study in mice. So my question would be, is there is no study has been done in mice, or is it just that negative results? So my question would be, I haven't seen anything studies. It seems like a pretty negative results.

So there's 2 questions, is any study has been done -- carcinogenicity study done in mice, is question number 1?

DR. RICKER: We did not identify any study in mice.

COMMITTEE MEMBER ZHANG: Okay. Have you identified any study that shows negative results?

DR. RICKER: I'm sorry?

COMMITTEE MEMBER ZHANG: Negative results? So it's just -- because, you know, the whole --

DR. RICKER: Negative studies, you mean, for cancer bioassay?

COMMITTEE MEMBER ZHANG: Yes.

DR. RICKER: No.

COMMITTEE MEMBER ZHANG: No.

DR. TSAI: In the HIDs we present all the studies that we could find, and the results are reviews. For the presentation here, we only selected the positive results, but in the HID you could find studies without finding any significant tumor increase. Yes, they are all included in the review. We didn't selectively include studies.

COMMITTEE MEMBER ZHANG: Okay. So the -- yeah, I didn't read through the whole report. So you're including everything.

DR. TSAI: Everything we could find.

COMMITTEE MEMBER ZHANG: So basically, it looks like -- you know, I'm amazed, you know, how published scientific results is so pretty consistent, you know, across the species and across the, you know, different -- even -- I would try to also examine the dose range as well.

Although, as you know, Dr. Thomas mentioned it seems that even at the low dose, but I think the low dose is only the low dose comparing what they have tested. You know, if we know that, they could even maybe go lower.

COMMITTEE MEMBER THOMAS: That was the essence of my question.

COMMITTEE MEMBER ZHANG: Right. That's basically -- I thought that was your question.

And clearly -- so I think this chemical, DMNM, not only is mutagenic and is genotoxic, and from the data we have reviewed today, and, you know, from what the staff presentation, I'm pretty convinced that it's carcinogenic.

CHAIRPERSON MACK: Thank you.

DR. TSAI: Mic, please, Dr. Mack.

CHAIRPERSON MACK: There. Now, it's on.

So let's begin with Dr. Dairkee. Do you have anything to add?

COMMITTEE MEMBER DAIRKEE: I'm just a little puzzled as to why there is such a preponderance of these nasal tumors and whether it is from the aerosol in the air -- although, the carcinogen has been given in drinking water, but why nasal tumors are so -- and the whole path from nasal, trachea, lung, that whole pathway.

COMMITTEE MEMBER ZHANG: That's a very good question. When I was reading the documents I had a similar question to ask. I ask myself, you know, why? But the drinking water, I first thought, you know, the nasal cavity generally from the breath. But I think for this compound mostly is maybe through -- you know, even though drinking water through the --

COMMITTEE MEMBER THOMAS: Aerosol.

COMMITTEE MEMBER ZHANG: Right. Yeah. No, it's not. I checked. It's very low though. Here. So it's

pretty low. So why nasal?

CHAIRPERSON MACK: Well, I would say the nose is connected to everything else.

(Laughter.)

COMMITTEE MEMBER ZHANG: That's right.

CHAIRPERSON MACK: And I don't think we should forget that. And it depends where on the nose, and it depends exactly -- you know, after all bloodborne carcinogens are going to get to the nose too.

So I think there are lots of questions about the.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, we still can't hear you.

CHAIRPERSON MACK: -- this cancer -- this compound -- I think there are lots of questions about site-specific carcinogenicity that this compound raises, but I won't say anymore right now.

Duncan, do you have any comment now?

COMMITTEE MEMBER THOMAS: Not really. I just wanted to clarify that my question was directed more at my general education, not at this specific chemical. I am certainly, in my previous service, seen discussion about the question of phenomena that are found only at high doses that are associated with extreme life shortening, and whether that evidence would be considered germane to the question of carcinogenicity at more realistic doses.

And so I just wanted to get up to speed on the Committee's thinking in general about that situation.

I agree with everything I've heard so far about the consistency of the evidence and so forth, and the multiple mechanisms and so on, that I don't think that's much an issue in this particular case.

CHAIRPERSON MACK: So let's go down to the other end of the meeting -- of the group and, Peggy, do you have any comment?

COMMITTEE MEMBER REYNOLDS: No. Actually, I thought the -- even though this is outside of my are of expertise, the data seemed pretty compelling. And I appreciated the reviews, both by staff and the Committee members, on this.

CHAIRPERSON MACK: Dr. Bush.

COMMITTEE MEMBER BUSH: I agree with the consensus as well that is being built here. There certainly is compelling data. One query I have for the authors who put the study -- this report together, when -- sorry, the toxicologists.

When you did compile the numbers for those animals that had multiple tumors, they were double counted essentially, weren't they? If an animal had multiple tumors, specifically referring to the gavage study in the Syrian golden hamsters, I think one of you indicated that

there were multiple tumors, is that true?

DR. TSAI: Which table are you referring to?

COMMITTEE MEMBER ZHANG: So your question is one --

COMMITTEE MEMBER BUSH: If an animal has --

COMMITTEE MEMBER ZHANG: -- if an animal had multiple tumors?

COMMITTEE MEMBER BUSH: If an animal has multiple tumor types, are you going to be counting them in each one of those categories?

DR. TSAI: The tumors were counted site specifically. We might combine benign and malignant, but I don't think we double counted.

COMMITTEE MEMBER BUSH: Okay. That's what I wanted to clarify.

Thank you.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. Again, I want to congratulate the authors. It's a very nice comprehensive hazard identification document. I agree it's clearly a very strongly genotoxic carcinogen. Strongly genotoxic. And it's clearly positive in multiple species, dual sexes, multiple tumor sites. And some of the yields of carcinogenesis are very, very high, 50 percent, almost 100 percent. It's really a strong

carcinogen.

The question about the nasal cavity is interesting. I've done some work with nasal carcinogens. It's very thin, but it has a very high activity of cytochrome P450, because it's a portal of entry. So when carcinogens hit there, they're very active. It metabolized.

So I have no trouble at all with this. There are a few holes here and there, but overall the data, I think, is overwhelming in favor of this being a carcinogen.

CHAIRPERSON MACK: Do you want to say something, George?

DIRECTOR ALEXEEFF: Well, I don't know, maybe Dr. Eastmond can clear up the question that -- I just wanted to clarify the question of Dr. Bush's. I wasn't sure if it was totally clarified. But in terms of the animal study reports, like the reports, certain number of animals having a certain tumor type. The same animal might have multiple tumors in different locations. I just wanted to make that clear. So we don't really consider it double counting, but it is the same animal might have nasal tumors and also stomach tumors or something like that.

