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

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

WEDNESDAY, OCTOBER 12, 2011

10:04 A.M.

JAMES F. PETERS, CSR, RPR
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APPEARANCES

COMMITTEE MEMBERS

Thomas M. Mack, M.D., Chairperson

David A. Eastmond, Ph.D.

Solomon Hamburg, M.D., Ph.D.

Darryl Hunter, M.D.

Joseph Landolph, Ph.D.

Anna H. Wu, Ph.D.

STAFF

Dr. George Alexeeff, Acting Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

Ms. Laura August, Research Scientist

Dr. John Faust, Staff Toxicologist

Dr. David W. Morry, Staff Toxicologist

Ms. Cynthia Oshita, Proposition 65 Implementation

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

Dr. Craig Steinmaus, Public Health Medical Officer

Dr. Lauren Zeise, Chief, Reproductive and Cancer Hazard Assessment Branch

APPEARANCES CONTINUED

ALSO PRESENT

Dr. Richard Adamson, TPN Associates

Dr. Arlene Blum, Green Science Policy Institute

Dr. John Butala, FERRO

Dr. James Coughlin, Coughlin & Associates

Mr. Mike Fuller

Ms. Kim Glazzard, Organic Sacramento

Dr. Robert Golden, International Fragrance Association

Mr. Jim Gray, 2,4-D Task Force

Mr. Jeff Green, Citizens for Safe Drinking water

Dr. Catherine Hayes, Consumer Healthcare Products Association

Dr. David Heimbach, University of Washington

Dr. Steven Hentges, American Chemistry Council

Dr. Fred Hess, BASF

Dr. Sarah Janssen, Natural Resources Defense Council

Dr. David Kennedy, International Academy of Oral Medicine and Toxicology

Dr. Barbara Kochanowski, Consumer Healthcare Products Association

Dr. Arthur Lawyer, Technology Sciences Group

Dr. Donald Lyman, California Department of Public Health

Dr. Jay Murray, Consumer Healthcare Products Association

Dr. Nancy O'Malley, Albemarle Corporation

Dr. Sabitha Papineni, Dow AgroSciences

APPEARANCES CONTINUED

ALSO PRESENT

Dr. Richard Peffer, Syngenta Crop Protection

Dr. Howard Pollick, University of California, San Francisco

Ms. Kathleen Roberts, North American Metal Packaging Alliance

Ms. Debbie Stubbs, Syngenta

Dr. Rebecca Sutton, Environmental Working Group

Dr. Andy Wang, ICL Industrial Products

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PROCEEDINGS

ACTING DIRECTOR ALEXEEFF: I'm George Alexeeff, Acting Director for the Office of Environmental Health Hazard Assessment.

And Dr. Mack's plane has been delayed. So what we thought we would do is we'd actually begin on actually Items 4 and 5, which we are at the end of -- or bottom of the agenda today. We're actually going to start with Item 5 and then Item 4 and then we'll see where we are and then we'll take it from there.

So we're going to begin with staff updates. I wonder if Cindy Oshita is available to give us staff updates.

Oh, actually, let me do this. Dr. Landolph has agreed to be Acting Chair in the interim, so he'll be Acting Chair until Dr. Mack arrives.

So do you want to make any opening comments, Dr. Landolph. Actually, let me just go ahead and begin with the introductions. I'm sorry. I was so concerned about Dr. Mack not being here, I should introduce everybody.

Okay. First of all, I want to welcome everyone here to our Prop 65 meeting on the Carcinogen Identification Committee. And there are a couple of housekeeping issues that we have to address. One, for example, is the restrooms are out the back and to the

left.

And then if there is a need to evacuate the building, we're on the second floor, so there's a number of stairwells, two exits here, that we can exit. And we could leave the building and go across the street to the park, if that's needed.

So in terms of people here today. On my left directly here is Dr. David Eastmond, and he's a professor of cell biology and research toxicology at UC Riverside.

And to the left of him is Dr. Darryl Hunter, who's a physician of radiation oncology at Kaiser Permanente.

And to my far left is Dr. Anna Wu, a professor in the Department of Preventative Medicine at the USC Keck School of Medicine.

And to my right, acting as Co-Chair today, or Chair today, Acting Chair today. Since I'm Acting Director, we may as well have Acting Chair, right? Anyway, to my right is Dr. Joseph Landolph, Associate Professor of the Department of Molecular Microbiology and Immunology at USC Keck School of Medicine.

And to his right is Dr. Solomon Hamburg. And he is the partner of the Tower Hematology Oncology Medical Group and the president of Tower Cancer Research Foundation and a Clinical Professor of Medicine at UCLA

David Griffin -- Geffen Medical School.

Okay. So those are the introductions. So now, thank you, Cindy, if you could give us a update, staff updates.

MS. OSHITA: Sure. Good morning. We have -- OEHHA has administratively added 21 chemicals to the Prop 65 list since the Carcinogen Identification Committee met last September 2010. Eighteen were listed as known to cause cancer, and three were listed as known to cause reproductive toxicity.

You will find a summary sheet of these latest additions to the list, along with the effective listing dates in your meeting materials behind the staff updates tab.

There are yet several other chemicals that are still under consideration for administrative listing. They include cocamide diethanolamine, tetraconazole, kresoxim-methyl. These are listed -- or are being proposed for listing as causing cancer.

And we have methanol, and Bisphenol A, and hydrogen cyanide and cyanide salts as being considered for listing for reproductive toxicity.

Methanol is in the notice of intent to list phase, while all the other proposed chemicals are in the date call-in phase. We have received comments on each of

these chemicals and they are currently under review.

OEHHA has also announced the proposed administrative listing via the Labor Code mechanism for additional chemicals, which include estrogen-progestogen, used as menopausal therapy. Wait. I don't know how to say this.

DR. SANDY: Etoposide.

MS. OSHITA: Etoposide. Thank you, Martha. Etopside. And then Etoposide in combination with cisplatin and bleomycin. Methyl isobutyl ketone and MOPP. And these are all being considered for listing as causing cancer. The public comment period for these chemicals will close on October 17th, 2011.

Also, since you last met, OEHHA has adopted two No Significant Risk Levels. One for 2,4,6-Trinitrotoluene and glycidol. And then four Maximum Allowable Dose Levels. And those are for DIDP, hexavalent chromium, acrylamide, and avermectin. And the levels and effective dates are also included in the summary table in your meeting materials.

OEHHA proposed to adopt three new NSRLs. They will be for chlorothalonil, 4-methylimidazole, and imazalil. Comments were received on the NSRL for chlorothalonil, and those are currently under review. The NSRL for 4-methylimidazole was recently renoticed for

public comment, and then again extended for public comment and the comment period will now close, I believe, on November 8th.

The NSRL for imazalil is open for public comment. We received a request for extension. So there will be an extension for that comment period as well.

Thank you.

ACTING CHAIRPERSON LANDOLPH: Are there any questions from the Committee or from the audience?

No questions. That means it was an excellent presentation. Thank you.

(Laughter.)

ACTING CHAIRPERSON LANDOLPH: Next up, we have attorney Carol Monahan-Cummings. She's the Chief Counsel for OEHHA, and she's going to give us a presentation.

Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm just going to give you a litigation update right now.

There's at least three cases that may be --

ACTING DIRECTOR ALEXEEFF: Can you move the microphone

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry. There's at least three cases that you may be interested in. One of them that you're being sued in is the Sierra Club case. It's been ongoing since 2007. And the CIC

members are all parties to that case.

Just a quick update to you. The discovery process has been put on a hold, informal hold. The court hasn't limited discovery, but there's an informal hold right now because we're working on a potential settlement of the case. So related to that, just a quick reminder, that you're still -- there's still a litigation hold in that case for you. And you need to maintain all your records related to the CIC and the listings that we do here.

One of the other cases that had been pending for some time is the Chamber of Commerce versus OEHHA, which was kind of a subset of the Sierra Club case. If you recall, it had to do with our listings of chemicals under the Labor Code listing mechanism, which doesn't affect your group in particular, but it does require us to list certain carcinogens, and reproductive toxins.

And we had been challenged by the Chamber of Commerce in that case for lack of authority to do those listings. And a recent appellate court case has confirmed our -- both our authority and our duty to complete those listings. And so we are continuing, as Cindy noted, with proposing listings under that listing process. Those are considered ministerial listings and there's very limited input from the public, in terms of those listings.

A related case to the Labor Code listings is the Styrene Information Council versus OEHHA. And I may have mentioned this to you before, because it's been pending on appeal for some time. About a year and a half we've been waiting for the court to schedule a hearing. And we expect it will be longer than that, given the cuts to the court system. But that one has to do with a finer point under the Labor Code about whether or not we can list chemicals that have insufficient evidence of carcinogenicity in both animals and humans, but other supporting data.

The last case I was going to mention is a new one that was filed since your last meeting. And that was filed on behalf of a number of beverage organizations. And it has to do with the recent listing of the chemical 4-MEI, 4-methylimidazole. And we listed that administratively, and there are challenging our ability to do that. And that is in the trial court right now. It's been briefed and argued. And we're just waiting for an opinion from the court. There's a fair likelihood that the case will also be appealed.

Do you have any questions on any of those cases?

ACTING CHAIRPERSON LANDOLPH: Anybody on the Committee have any questions?

Carol, just a quick one. So for the CIC members,

do they have to keep all today's prioritization documents in their offices?

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct. Anything related to the business that you do on the CIC Committee, you need to keep.

ACTING CHAIRPERSON LANDOLPH: We can't rely on you keeping them and producing them later?

CHIEF COUNSEL MONAHAN-CUMMINGS: No, to the extent that you're writing on them and things like that, we just really need you to keep them. My hope is you won't have to produce them, because I don't want to go through them myself, and you probably don't either. But we do have to keep them for now. And I'll let you know as soon as I can release that hold.

ACTING CHAIRPERSON LANDOLPH: Thank you. Any other questions on that issue?

Dave.