CHAIRPERSON MACK: I had 2 comments. Oh, David.

COMMITTEE MEMBER EASTMOND: Go ahead.

CHAIRPERSON MACK: Go ahead.

COMMITTEE MEMBER EASTMOND: Just to respond on the nasal cavity tumors for me. Well, in general, nitrosamines tend to have many different target organs. They're very genotoxic, and it may be related to bioactivation, as Joe Landolph said. But this was highly carcinogenic when given by subcutaneous route of exposure. So it's not a route-of-exposure issue, it's basically a target organ specificity, at least from my interpretation, because almost every animal developed nasal tumors when it was given by subcutaneous route.

CHAIRPERSON MACK: I had a couple of observations or comments.

One, I had the same observation that Duncan did that this killed animals very fast. And that suggests that there's a lot going on in different tissues, in addition to carcinogenesis. And it just means it's a really scary chemical.

The other thing I wanted to comment on, you list in the tables each time both benign and malignant together. I'd like, in the future, if you would put in parenthesis how many are malignant, because the trend over dose as to what portion become malignant would be a piece of interesting information, that might, in other chemicals, be more pertinent than it is now, because this is such an overwhelmingly nasty stuff.

And I guess the other comment I had, pancreas popped up here. Pancreas doesn't pop up very often. I don't know -- at least in our experience here. And pancreas is a really important cancer, and we really don't understand it very well.

But there are a whole bunch of occupational studies, which are usually confounded by smoking, but nonetheless pretty convincing that people who work in certain occupations, including occupations that have to do with cutting oil, for example, may have high risks of pancreas cancer. And they're never really totally convincing on their own, but one wonders whether or not somebody ought to think about looking at DNA adducts in people who have those exposures with respect to this particular set of stuff, because it might be worthwhile following up.

Other than that, I certainly don't have any comments.

Dr. Zhang.

COMMITTEE MEMBER ZHANG: Since you make a recommendation to the staff, and one other thing come up to me, is about the dose. From your presentation today, you have one table. You have the concentration -- you know, dose concentration times the time, the treatment -- you know, period, so you had both. I think it would be

really hard for us when you have the table in the documents, if you would have, you know, how many milligrams per week, but then how many weeks. That would help us to compare studies from different studies, because the treatment period of time could be different. So not only is the concentration different but the period is different. So when we try to cross from one table to another table, I had to do another mental math to look at it. So if you have that -- already list that, it's going to be a little bit easier. This is one.

Two is, I think this chemical seems very convincing, but when I was reading at the one thing, not -- I just wonder why no other agency have previously listed this as a carcinogen.

CHAIRPERSON MACK: I think it's probably they just haven't gotten to it, but I think that's a legitimate question.

Anybody else have any comments on the Committee?

Yes, Martha.

DR. SANDY: I was going to clarify on your point, Dr. Mack, about presenting the benign tumor incidence and then the malignant separately. We do that when we have the information from the published report always. But when we don't have that information, we can't separate it out.

CHAIRPERSON MACK: It would be nice if you told us that it's not there. Just put a question mark there somehow.

(Laughter.)

CHAIRPERSON MACK: Thank you. Always good points.

Now, we didn't have any requests for community comment. We didn't have any requests for community comment in the form of slips. Is there anybody in the group who would like to make any comment on this compound?

I guess not. Then I think we can proceed to the important question. So I will phrase it as written and we need responses as I indicate.

Has 2,6-Dimethyl-N-Nitrosomorpholine been clearly, through scientifically valid testing, according to generally accepted principles, to cause cancer?

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: It looks like we have 7 yeses and 0 noes and 0 abstentions. I presume there are no abstentions.

DIRECTOR ALEXEEFF: Eight.

CHAIRPERSON MACK: Eight, sorry about that.

I'm numerically deficient.

(Laughter.)

CHAIRPERSON MACK: Therefore, the Committee has found that this particular compound 2,6-Dimethyl-N-Nitrosomorpholine has been clearly shown, through scientific valid testing, according to generally accepted principles to cause cancer, and it will therefore be recommended for listing.

So now we proceed to the second chemical, which has a peculiar name, which I will require an explanation for.

CHAIRPERSON MACK: You get a break.

We'll resume in a moment.

DIRECTOR ALEXEEFF: 10, 15?

That's right.

CHIEF COUNSEL MONAHAN-CUMMINGS: Could they -- are we taking a lunch break? It's 12 o'clock.

COMMITTEE MEMBER EASTMOND: You want to take a lunch break?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm just wondering, Dr. Mack, if this is a lunch break?

DIRECTOR ALEXEEFF: Do you want to take a lunch break or a --

CHAIRPERSON MACK: All those wishing a lunch

break, please raise your hands?

(No hands raised.)

CHAIRPERSON MACK: I guess we're not.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So I think the court reporter needs at least 10 minutes. You want 15?

THE COURT REPORTER: (Nods head.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Fifteen is good.

DIRECTOR ALEXEEFF: Fifteen minute break then.

CHAIRPERSON MACK: Fifteen minute break.

(Off record: 11:55 AM)

(Thereupon a recess was taken.)

(On record: 12:14 PM)

DIRECT ALEXEEFF: All right, everybody, I think we're ready to reconvene, if you'll take your seats.

(Thereupon an overhead presentation was presented as follows.)

DIRECTOR ALEXEEFF: Our next item, C.I. Disperse Yellow 3.

CHAIRPERSON MACK: Yes. Martha, would you tell --

DIRECTOR ALEXEEFF: Oh, so let me introduce actually the staff members for this. Dr. Kate Li and Dr. Jay Beaumont. So they'll be making the -- oh, and is -- no. They'll be making the presentation.

Thank you.

DR. SANDY: And, Kate, before you start, I wanted to give some introduction to the Committee members as to how this compound has come to you as well.

So we briefed the CIC on this chemical, C.I. Disperse Yellow 3 in October of 2011. And the Committee recommended that the chemical be placed in the high priority group for preparation of hazard identification materials.

So OEHHA issued a request for relevant information in November 2011. One submission was received. And we completed the HID and released it in August of 2012. And I'll turn it over the Kate.

DR. LI: Hello. I'm Kate Li. For this chemical, C.I. Disperse Yellow 3, Dr. Beaumont will present the human epidemiological evidence, and I'm going to present the animals -- animal carcinogenicity evidence and other relevant evidence to the Committee. And all the details are available in the HID document.

So to start with, we're going to start with the chemical properties of C.I. Disperse Yellow 3. As here, a circle in the center, it is a monoazo dye. And it's soluble actually in acetone, ethanol, and benzene, but with very limited water solubility as indicated here. The chemical appears as a powder form.