COMMITTEE MEMBER EASTMOND: Just as a reminder, Carol. Do you remember when the start date is on that or is that indefinite? I think you said the start of 2007 was the court dates.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. It's three years prior to 2007 is what we're holding. So it's quite a long time.

COMMITTEE MEMBER EASTMOND: It's 2004 on. Okay.

ACTING CHAIRPERSON LANDOLPH: Any other questions on that issue?

No. We're going to move to Item number 4 now, which would be procedures for presentation of public comments, Committee discussions, and Committee votes during meetings. And Dr. Alexeeff, the Director, will deal with that one.

ACTING DIRECTOR ALEXEEFF: I'll just mention for those individuals that have joined us in the last 10 or 15 minutes, we're waiting the arrival of Dr. Mack. And he should be here within a half an hour or so. We're taking up a couple of items prior to beginning with the listing items.

(Thereupon an overhead presentation was Presented as follows.)

ACTING DIRECTOR ALEXEEFF: Okay. The item we're discussing now, Procedures For Presentation of Public Comments. This item had its origin in a letter that Dr. Denton received from several non-governmental organizations, or NGOs. And she received it on July 22nd 2009. And that was the week after the Developmental and Reproductive Toxicity Committee meeting in 2009. The letter contained several specific criticisms of the way that the meeting was held, and OEHHA met with Dr. Burk, the chair of the DART Committee, and met with

representatives of these groups in April 2010 to listen to constructive criticisms to see if there are ways to improve our processes.

So Dr. Denton responded to the NGOs in a letter dated September 1st, 2010. And in it Dr. Denton identified some changes suggested by the NGOs. One change is to improve the clarity of the information that we, OEHHA, present to the panels in -- for the deliberations.

And we've streamlined the presentation of hazard identification materials. And, you know, towards the end of this meeting we'd appreciate any comments along those lines.

This issue of streamlining the materials has not been as big an issue for the CIC as the DART IC. And that's simply because there could be many more studies and different types of study designs for the DART IC than for the CIC. But this is something we continually strive to do to improve the quality of the materials we provide you.

Also, there were three specific items relating to meeting procedures that were brought to the DART IC and we're going to bring those same three items to you today for discussion. And these are items that would affect the Committee's deliberations at future meetings. So our Chief Counsel, Carol Monahan-Cummings, will give a short presentation on these three items concerning meeting

procedures.

Thank you.

ACTING CHAIRPERSON LANDOLPH: And we have listed for attorney, Carol Monahan-Cummings to make some comments here, too.

(Thereupon and overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

I've got a couple slides up here for you guys to look at. As George -- or Dr. Alexeeff mentioned, we may made a similar presentation to the DART committee. And I'll let you know what their decision -- or their general consensus was on those items as we get to them. What I wanted to point out to you just procedurally is that you're not being asked to make any votes or binding decisions today. This is just a discussion item for you. We wanted you to be able to give the Chair some advice on these, and we'll certainly pass that advice along to him.

So if you make suggestions concerning changes or other things for this Committee, meetings or your materials, those are suggestions and they could be changed, you know, based on the situation, if needed. It's not going to be any mandatory kind of requirements.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: The first item is structure of public meetings. I wanted to remind you, as you've been reminded before, that these meetings are subject to the Open Meeting Act, the Bagley-Keene Open Meeting Act for California. And so there are requirements for public comment periods for decision-making items, but the Committee does have the ability to place time limits on public comments.

Some of the other boards and departments at CalEPA do place time limits on speakers. Generally, it's about three minutes. It depends on the subject matter. And some -- most of them publish the limits in advance, so that people are aware of the fact that they'll have a short time to present, so that they don't make a -- you know, take the time to make a half hour presentation that gets truncated.

And there's also similar rules with federal advisory committees and certainly Congress and the Legislature limit the timeframes for comments.

Next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So there are a couple of suggestions that we have in -- that were made by the NGOs and were also discussed by the DART. For example, keeping related -- woops. Am I on the right

slide?

Yes.

Keeping related speakers together tends to provide for more coherent presentations, where you may have several speakers that are speaking on this -- on behalf of a company or industry or perhaps the environmental group. Sometimes it's best to keep them together and so just shuffling the cards and calling for someone or basing it on first come first serve sometimes isn't the best approach.

Some questions for the Committee to discuss. We were going to ask you whether or not you liked the approach we used today at this meeting.

COMMITTEE MEMBER HAMBURG: So far so good.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, but the suggestion that Dr. Mack and George had discussed to approach today's meeting would be to limit speakers to five minutes. And that we were using the little -- the light box here on the podium rather than having somebody have to, you know, hold up a card or something for the speakers, so they know how much time they have left and when they need to stop.

Similar formats are used for groups like the Air Resources Board and the Water Resources Board hearings.

There is a question, because it actually came up at the DART committee meeting. I don't think it's happened at this committee, where some speakers would -- you know, they put in a speaker card, and they'd have five or six people that had speaker cards and then they would cede their time to someone else. And the effect of that is that one person got 15 minutes to talk versus five minutes.

And I really couldn't find anybody else that does that, other than maybe congressional debates where, you know, you'll have somebody say I cede two minutes of my time to, you know, the gentleman from Alabama or something. And really that doesn't lend itself well to this kind of a setting either. And the DART Committee did decide not to allow people to cede time.

The other question could be that should we or shouldn't we set the time period in advance so that folks know how much time they have or should it be based on the number of requests for comments. You know, if only one person wants to comment, should they get more than five minutes, that sort of thing. Or as I mentioned, you could do something along the lines of looking at the complexity of an issue and saying, you know, you need more time.

I think that's one of the reasons that Dr. Mack suggested five minutes rather than three minutes for

discussion, you know, just for content.

And lastly, the -- next slide.

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CHIEF COUNSEL MONAHAN-CUMMINGS: In terms of voting, one of the things that we had suggested to the DART committee, although they didn't adopt it at that time, was a new practice that's coming, particularly at the federal advisory committee level, where people are voting by written ballot rather than, you know, putting your hands up in the meeting. It's not a voting method where people don't know which individual voted in which way. But what you do is the questions are on a written ballot, you check off whether or not you think that they -- you know, the chemical has been clearly shown to cause cancer, for example. And then the Chair collects those and reads them off.

The argument for that is that people on the Committee have a little more discretion, I guess, to make their own decisions and are not influenced by the decisions of others so much. And that's entirely up to you whether or not you want to cast the votes without a show of hands.

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CHIEF COUNSEL MONAHAN-CUMMINGS: So the next slide is just -- we just wanted to suggest you could have

some discussion of those items and perhaps give some advice to Dr. Alexeeff or Dr. Landolph that he can pass along to Dr. Mack.

Any questions on this?

ACTING CHAIRPERSON LANDOLPH: Anybody on the Committee have any points they want to make or questions they want to ask?

ACTING DIRECTOR ALEXEEFF: I just wanted to add one point in my conversations with Dr. Mack. And he simply wanted to make the point that any -- that public comments should be based upon the scientific issues that are before the Committee. And that's something he wanted to urge the public. So I'm sure he'll mention that when he comes in, but I thought I'd just mention to the Committee here.

ACTING CHAIRPERSON LANDOLPH: Dave.

COMMITTEE MEMBER EASTMOND: Just a point of clarification. Maybe I wasn't paying close enough attention, but -- so this idea of the proposal was for five minutes per public comment. But if there were groups that were from the same organization or on the same topic, those would be -- the idea would that they would be back to back, but they would still be limited to five minutes each or you would give the group as an entire -- so you do five minutes per person, but try to schedule them, so that

they were sequential.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right.

COMMITTEE MEMBER EASTMOND: Okay. And I think that's -- I mean I think that's what's been done with the current practice. Although, the five minute may be a different period. Sometimes we've been flexible on that.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right, and some -- kind of the opposite of that is saying, you know, if you are just agreeing with the last person, you don't necessarily have to take five minutes. You can just come up and say you're -- you know, you're representing this position and you agree with the last three people that spoke or something to that effect.

COMMITTEE MEMBER EASTMOND: If I can continue. One of the -- I prefer to have a little bit of flexibility. Certainly when you have very complex issues, that maybe at the discretion of George or the Chair, to allow someone more time than that -- if it's thought it's warranted to go into much more complex issues.

Because I remember once, a couple years ago, we had -- someone came in and actually had a much longer period of time, had a lot of extra time. And they got in the nitty gritty of -- it was actually much more interesting to get into the full discussion of what was going on with that particular chemical.

So I prefer to have some flexibility in there personally. But obviously, it's not feasible to do that all the time. So you'd -- essentially, you'd make that kind of a special case or rare case, I think.

ACTING CHAIRPERSON LANDOLPH: Yes.

ACTING DIRECTOR ALEXEEFF: That's a good point. One of the issue that had been raised in the letters that were written -- or the letter written to Dr. Denton was sort of a fairness kind of issue, that if -- I agree with the flexibility issue, but if there's a change made at the last minute and one -- let's say there's two positions, you know, say list or not list, let's say. And one side is given a lot of deference to additional information and clarifying, and the other side hadn't prepared to do that, then they feel as though they really haven't been able to speak their -- you know, what they wanted to say.

So that was sort of the -- what one of the questions that had come up in the letters we'd received. Although, possibly it could -- the issue you're raising could come up if there's questions being raised by the Panel members to delve in more.

ACTING CHAIRPERSON LANDOLPH: Other comments from the Committee?

Sol, Darryl, Anna?

No.

My only -- I guess my only preference would be that as we do each chemical, I would like to see us do the chemical, have the Committee report, the staff discussion, the Committee discussion by the leads, and then at the end of that, I would like to see the public comments come up for each chemical, and then we vote on it and end it and then move to the next one. That's my only preference.

Dave, you're wrinkling your face. Did you have a comment?

COMMITTEE MEMBER EASTMOND: No. I just wondered if that was -- I think historically we've done that order a little bit differently, if I'm not mistaken on that, but maybe I'm incorrect.

Because frequently we only have the staff presentation, then we've had public comments and then the Committee has discussed, and then gone to the vote.