So C.I. Disperse Yellow 3 is used in clothing, hosiery, and carpeting products as a textile for coloring a number of -- a variety of synthetic fibers and wools and furs, and other plastic type of materials. It's also used as dyes in ink products and in pulp and paper manufacturing.

So I'll turn this to Jay.

DR. BEAUMONT: I'll try this one. This one seems like a better quality microphone.

I would like to tell you what we've found about the occurrence of human exposures to Disperse Yellow 3. And, as Kate mentioned, it's been written about, in particular in documents by IARC and others, as having been used in some industries like -- or for some products like wools and furs that we haven't -- at OEHHA, haven't been able to confirm.

As far as we can tell, it's used almost entirely on synthetic textiles. And there may be some small amount used in inks, but we haven't identified how much yet.

Let's see. So there are 2 populations potentially exposed, those working with the chemical in textile manufacturing, and also the general public may be exposed when they are using or wearing these textiles.

As a documented example of exposure to workers, C.I. Disperse Yellow 3 is listed as 1 of 39 dyes --

disperse dyes known to cause allergic contact dermatitis in textile workers, and it's been known to do that for some time.

Then with regard to the general public, there isn't much information, but there have been reports of again allergic contact dermatitis associated, in one case, with nylon hosiery using this exact dye.

I'd like to mention that disperse dyes in general are especially good for synthetic fabrics. In fact, they're really the only dyes that work on most synthetic fabrics. They're especially good on nylon, but also polyester. In this photograph in the slide, that's a picture of the dye at various concentrations on polyesters.

The takeway from this slide is the synthetic materials, and this will come up later when we talk about some epidemiology studies.

Oh, and I should have mentioned that the only epidemiology evidence that's relevant at all so far has come from occupational studies. We don't have anything on human population exposed. And in textile manufacturing, there are basically 2 areas of opportunities for workers to be exposed. One is at the dyeing stage -- I'm getting my stages mixed up, up here.

Two different kinds of stages. Dyeing can occur

when the textile is still a yarn. And so then the workers are working with colored yarn and that yarn can be woven into fabrics, and so the workers are working with colored fabrics. So that's if the yarn is dyed initially, but it can be dyed later on. They can make the yarn, make the fabric, the whole 9 yards and then dye it at the last stage almost, in which case there would be much less exposure.

And, let's see, in this photograph -- 2 photographs, I'd like to point out the first one is called -- a process called winding. Surprise. Surprise. They're winding from one type of spool onto a different kind of spool, because the different machines have different spool requirements.

And when they're working with colored yarns, I think there's potential for dermal and respiratory exposure. And then when they go to make the fabrics, they first do a process called warping. And that's the second photograph, which is the laying out lengthwise of the yarns. And so that's warping. Both the terms, "warping", and, "winding", will also come up in a few minutes.

And it's -- I guess I should say this is my opinion, that exposures to direct dyes, including Direct Yellow 3 -- I'm sorry, disperse dyes, including Disperse Yellow 3, may be more likely in handling dyed materials

rather than in the dyeing process.

And I should say that dyes in textile manufacturing, going back to the 1950s, some have turned out to be carcinogenic, and, in fact, bladder cancer was one of the first occupational epidemics I learned about in grad school.

Okay. I am now going to talk about the carcinogenicity studies, and the epidemiologic evidence. As meager as it is, there is some evidence that is relevant. I'd like to first say that there are no studies of humans with documented exposure to this exact chemical, but there are some studies with job categories with workers who had good potential for exposure. And there are four of those studies. So even though they aren't direct evidence, they're probably relevant.

Okay. And I'd like to start with things that the studies have in common. This will make the process faster.

First of all, all 4 of the studies were of bladder cancer and only bladder cancer. All 4 were case control in their epidemiology study design. Three of the 4 were conducted in Spain and 1 in New Zealand. All 4 studies used interviewer administered questionnaires to collect their exposure data. And they collected exposure data, lifetime occupational histories, and smoking -- in

fact, I should have added to this slide that all 4 studies collected data on and adjusted for cigarette smoking which is a known cause of bladder cancer.

Then all 4, for coding the occupational histories, they used some sort of a standard occupational industry coding system -- preexisting system. They didn't make it up. So this would be a system like the census -- the U.S. Census uses to code our occupations into categories.

But one study additionally designed a specific questionnaire for the textile industry. So that may be more informative.

In chronological order, the first study was by Gonzales et al., in Spain. In 1988 it was published. And it was a case control study in 1 county in Spain, where there was 1 hospital. And to get enough cases, they took all of the cases they could identify through the hospital and through the local death registry. And in the end, about 3/4 of their cases were actually deceased before interviewed, and 1/4 were still alive.

So that was 57 bladder cancer cases, and then roughly a double number of controls. They were matched on type of case, so hospital cases got hospital controls.

In their standard coding they had a job category for the textile industry of textile dyeing or printing.

So if there are exposures during dyeing or printing, as captured by this that could cause cancer, this is where we might see an effect. And they did, in fact, find a significantly increased odds ratio for 4.4, based upon small numbers, 8 exposed cases and 3 exposed controls.

This study, unlike the other 3, actually mentioned Disperse Yellow 3 as being one of the dyes used in the industry in this town. So a major limitation of this study was that most subjects were deceased and proxy interviews with spouses and close friends were required. So the data wasn't as good a quality.

Okay. Then the second study has the same first author. And just to back up a little bit, he did the first study, he says in the article, because their county, relative to the rest of Spain, had seen an increase in bladder cancer incidence, or mortality, I guess.

So they did the second study, but this time much larger, based at 12 hospitals in 4 different geographic regions within Spain, almost 10 times as many bladder cancer cases, almost 500. And they had 2 control groups. They matched hospital controls and also general population controls. I believe the results they presented were for the hospital control.

I'm not sure about that at the moment.

They had a job category called textile dyer. So

again, this is a potential exposure job classification. But this time they did not see a significant excess risk. It was slightly elevated. And in this article this particular dye was not mentioned.

The third study was a case control study in New Zealand that was population based. So is the first of the series of studies -- case control studies that was population based from a nationwide cancer registry and the controls were chosen from the general population.

And in this study they had a job category of textile products machine operators, textile bleaching dyeing and cleaning. So a potential exposure in this category. And they actually saw a little less bladder cancer than expected, but not significantly. And they weren't studying Disperse Yellow 3, and it wasn't even mention in the article.

Then finally the last study is again in Spain, different investigators Serra et al. A case control study at 18 hospitals in Spain with almost 1,200 bladder cancer cases. So this is the largest study.

And controls from the same hospitals, and this is the study that had a module designed in the questionnaire specifically for the textile industry. And they reported for one of the job categories that they made up, called winding, warping, and sizing with synthetic materials. A

significant odds ratio of 15 based on 11 exposed cases and just 1 exposed control.