ACTING CHAIRPERSON LANDOLPH: Yeah, that's fine. What I meant was I just want to see us stay focused on a chemical and get everything done and then vote on it and move it out of the way. That's all. That's what I meant to say.

COMMITTEE MEMBER EASTMOND: I would agree with that.

ACTING CHAIRPERSON LANDOLPH: Other comments from the Committee?

No. Carol and George, can I ask you a question. Have you received any criticisms about the CIC and the way we operate or are people, in general, satisfied with the way we've operated?

ACTING DIRECTOR ALEXEEFF: I don't think we've -- I don't know. Maybe Carol can respond to this. But what this -- these particular issues were raised in response to criticisms that were raised resulting from a DART Committee meeting. And part of it had to do with a very long technical discussion, and the amount of time different organizations had to provide their information. So I don't know if, Carol, if you had a comment on that.

CHIEF COUNSEL MONAHAN-CUMMINGS: No, I agree that that's where it came up. Although, in some of our discussions with the folks that raised the issue, they wanted some consistency between the two committees, and that there be kind of a recognition that there can be kind of two sides to the question and that one side doesn't get more of an opportunity.

But in terms of just the legal requirements, you do have to have public comment before you make a decision. It can be before or after you make -- have your own discussion. And if you are asking follow-up questions of either staff or the public commenters, that doesn't count towards the five minutes. You know, we're talking about

their initial presentation. And, you know, our feeling is that you've already seen their comments in writing, for the most part, and you've had a chance to look at them, and so they don't really need to reiterate that whole discussion. It's more like they hit kind of the high points of what they wanted you to consider for sure.

ACTING CHAIRPERSON LANDOLPH: Thank you. And could we just quickly address that issue of show of hands versus voting on a ballot. Does the Committee members -- do the Committee members have a preference for one method or the other at this point in time?

COMMITTEE MEMBER HAMBURG: I would suggest that that's a non-problem, and we can do it either way. It's just very simple to do. The Committee is small enough. Show of hands. I don't think people are biased to the point that if you vote yes, I won't vote no.

ACTING CHAIRPERSON LANDOLPH: Anybody else?

Dave.

COMMITTEE MEMBER EASTMOND: I'm flexible about it too. I don't think it's going to make too much of a difference.

ACTING CHAIRPERSON LANDOLPH: Darryl.

COMMITTEE MEMBER HUNTER: I'm all right. Show of hands I think we've done typically on that.

ACTING CHAIRPERSON LANDOLPH: Anna.

COMMITTEE MEMBER WU: I'm fine.

ACTING CHAIRPERSON LANDOLPH: And I'm the same way. I'm fine with a show of hands. But if there outside legal forces that force us to check a ballot, it's okay too. I don't have a problem either way. I'm fine either way.

Okay

ACTING DIRECTOR ALEXEEFF: Well, I could say that this particular committee has had a history of having very close votes. So something to point out.

CHIEF COUNSEL MONAHAN-CUMMINGS: I wasn't sure if George -- if Dr. Alexeeff brought it up earlier, but this Committee meeting is being webcast. And so two things about that. One is you've got to use your microphones, and which means you've got to be up close like I am. And also when you take a vote -- and Dr. Mack and others are real careful about that, we will say, you know, okay, it's three versus, you know, four or whatever, in terms of the vote. But it is -- you know, it's public information concerning who voted, which way. And so that's -- I don't think we have to do roll call type votes, so whichever you prefer.

ACTING CHAIRPERSON LANDOLPH: So, Dr. Alexeeff, your comment that we made we often have close votes. Did you mean that to indicate -- suggest a preference for one

way of voting over the other?

ACTING DIRECTOR ALEXEEFF: No. I was actually suggesting that the current show of hands has not been an issue as far as I can tell.

ACTING CHAIRPERSON LANDOLPH: Thank you for that clarification. Any other questions on the way the Committee operates or discussion?

Everybody seems to be reasonably satisfied.

Okay. So shall we move to our break --

(Laughter.)

ACTING CHAIRPERSON LANDOLPH: -- not, George and hope that Dr. Mack will show up? How long would you like to have?

DR. LAWYER: George, do you want public comments on that session you just had. More than happy.

ACTING CHAIRPERSON LANDOLPH: Sure. Would anyone from the public like to make a comment on the procedures?

DR. LAWYER: It's Dr. Arthur Lawyer. I'm with the Technology Sciences Group in Davis, California.

The reason I thought I'd speak on this issue is a couple of us in this room have been doing this for -- since the beginning, for 25 years, many times in front of the committees. And I was struck by one thing that Dr. Eastmond was mentioning.

There are times when we have, as members of the

public giving public comments, the opportunity to really expand upon the science. All right. Maybe stating the obvious today is not going to be that day, because there's so many people interested in the issues coming before you this time. But there are times -- and I can remember one time in the City Hall we had a single compound. It was only one side that was there. It was scientists. It was dimethylformamide.

And we really got a chance to deal with the issue scientifically, and it wasn't five minutes. But that was a luxury. And I just -- so to your comment, I think there are times where if we can get away with public comments and valuable discussion of the science, I think it's very helpful for those of us who work so hard to do the communication, even if we've done the written comments before.

I only have a question then for you. We asked the same question to the DART IC Committee. A lot of us put those comments together over and over again, but we rarely get feedback about what your general thoughts are about the comments you get from the public, both the industry side and the public side. Helpful, like more, like less?

It's a tough job that you have to focus in on these things in your busy schedules. Just wondering what

your comments are.

ACTING CHAIRPERSON LANDOLPH: Anybody on the Committee like to address that question?

COMMITTEE MEMBER HAMBURG: Let me just start that the industry comments and the public comments are very helpful, very informative, often very complete, give me an opportunity to think about both sides of all of these questions. There's clearly appropriate bias. Bias is helpful, because we're trying to make decisions here that impact industries people. And so I would ask you not to do anymore, but what you're doing right now seems to be very appropriate.

ACTING CHAIRPERSON LANDOLPH: Dave.

COMMITTEE MEMBER EASTMOND: I echo that as well. I find the public comments to be quite valuable, partly because they call attention to things we may not be focused on or aware of. Certainly, those of you out there oftentimes have a vested interest or very definite interest in a particular chemical and spent many months to years studying it, and it's very hard for us to get up to speed very quickly, so those comments are appreciated.

Just from a point of my perspective. It's very useful to have really succinct summaries, kind of executive summaries to boil things down. And then the supporting material is okay, but you want to get your

point across efficiently.

The other point I might make is some of the CDs that we've been getting are not readable on my computer, so they're kind of a waste of time for many of you. So I'd make sure that the CD ROMs are easily readable. It's not only one computer, it was a couple of computers I tried. So just to make sure that they are easily compatible with multiple types of computer systems, and so someone can access the information if you choose to provide it.

ACTING CHAIRPERSON LANDOLPH: Any other comments from the Committee? Anna, Darryl?

No.

I would add my comments. I completely agree with Dave, and Sol as well. One thing I would urge is that conciseness is a virtue. So if I've got this much to go through, there's a point at which I begin to tune out if it gets too long. But I appreciate that sometimes you have to go lengthy in order to get all the details in. But if you have a choice, your presentation, to my mind, would be more effective if it's more concise in any specific time, just because of our limited time, and large amount of reading material. And I am a speed reader.

Any other discussion on that issue?

Please.

DR. JANSSEN: Good morning. I'm Dr. Sarah Janssen with the Natural Resources Defense Council. We are one of the groups that authored the letter that was being discussed this morning. So I just wanted to provide a little bit of context. I agree that having discussions, you know, as a scientist, I find it really educational. I think it's really beneficial for the Committee. But we're really asking for fairness.

There's been situations at the DART where industry groups have been given twice or three times the amount of time as academic groups who have come in from across the country to talk about their research. And it's not made clear -- in the past, it hasn't been made clear up front that this is what was going on. Our experts prepare presentations to comply with the time requirements, and then industry groups are let go on and on and on.

So I welcome the detailed discussions, but I ask that the length that speakers are given to discuss the science is fair.

Thank you.

ACTING CHAIRPERSON LANDOLPH: Thank you. Any other comments from the public or the Committee?

ACTING DIRECTOR ALEXEEFF: So I appreciate all the comments made by the Committee members and the public.

And as our Chief Counsel mentioned in discussions with Dr. Mack, he asked that today that public comments be up to five minutes, and that they focus on the scientific issues.

I think what we'll do right now, we'll take a break until 10 to, so 10:50, and then we'll reconvene and hopefully Dr. Mack will be here by that -- oh, Carol has a comment.

CHIEF COUNSEL MONAHAN-CUMMINGS: Just the usual reminder not to discuss the issues that are before the Committee today with -- among yourselves, especially a quorum of the group

Thank you.

ACTING DIRECTOR ALEXEEFF: Okay. I've been asked by the Chair to extend the time period to 11 o'clock, a round number, okay. So we'll reconvene at 11 o'clock.

Thank you.

(Thereupon a recess was taken.)

CHAIRPERSON MACK: I'm sorry I was late. I blame it all on -- I could blame it all on my wife or I could blame it all on myself, but I'm actually going to blame it all on the security at the --

ACTING DIRECTOR ALEXEEFF: Let me see if I can adjust this.

CHAIRPERSON MACK: It's not working?

ACTING DIRECTOR ALEXEEFF: I think it's a little better one. Let's try it again.

CHAIRPERSON MACK: Is that better?

MEMBERS OF THE AUDIENCE: No.

CHAIRPERSON MACK: No, not better.

ACTING DIRECTOR ALEXEEFF: Let's go back to trial one then

CHAIRPERSON MACK: All right. Now is that better?

MEMBERS OF THE AUDIENCE: Yes.

CHAIRPERSON MACK: I apologize on behalf of the -- what is it called, the TIA?

DR. SANDY: The TSA.

CHAIRPERSON MACK: Everybody in front of me had a pacemaker, and they funneled three lines through one thing. I sat there and fumed and it took me 55 minutes to get through. And I was really irritated, but now I'm calm.