And I'd just like to remind everybody that remember we saw winding and we saw warping. Sizing is just adding chemicals, often just starch, to do something with the properties of the textile.

And then they had another category that was just synthetic materials. And then when they looked at having worked with synthetic materials for 10 or more years, they found a significant odds ratio of 2.6, based upon 21 exposed cases and 9 exposed controls.

So we have associations here with winding, warping, and the use of synthetic materials. And that's, I believe, the end of my talk for now. We'll come back to conclusions on this.

DR. LI: So now we move on to the carcinogenicity studies in animals. The available studies are the carcinogenicity studies conducted by NTP in 1982 in male and female rats and mice.

So in rats in a 2-year feeding study, it was 2 doses. As I have details of the dosing and the duration of dose. And liver and stomach tumors were observed in male rats.

And in this table, in male rats in livers, and hepatocellular adenoma and the combined adenoma and

carcinoma are increased by pairwise comparison with controls, and also significant increase in trends are reported.

Stomach tumors are rare in rats -- male or female rats. And in NTP historical controls, the background information we have is 0 out of 1,000 concurrent controls in the other 20 -- out of 20 or more studies had incidence information for controls.

So here incidence of stomach tumors, different tumor types, were observed in glandular and non-glandular portion, as we have in the lower portion of the table. No tumor-related tumors were found in female rats.

In mice, 2-year study -- 2-year feeding study with 2 doses, and lung tumors were observed in male mice. And hematopoietic system and liver tumors were found in females.

In this table in male mice, lung tumors in lungs and alveolar bronchiolar adenoma, incidence were increased in high dose group by pairwise comparison. And combined adenoma and carcinomas showing a P value of 0.055 in the high dose group by trend test both increased.

In female mice, malignant lymphoma and combined malignant lymphoma and leukemia were increased in high dose group, and the trend test is significant. In livers, the adenoma and the combined adenoma and carcinoma are

significantly increased in both dosing groups, and also by trend.

So now in addition to the carcinogenicity evidence, there are also genotoxic evidence for C.I. Disperse Yellow 3 in non-mammalian species. Positive results were found in salmonella mutation tests in a number of strains in the presence or absence of metabolic activation system, S9.

And the chemical it's negative in a couple of salmonella strains, as I have it here. And these strains are indicated for the base pair substitution. And this chemical, it's also positive in inducing chromosomal aberrations in frog larvae.

In mammalian species in vitro, C.I. Disperse Yellow 3 is positive in the presence of metabolic activation in inducing mutations in mouse lymphoma cells. And it's negative in the absence of metabolic activation.

In Chinese hamster ovary cells, the chemicals inducing sister chromatid exchange in the presence or absence of S9. However, there's another study. It has a negative result when S9 is absent. And also it's negative in the chromosome aberration test. The chemical induced unscheduled -- UDS or unscheduled DNA synthesis in rat hepatocytes without S9 activation.

Negative results were found in in vivo

genotoxicity tests in mammalian species in this couple of assays I list here. And also, it's negative in -- it doesn't induce in vitro cell transformation. So cell transformation assay, it's looking at the -- detecting the cell growth pattern and also loss of contact information -- inhibition.

So moving to pharmacokinetics and metabolism. C.I. Disperse Yellow 3 is expected to enter -- expected by the route of -- dermal route of absorption. It's also possible by the oral route and inhalation route is unclear. And remember the structure we mentioned earlier on, it's monoazo dye. So azo reduction it's one of the major metabolic mechanism. And the reduction of azo bonds in a chemical results in the formation of aromatic amines. And aromatic amines has been contributed to carcinogenicity of many other azo dyes.

So this is the general proposed scheme of azo reduction, which we can see starting from parent compound and go through a number of intermediate reactions result in the product of -- the 2 different aromatic amines. And this kind of reaction can occur in mammalian cells or in by bacteria in the gastrointestinal tract or on bacteria on skins.

So for C.I. Disperse Yellow 3, its azo reduction results in 2 expected metabolites 4-aminoacetanilide and

the 2-amino-p-cresol. So these 2 metabolites are genotoxic in some in vitro assays and also in vivo assays, as I detail here in the table. Thus, no carcinogenicity studies has been conducted for these 2 chemicals. And both chemicals hasn't been reviewed or evaluated for cancer classifications.

In addition to the genotoxicity evidence, we found C.I. Disperse Yellow 3 also as structurally similar to a number of known carcinogens. As we list here, 4 of those with the core structure similar to the chemical Prop 65 listed carcinogens, and 3 of them are IARC -- among them, 3 of them are IARC 2B chemicals, and one is IARC 3 chemicals.

And moving on to the metabolites. We mentioned earlier it has 2 aromatic amine metabolites. And this metabolite is also structurally similar to a number of known carcinogens. All these 3 listed here are Prop 65 carcinogens. And they have -- they are either IARC 1 group chemical or Group 2A, 2B chemicals.

So look into the target tumor sites of C.I. Disperse Yellow 3, and comparing to structurally similar chemicals, we list earlier 7 of them here. Most of these are causing -- targeted liver as a major -- one of the target tumor sites.

And also, just like many of known carcinogens,

they have multiple sites of -- induced tumors in multiple sites. And I have details here, and would not go into details of each chemical -- of each of them, either in mice or rats.

So wrapping up about a possible mechanism of carcinogenicity, it's likely genotoxicity might be involved, because of the mutagenicity and the clastogenicity evidence by the parent compound and metabolites. And also, we mentioned about the genotoxicity of the metabolites as well as the carcinogenic monoazo compounds are similar to C.I. Disperse Yellow 3. And, in addition, other mechanisms might also be corroborative, which is unclear so far.

DR. BEAUMONT: Thank you, Kate. So I'll now summarize the human epidemiology evidence. There were -- we could identify just 4 studies of textile workers that appeared to have relevant occupational classifications. All 4 were of bladder cancer.

And they had limitations -- well, first of all, with regard to exposure, they all had the limitation of not having any data specifically for Disperse Yellow 3. And then so by extension, there are no cancer results specifically for this particular dye.

On the other hand, 2 of the 4 studies did report significant associations for bladder cancer with

occupational categories with potential exposure. And the findings, I think, for synthetic materials in that one study are very interesting, but it hasn't been replicated one way or another elsewhere.

So, in conclusion, OEHHA finds the Epi evidence to be inadequate to assess the relationship with this particular dye.

DR. LI: So summary of the animal evidence. There are more than 2 positive. As in our screening process, we have this scoring -- screening scaling. It's more than 2 positive carcinogenicity evidence here.

One that's in male rats, C.I. Disperse Yellow 3 increased liver tumors and also induced rare stomach tumors. And in mice, in male mice, that's count number 2 positive. It's also -- it's the increase of lung tumors. And in female mice, an increase in both hematopoietic system and the liver tumors.

And other evidence, including evidence of genotoxicity in non-mammalian system and in a number of in vitro genotoxic test systems. And in addition, it's expected to form genotoxic metabolites. And this chemical is structurally similar to a number of other known carcinogens.

Thank you.

CHAIRPERSON MACK: Thank you, guys.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I'd like to thank Dr. Beaumont and Dr. Li also. I think you gathered the data very nicely. Wrote it up very clearly. Everything is very clear.

The Table 1 on the tumor incidence in the male Fischer 344 rats is interesting, but -- and hepatocellular adenomas increased in a dose-dependent fashion. They're statistically significant. The trend is statistically significant, but these are benign tumors. And the combination of the benign and the malignant doesn't add much.

The stomach argument is a good one that these are rare tumors, but these are combinations of the benign. So I take out of that the stomach tumors is interesting, that it is a tumorigen. I'm just not -- we're just not seeing malignant disease by itself, because that's the way they reported it.

And the Table 2, the tumor incidence in the male and female B6C3F1 mice is better. That's a dietary study. And you again see the alveolar bronchiolar adenomas increase in a dose dependent manner. The trend is statistically significant. The high dose is statistically significant.

The combination of the carcinomas to that doesn't

1 add much, because they're not separated out, which is the
2 way they reported it. So that again tells you they're
3 certainly tumorigenic and it's dose dependent. The female
4 mice has the most useful data I think. The background is
5 a little high, but the malignant lymphomas and the
6 combined malignant lymphomas and leukemias go up in a
7 dose-dependent manner. The trends are statistically
8 significant. The high dose is statistically. So that's
9 useful data.
10 And the hepatocellular adenomas increase. It's
11 dose dependent, and statistically significant at 2 of the
12 high doses. The trend test is statistically significant.
13 So that's a benign tumor, but everything looks good
14 otherwise.
15 The hepatocellular carcinoma helps out, because
16 you're going from 2 to 4 to 5 tumors. The trend is not
17 statistically significant. The other 2 doses are not
18 statistically significant, but they're elevated, so
19 there's a dose response for a malignant tumor, and the
20 combination of the malignant and the benign tumors,
21 adenoma and carcinomas, are dose dependent, statistically
22 significant, and the trend test works. So I think the
23 data that's most helpful is the female mice in Table 2,
24 and that begins to convince me.
25 And then I looked at the genetox data, which is

very interesting. And it seems like it's with S9 predominantly gives you base pair mutations. And then you also get some chromosomal aberrations in the frog. You get the forward mutations with S9 in the L5178Y mouse lymphoma cells, and you get sister chromatid exchange, unscheduled DNA synthesis. So there's a lot of genotoxicity data here.

And then I looked over that nice table you prepared on the compounds, which were similar. And obviously, this is cleaved in the center to generate 2 aromatic amines. And many of these aromatic amines are interesting.

So azobenzene itself, which is the core structure you have under evaluation -- and, I'm sorry, Disperse Yellow. That's the first one. The aminoacetanilide, which is one of the metabolites, you get mutagenesis and bone marrow chromosomal aberrations.

And the 2-amino-p-cresol, the other one, you get salmonella reverse mutations in L5178Y lymphoma cell forward mutations. And a lot of these compounds, even all the way down to phenacetin. Phenacetin is listed in this Group 2A, which is like acetanilide.

So I think if you add all that data together, to me, the case is certainly not as strong as the first compound, which was overwhelming, but to me this is

positive enough that I would eventually vote to list.

CHAIRPERSON MACK: Dr. Bush.

COMMITTEE MEMBER BUSH: Thank you, as well Drs. Li and Beaumont for the clarity of the report that you generated.

I, too, after reading the epidemiological human cancer study essentially gave it no weight to my decision. So then I went on to look further at the feed studies in rat and mice, which I think was certainly more compelling.

As Dr. Landolph mentioned, it's interesting to see that there was certainly a distinction in the kinds of malignancies that were occurring. The predominance of the lymphoma/leukemias in the female mice, you know, that could potentially -- you know, if we were to speculate, maybe there's a role of some hormone dependence there, because again with the rats, comparing male to female, certainly different tumor profiles as well.

Knowing or seeing the data that liver was definitely involved in, that helped corroborate some of the other data that you mentioned in summary.

It's clear in the recent literature that the -- that C.I. Disperse Yellow 3 has a role in contact dermatitis as an allergen. And so, you know, that's suggestive of some kind of immune response. And that may be one of the predisposing factors to some of the

malignancies that we are actually seeing.

So, for me, that was some intriguing data and I think definitely supportive of the carcinogenicity of this particular chemical.

Moving on to the in vitro studies. I think it's clear that this particular compound definitely needs to be metabolized in order to see any of it's carcinogenicity or the genotoxicity in some of the mutagen studies. And I think that could probably be the reason why we weren't seeing that or the lack of positive data for the in vivo, micronucleus assays, sister chromatid exchange, and the cellular transformation assay, because accordingly that the compound wasn't actually metabolized.

So the fact now that some of the metabolites of this chemical show a structural similarity to some of the other listed chemicals, I think, lends strong support to its genotoxicity.

And I would echo what Dr. Landolph has said. And I believe that the weight of the evidence convinces me that this chemical ought to be listed, in spite of the fact that it has not been reviewed at another agency.

CHAIRPERSON MACK: Thank you, Jason.

Let's start at the other end. Now, Peggy, do you have anything to add?

COMMITTEE MEMBER REYNOLDS: Oh, gee. I hate

to -- so I just -- I certainly -- I want to congratulate you, Jay, on trying to find human health evidence, a rather heroic effort, but I agree that that was really uninformative in terms of this particular chemical.

And it struck me that the animal studies were rather mixed with results. So I wasn't feeling like there was really compelling evidence there. And it seemed like, sort of, the strongest evidence to me is, as you mentioned, the structural similarity of some of the metabolites. And I am feeling a little uncertain about how much weight to put on that in the absence of compelling evidence from these other venues.

So I'd really like to hear from some of the members of the Committee sort of what your take might be on that.

CHAIRPERSON MACK: You want to respond, Joe.

COMMITTEE MEMBER LANDOLPH: You know, I would just repeat myself. I think the female mice study, where there's feeding, you have the combined lymphomas and the leukemias. Those are malignant tumors. And in the other one you had, in that same study -- let's see -- was the hepatocellular carcinomas going from 2 to 4 to 5. The trend test wasn't significant, but it is does dependent.