(Laughter.)

CHAIRPERSON MACK: So let's get the show on the road. George, as the designated bureaucrat, please proceed.

(Laughter.)

ACTING DIRECTOR ALEXEEFF: Thank you very much. I will proceed.

So this morning we have a presentation from staff. We have a Dr. John Faust and Laura August presenting tris-dichloropropyl phosphate.

Do we have -- oh, I'm sorry. First, we have -- before we -- but before we begin that, we'll have a statement from our Chief Counsel here.

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. Me again. I just wanted to -- and I know I've done this before, but it's a reminder to all the Committee members since you're only at these meetings once a year, that in your binders you do have criteria for listing chemicals, and what the basis for that listing can be. And as you know, we -- the Chair will ask you whether or not the chemical has been shown to cause cancer, and he will give you the entire phrase at that time.

Your listing decision should be based on that scientific criteria and your discussions concerning that. You don't need to and shouldn't consider the future impact of a listing, for example, whether a warning will be required or whether a chemical will not be used in the future.

The clearly shown standard that is in the statute that you would be needing to apply is your -- is a scientific judgment call on your behalf. It's not a legal standard of proof. You're not a jury. You don't have to

find beyond a reasonable doubt, for example, that the chemical causes cancer.

This Committee is also allowed to decide to list a chemical based on animal evidence only. There need not be any evidence that a chemical causes human cancer.

And you don't need to, and shouldn't consider, whether or not the current human exposures to the chemical are sufficiently high enough to cause cancer. That's a dose-related question, and it's not something you need to make a finding on.

You, as members of this Committee, were appointed by the Governor because of your scientific expertise and so you need not feel compelled to go outside that charge regardless of the comments you may hear from the public.

In the event that you feel you have insufficient information or need more time to think about a listing or discuss it, there is no requirement that you make a decision today or this morning. You can table discussion and ask us to get you more information, for example. So you are not required to make any decision, pro or con, today.

Do you have any questions on that?

All right.

COMMITTEE MEMBER EASTMOND: Never mind.

CHAIRPERSON MACK: Change your mind?

COMMITTEE MEMBER EASTMOND: Yes.

CHAIRPERSON MACK: Okay.

ACTING DIRECTOR ALEXEEFF: I'D also just, before we begin with the presentation, just introduce at the staff table. We have Dr. Lauren Zeise and Dr. Martha Sandy, who may be answering questions when we get to the discussion period. So we'll begin with Dr. Faust or Laura August.

(Thereupon an overhead presentation was Presented as follows.)

MS. AUGUST: Great. Good morning. So John and I will be presenting the evidence on the carcinogenicity of tris(1,3-dichloro-2-propyl) phosphate or TDCPP.

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MS. AUGUST: So beginning here is the structure TDCPP. It's a halogenated phosphate triester. It's a high production volume chemical, which is primarily used as an additive organophosphate flame retardant in flexible polyurethane foams, items such as sofas, car seats, and seat cushions. Other uses include as a flame retardant, and plasticizer in rigid polyurethane forms, resins, plastics, textile coatings and rubber.

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MS. AUGUST: So regarding its occurrence in the environment, it has been measured in a variety of indoor

air as well as dust in both the U.S. and abroad. In the outside environment, it has been measured in streams, sewage influent and effluent, as well as agricultural runoff.

And biomonitoring in humans have found that it is present in adipose tissue, as well as seminal plasma, and human milk.

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MS. AUGUST: So to date, there has been only one unpublished retrospective cohort study in humans of 289 workers at TDCPP plant conducted by the Stauffer Chemical Company for the years 1956 to 1980. Over the study period, 10 deaths due to cancer were observed, where three of these deaths were due to lung cancer.

The authors calculated standard mortality ratios for the observed deaths in the study compared to expected deaths in a representative sample of U.S. males. Although the standard mortality ratios were higher than expected, no P values could be calculated due to small sample size. And overall, we are unable to draw any conclusions from this study due to sample size issues, as well as confounding factors the cases of lung cancer were smokers as well.

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DR. FAUST: Okay. Now, we'll turn to the

evidence in experimental animals. So the key studies in experimental animals that tested for the carcinogenicity of TDCPP are described in this slide. These studies were conducted by bio/dynamics for the Stauffer Chemical Company and completed in 1981.

However, the results of the studies were not published in the open literature until the year 2000 by Freudenthal and Henrich. So briefly these studies were conducted in male and female Sprague-Dawley rats. The rats received TDCPP in their diets for two years at concentrations that resulted in doses of 0, 5, 20, or 80 milligrams per kilogram day. The dose groups consisted of 60 animals of each sex per dose, 10 of which were sacrificed after 12 months of exposure.

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DR. FAUST: So the tumor results are described in the next three slides. The numbers presented here do not include the 10 animals from the interim sacrifice. So both male and female rats developed liver tumors. High dose male rats showed significant increases in the incidences of hepatocellular adenomas, hepatocellular carcinomas, as well as combined hepatocellular adenomas and carcinomas by pairwise comparison.