So that, plus all the genotoxicity data, plus the fact that you've got aromatic amine metabolites and

they're similar to the aromatic amines that have been listed, in the aggregate, I feel, is compelling.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: I have a bunch of comments and questions.

First of all, let me thank Dr. Li and Beaumont for putting together the document. I did have a question or 2. Apparently, your conclusions differ from those of the NTP bioassay. Certainly, for the -- in the lung and the mouse, they did not consider that to be treatment related, the increase in tumors that was seen there. And I wondered why you felt like you should list it?

DR. SANDY: If I can -- we don't recommend whether something should be listed.

COMMITTEE MEMBER EASTMOND: I mean, why you -- no. Why you chose to present it as a clear evidence or -- I mean, I guess, I don't know if that's clear enough. But basically, there's a dose-related trend, that's true. When you combine the high doses -- neither of the individual dose is statistically significant. One is marginally.

But in the NTP bioassay, they attribute that to an unusually low control value. And that was driving the trend. And that's why the high dose approached statistical significance. But because the variability in

the historical controls, they didn't feel confident to call that treatment related. So I'm just curious why -- if there was some reasoning why you went forward and put as much weight on it?

DR. LI: We actually, at least for the combined, I have the mark, if you see the P-value is 0.055. It is fell out of P less than 0.05.

COMMITTEE MEMBER EASTMOND: It's not less than. It's greater than.

DR. SANDY: That's what she's trying to say.

DR. LI: It's equals to. Close to.

And therefore, adenoma NTP did come and it's increased. And it is a benign tumor. I agree with what you say about NTP. They finally did not conclude. It is clear evidence, because the -- if you look at accounts, there's no dose related increase in high dose group for the combined, because there's no carcinomas.

COMMITTEE MEMBER EASTMOND: But do you understand it's because the control value was unusually low?

DR. LI: Yes.

COMMITTEE MEMBER EASTMOND: And so I felt that might have been driving the trend.

DR. LI: Driving the trend, yeah, right.

COMMITTEE MEMBER EASTMOND: And that's why you would have both the trend test and you might have had

statistical significance. So when they concluded, they decided not to -- they did not consider treatment related. So I was just curious, I mean, it was just an interpretation of the analysis apparently.

DR. LI: On our calculation in the exact trend test, it's less than 0.05.

COMMITTEE MEMBER EASTMOND: Oh, it is statistically significant for trend. But the reason they believed was because there's a lot of variability in the controls. In this case, the control was low. Historically, this is a low control compared to normal.

DR. LI: Right.

COMMITTEE MEMBER EASTMOND: And they felt like that might have been driving it.

The other one which I didn't -- the NTP bioassay -- I just finished serving several years on their Board and on their technical subcommittee. And there's different ways that they word things, so you get a different sense.

So on the hematopoietic system, they considered that may have been associated. So for them it was kind of in this borderline zone. But I think there's some evidence there. The one concern I had about this one. I don't know if you looked at it, but the -- in the list of the individual lymphomas, one of them -- one of the major

1 categories is histiocytic lymphoma. And that's an old
2 name for histiocytic sarcoma.
3 And more recent sort of pooling of evidence
4 generally doesn't combine that. So I'm not sure if it's a
5 separate tumor type or if it's a terminology difference.
6 So, for me, in weighing this, I didn't know how to
7 evaluate that. Just coming back to the key thing on this,
8 is the dose related increase in the hepatocellular tumors.
9 And you have increased clearances in adenoma. There's a
10 suggestion of an increase in carcinomas, although it's not
11 significant, but the combined combination has increased.
12 And based upon our earlier discussions, if
13 there's an increase in benign tumors of a type that
14 progress on to become malignant, we consider that evidence
15 of carcinogenicity. And I believe hepatocellular adenomas
16 clearly progress onto carcinomas, if I'm not mistaken.
17 And so for both, in the mice and the rats, that, for me,
18 is probably the strongest evidence.
19 I should say also that the stomach tumors are
20 very, very rare. In fact, if you go to the NTP, they've
21 never seen one in a control in 20 studies. So the fact
22 that you have them in the 2 dose levels, and basically --
23 that's certainly in the glandular portion. But I think
24 it -- I can't remember on the forestomach, but these are
25 very rare. So, for me, that's another piece of evidence.

1 So the combination for me of the liver tumors in
2 both the mice and the rats, which we believe would
3 progress, and the forestomach, is probably the strongest
4 argument, combined with the other evidence on structure
5 activity relationships and genotoxicity. But I just was
6 going to point that out. I got into this one a little
7 more in depth than usual.
8 (Laughter.)
9 CHAIRPERSON MACK: Dr. Zhang.
10 COMMITTEE MEMBER ZHANG: Yeah, I think --
11 basically I don't have that much comment, but, you know,
12 comparing with the first chemical, this is a little bit
13 less. But I still think -- you know, I mean, we're
14 discussing about the, you know, dose response at a single
15 doses. But I do agree the dose response, you know, to
16 look at the P trend it gave us a little bit of, you know,
17 better idea about, you know, treatment specific effect.
18 So I don't have a problem with it.
19 CHAIRPERSON MACK: Duncan.
20 COMMITTEE MEMBER THOMAS: I agree with the
21 staff's assessment about the utility and usefulness of the
22 epidemiologic data here. My main concern is that we've --
23 I believe arylamines are maybe the very first, or at least
24 one of the very first, established bladder carcinogens
25 dating back to the 19th century. And it makes me wonder

whether or not the specific arylamines are well established as occupational carcinogens have any overlap with the particular chemicals that's being looked at here.

But anyway, we don't know. And so I think we can't answer that. What puzzles me a little bit is the amount of epidemiologic evidence implicating arylamines in bladder cancer. And it almost never comes up in your table of the animal literature that what we're seeing here is liver, stomach, lung, hematopoietic. I was just wondering whether any of you wanted to comment upon, you know, why we don't see more animal literature for bladder cancer.

CHAIRPERSON MACK: Do you have a comment?

COMMITTEE MEMBER DAIRKEE: I had the same question that Dr. Thomas had, that the validation in the mouse -- or the rodents is very different from human.

CHAIRPERSON MACK: Basically, I had exactly the same question that Duncan did, because the arylamine bladder relationship must have been why they looked at bladder and bladder only, which I find curious, because certainly the animal evidence wouldn't suggest that's what you should look at.

And I also wondered whether or not we might be getting some spill over in Spanish workers that came from arylamines from some source.

The other comment was that these were hospital controls. And that means that -- I don't know how they adjusted for smoking, whether they made a really sincere effort to try and adjust dose. My guess is that was never done or not done efficiently, and that means -- I'm sorry -- and that means that is there underestimate of the relative risk, because undoubtedly a lot of the controls would have been smokers, underestimate of it. And so I don't know what to make of that.

But on the other hand, when they restricted the analysis to just the synthetics, the relative risk went down a lot, so maybe that's relevant. But overall, of course, the epidemiology is useless, because we just don't know what it's confounded by, but you have to -- being an epidemiologist you have to get into a little bit.

With respect to the animal evidence, I'm also suspicious, maybe a little bit more than David, of what I think is the best evidence, namely the liver evidence, because of the difficulty sometimes in classifying adenomas and carcinomas of the liver, and because these animals tend to produce adenomas when you look at them cross-eyed. So I think it's a borderline issue.

Maybe you can respond to that.

COMMITTEE MEMBER EASTMOND: Oh, on the adenomas?

CHAIRPERSON MACK: Yes.

1 COMMITTEE MEMBER EASTMOND: I can comment on
2 both. It's my understanding that certainly in the rat, I
3 looked up the historical range for adenomas -- combined
4 hepatocellular adenomas and carcinomas. And the average
5 is 3.3 percent for the historical range. And that's I
6 believe -- and that's -- so you're looking at 11 out of
7 39, so it's way over the historical. So that would
8 indicate to me it was clearly treatment related.
9 The other comment I was going to comment on --
10 and this goes back to in the early days of cancer testing,
11 I believe there was a lot of attempts to try and show that
12 aromatic amines would cause bladder cancer in rodents. It
13 was largely unsuccessful. And so they eventually went
14 into dogs, which was a very good model for the aromatic
15 amines causing bladder cancer.
16 But the aromatic amines do frequently cause liver
17 cancer in rodents. And the thinking is basically the
18 bioactivation happens more quickly, it's more rapidly, so
19 that you get the reactive intermediates formed in the
20 liver. And that's why you get the toxicity and
21 carcinogenicity in the liver in the rodents.
22 Whereas, you have different metabolic pathways,
23 and that's why it will happen in the bladder in humans and
24 dogs. So, for me, that's consistent with the idea that
25 we're seeing liver tumors here. Although, I would like to

see more carcinomas. But, as I said, because these are a tumor type, which can progress, usually we'd use that as evidence to go forward. But, for me, it's not nearly as strong as certainly the other chemical.

CHAIRPERSON MACK: Does anybody else have any other comments?

COMMITTEE MEMBER THOMAS: Can I just raise one other question. Again, this is for my education, and I'd appreciate some feedback from the toxicologists on the Panel. How are we to interpret borderline significance of 1 or 2 cancer sites? With the exception of the bladder -- of the liver adenomas, everything is borderline, and these are doubtless one of just many different cancer sites that have been examined. Should we be concerned about this sort of thing? As a statistician, I can't help but ask that question.

CHAIRPERSON MACK: You pays your money and you take your choice. And what you decide depends on your own background and your own education. But my inclination is to not pay very much attention to borderlines in several sites, because that's my background, and that's my behavior.

So I'd like to see something solid. And, as usual, I learn something from David when we have these meetings, so my inclination is to go with the liver. But

I do think we should answer another question, the one that Peggy had raised, and that was the how you treat the in vitro studies.

And my inclination is to go like the people at the IARC do and say, it's worthy of an upgrade, but they're very treacherous on their own, usually because nobody has really looked in controls to see if the same things happen, and they usually do. You know, things like, for example, chromatid exchange is really common, if you start looking in normal people. And so to use it as a primary criterion I think is not very good business, but I would defer to the toxicologists on that, too.

COMMITTEE MEMBER EASTMOND: I mean, I think the in vitro and the genetic toxicology evidence and that in bacteria as well is pretty strongly positive. You've got it positive in multiple assays.

So, you know, that, for me, indicates an in vitro positive. It's pretty strongly mutagenic. Or the weakness is there aren't the corresponding in vivo studies that you'd like to see. Now, it hasn't been tested extensively in vivo, and it hasn't been tested in assays in vivo where you'd measure the same sorts of base pair substitutions or frameshifts, so it leaves you uncertain there, but it's -- again, it's not a super clean data set, that's for sure.

CHAIRPERSON MACK: Anymore comments?

Okay. Let's pose the question.

DIRECTOR ALEXEEFF: Is there public comments?

CHAIRPERSON MACK: Thank you. I forgot the public. We, again, didn't receive any requests for comments, so is there anybody who'd like to vent their spleen on this particular compound?

Seeing no responses, I guess we'll go to the question.

Has C.I. Disperse Yellow 3 been clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer?

All those voting yes, please raise their hands.

(Hands raised.)

CHAIRPERSON MACK: We have 1, 2, 3, 4, 5, 6. How many -- all those voting no, please raise their hands?

(Hands raised.)

CHAIRPERSON MACK: Two.

So it's 6 and 2. Are there any abstentions?

Obviously not.

So we conclude that the compound will be a listed compound -- the compound will also be recommended for listing, although with some reluctance, but we don't write that down.

Now, do we go to Carol or do we go to...

CHIEF COUNSEL MONAHAN-CUMMINGS: I think it's me. We're just going to put a slide up real quick.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: If you recall in my earlier comments to you when I was saying what your various duties are, I mentioned that there was one that was pretty obscure that had to do with another list under Prop 65. And this is the one that we're talking about.

There's a second list that was established by the law back in '86. And it's a list of chemicals that have not been sufficiently tested for carcinogenicity or reproductive toxicity. And our practice has been to inquire with the California Department of Pesticide Regulation and U.S. EPA about all of the chemicals on that list each year. And then when they tell us that the testing that they require has been satisfied, then we bring this list to you of the chemicals where the testing has been satisfied or where there's new ones that need to be added, and you essentially just agree with us.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Sorry. There really isn't -- it's not a deliberative thing. It's just that you're required -- we're required to put this in the regulations that there's these chemicals that still need

testing, and we rely, and I hope you do, on determination by the Department of Pesticide Regulation and U.S. EPA that they have sufficient evidence.

So if you wouldn't mind, if -- Dr. Mack, if you want to ask if the Committee agrees with DPR and U.S. EPA.

CHAIRPERSON MACK: So this is not a scientific issue. It's only a matter of whether or not the members of the Committee can trust the veracity of the EPA for telling us that they have done something?

CHIEF COUNSEL MONAHAN-CUMMINGS: Exactly.

CHAIRPERSON MACK: Based upon the information you've been provided from U.S. EPA, should the 8 chemicals as identified on the Section 27000 slide be removed from the list of chemicals required by State or federal law to be tested, but which have not yet been adequately tested as required? All those voting yes, please raise your hands?

(Hands raised.)

CHAIRPERSON MACK: All those voting no, please raise your hands?

(No hands raised.)

CHAIRPERSON MACK: It's 8 to 0.

And no abstentions.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

CHAIRPERSON MACK: Staff. That's the fun part.

Staff updates.

(Thereupon an overhead presentation was Presented as follows.)

MS. OSHITA: Good afternoon. I would just like to give you an update on the administrative listings that OEHHA has been working on since the Committee last met.

OEHHA has administratively added 16 chemicals to the list. There are 14 listed as chemicals known to cause cancer, and 2 as chemicals known to cause reproductive toxicity. The additions to the list, along with their effective dates, are shown in these slides here.

This first slide -- woops. This slide. Sorry about that.

This first slide showing the chemicals that were listed effective November 4th, 2011, and February 3rd, 2012. These listing the chemicals that were added effective June 22nd, 2012, July 24th, 2012, and November 2nd, 2012. And this last slide with the chemicals that are added for reproductive toxicity effective February 17th and March 16th.

There were several other chemicals that are under consideration for administrative listing, which includes tetraconazole, beta-myrcene, pulegone, and styrene as causing cancer. And also bisphenol A, and hydrogen cyanide, and cyanide salts as causing reproductive

toxicity.

The Notice of Intent to list bisphenol A was announced today, and the public comment will close on February 25th, 2013.

The public comment period for styrene will close on February 4th, 2013.

For all the other proposed chemicals, the request for information periods have closed, and comments were received on each of the chemicals and they're under review.

Also, since the last meeting, OEHHA has adopted 6 No Significant Risk Levels. This next slide here will show the chemicals and their respective levels. That would be for 4-methylimidazole, chlorothalonil, imazalil trichloroethylene, TDCPP, and bromoethane

OEHHA has also proposed to adopt 4 Maximum Allowable Dose Levels. And those are for methanol, chloroform, sulfur dioxide, and butyl benzyl phthalate. And staff are currently working on the final rule-making packages for each of these chemicals. And they will be submitted to the Office of Administrative Law for approval shortly.

Thank you.

CHAIRPERSON MACK: Summarize the action.

CHIEF COUNSEL MONAHAN-CUMMINGS: George, do you

want me to tell them about litigation or shall we just let that go?

DIRECTOR ALEXEEFF: Litigation. I guess we have litigation.

CHAIRPERSON MACK: Please tell us about that.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. I promise this is the last time I'm going to talk. But I usually give an update on litigation that is pending or has been resolved since the last meeting.

And so I want to go in kind of reverse order here timewise. We had a case that was recently decided in the court of appeals. It was the Styrene Information and Research Center versus OEHHA. We had the proposed listing of styrene under a finding by the International Agency for Research on Cancer that it caused cancer. And we were -- the court of appeal and the court -- the trial court decided that we didn't have sufficient evidence to list the chemical based on the IARC findings. And so the court told us not to list under that basis.

However, as you heard from Ms. Oshita, we recently proposed the listing of styrene based on a report from the National Toxicology Program that it causes cancer, and with sufficient evidence in animals. So you may hear about this again. I don't know, but we've

reproposed it.

The next case, I just -- I don't remember if this had come out. It was right about the same time as your meeting was the case about whether or not we should have listed the chemical 4-MEI, 4-methylimidazole, which you heard we just adopted a No Significant Risk Level for.

And we were successful in that court case in defending our basis for listing as a National Toxicology Program technical report. That was a case in the California -- or in the trial court, and so it's not recorded, but it is -- it hasn't been appealed, and so it's effective.

And then I wanted to mention to you that we also have litigation pending with Syngenta Crop Protection regarding our proposed change to -- or we did change, I'm sorry, the No Significant Risk Level for chlorothalonil. We reduced the number fairly recently, and we were sued by Syngenta arguing that our number is much too low. That's currently in Sacramento superior court.

And then lastly, I mentioned earlier that we have this case that's been pending since 2007. It's the Sierra Club et al., versus Governor Brown. And that includes CIC members, the Governor, the Director of the Agency, who's now George, and the Secretary of CalEPA. We're hopeful that that case is going to be resolved. We have been

hopeful for 5 years now that that case is going to get resolved. So as soon as I know that it's done, I will certainly let you know, and then you can discard all that paper and electronic stuff you've been keeping.

Does anybody have questions?

Thank you.

CHAIRPERSON MACK: Okay.

DIRECTOR ALEXEEFF: Okay. This is George Alexeeff. I'll summarize today's Committee actions.

First, the Committee voted 8 yes to 0 no that 2,6-Dimethyl-N-Nitrosomorpholine has been clearly shown, through scientifically valid testing, according to generally accepted principles to cause cancer.

And the Committee also voted on a basis of 6 yes and 2 no that C.I. Disperse Yellow 3 has been clearly shown, through scientifically valid testing, according to generally accepted principles to cause cancer.

And finally, the Committee also voted unanimously 8 yes, 0 no that based on the information they were provided from U.S. EPA that 8 chemicals identified under Section 2700 were to be removed from the list of chemicals required by the State or federal law to be tested, but which have not been adequately tested as thus far -- had not been adequately tested to that point.

Okay. So I guess I just want to thank the

Committee members, particularly the new committee members, welcome. And I also want to thank the staff for their presentations and addressing every question that they could that the Committee had asked, and also preparation of the reports. And I also want to thank the members of the public who are present here, as well as those listening, for their attention and interest in this activity.

And I'll hand it over to Dr. Mack.

CHAIRPERSON MACK: Who has nothing to say except this concludes the meeting. Thank you for your participation, and we'll see you next time.

(Thereupon the Carcinogen Identification Committee adjourned at 1:24 p.m.)

1 CERTIFICATE OF REPORTER

2 I, JAMES F. PETERS, a Certified Shorthand
3 Reporter of the State of California, and Registered
4 Professional Reporter, do hereby certify:
5 That I am a disinterested person herein; that the
6 foregoing California Office of Environmental Health Hazard
7 Assessment, Carcinogen Identification Committee was
8 reported in shorthand by me, James F. Peters, a Certified
9 Shorthand Reporter of the State of California, and
10 thereafter transcribed under my direction, by
11 computer-assisted transcription;
12 I further certify that I am not of counsel or
13 attorney for any of the parties to said workshop nor in
14 any way interested in the outcome of said workshop.
15 IN WITNESS WHEREOF, I have hereunto set my hand
16 this 4th day of February, 2013.
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22
23 JAMES F. PETERS, CSR, RPR
24 Certified Shorthand Reporter
25 License No. 10063

2/11/2013
JPETERS 16:40:39
PM;