Each of these three endpoints showed a significant positive trend with dose. Three additional

adenomas were observed in the high dose group of male rats. But as I said, these aren't on this slide.

High dose female rats also showed significant increases in hepatocellular adenomas, as well as combined hepatocellular adenomas and carcinomas. And both of these endpoints showed significant positive trends with dose.

Hepatocellular carcinomas in the female rats also showed significant positive trend with dose. Although there was no significant increases by pairwise comparison.

One additional hepatocellular adenoma was observed only in the high dose group of female rats at the 12 month interim sacrifice.

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DR. FAUST: So kidney tumors were also elevated in treated rats. The incidence of benign cortical adenomas were significantly increased in both male and female rats in the mid and high dose groups by pairwise comparison. And both of these endpoints were also significant for positive trend with dose.

Male rats also showed an increase in the incidence of interstitial cell tumors of the testes at both the mid and high dose levels. And there was a significant positive trend for dose with this endpoint. Three interstitial cell tumors were also observed in the mid and high dose group at the 12-month interim sacrifice.

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DR. FAUST: So increases in adrenal gland tumors were also found in female rats. Significant increases in cortical adenomas, as well as combined cortical adenomas and carcinomas occurred in the high dose group with positive trends for both of these endpoints. However, there was no positive trend with dose for the carcinomas.

Further, five adenomas were reported in the control group of female rats at the 12-month interim sacrifice. So if these tumors are included in the statistical analysis, the increase in the high dose group is no longer significant. Although, the positive -- there is still a significant positive trend with dose.

So now, we'll turn to evidence on the genotoxicity.

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MS. AUGUST: Okay. All right. Well, we identified a variety of studies in the peer-reviewed literature as well as other government agency reviews of the chemical.

So starting with the in vitro genotoxicity, positive studies. We identified a variety of positive salmonella reverse mutation assays in strains both capable of detecting frameshift as well as base-pair substitution mutations.

Positive mutations were also seen in mouse lymphoma cells, as well as chromosomal aberrations in mouse lymphoma and Chinese hamster fibroblast cells, and also positive in sister chromatid exchanges in mouse lymphoma cells.

Moving to the negative studies, in vitro studies. Various strains of salmonella assays both frameshift and base-pair mutation strains were negative, although to a slightly lesser degree than the positive studies.

One study of yeast was also negative, as well as TDCPP was negative at inducing mutations in mouse lymphoma cells and Chinese hamster cells, as well as chromosomal aberrations in Chinese hamster ovary cells.

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MS. AUGUST: Moving to the in vivo genotoxicity data. A positive study was identified of TDCPP inducing DNA binding in mouse liver, kidney, and muscle tissues. Negative studies for the following:

Negative for sex linked recessive lethal mutations in Drosophila. TDCPP did not induce chromosomal aberrations in mouse bone marrow and chick embryo, as well as the mouse bone marrow micronucleus assay and the unscheduled DNA synthesis in rat hepatocytes was also negative.

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MS. AUGUST: And lastly, we identified in vitro cell transformation assays, which are capable of detecting change in a growth pattern of fibroblasts. So TDCPP was positive in two experiments using Syrian hamster embryo cells, and was negative in a BALB/c 3T3 mouse cell assay.

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DR. FAUST: Okay. Turning to pharmacokinetics and metabolism. There are limited data that are available related to pharmacokinetics and metabolism, primarily from studies that were conducted in the early eighties.

Studies in animals have shown that TDCPP is widely distributed following exposure, and is eliminated in the urine, feces, and exhaled air. Several specific metabolites have been identified in urine. The primary metabolite is BDCPP, the diester of the parent compound.

Other metabolites have included 1,3-dichloropropanol or 1,3-DCP; 3-monochloropropanediol 3-MCPD, and the monoester has also been identified as a metabolite and the structures are all presented on this slide.

So both 1,3-DCP as well as 3-MCPD were considered by the CIC at its last meeting, and both chemicals were added to the Proposition 65 list. So some of the evidence on the metabolism of these two compounds is included in the next slide, and this is material that was featured in

the hazard identification documents last year.

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DR. FAUST: 1,3-DCP and 3-MCPD undergo metabolic processes that can ultimately result in the formation of carbon dioxide cystein derivative oxalic acid, as well as 1,3-dichloroacetone.

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DR. FAUST: So several of these metabolic products or intermediates are of concern for carcinogenicity. And these include epichlorohydrin, glycidol, and 1,3-dichloroacetone.

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DR. FAUST: So on the next slide we've put a tumor comparison for some of these metabolites in terms of the carcinogenic endpoints. So as we've seen TDCPP produces tumors of the liver, kidney, and testes in rats. 1,3-DCP also produces liver and kidney tumors in rats as well as thyroid tumors. Epichlorohydrin has been shown to cause forestomach and nasal cavity tumors. And glycidol causes tumors at multiple sites in rats and mice. And each of these chemicals is on the Proposition 65 list.

So the other potential metabolite that I identified 1,3-dichloroacetone is a direct metabolite of DCP and is a mutagen and skin tumor initiator.

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DR. FAUST: So there are also chemicals that are structurally related to TDCPP that have been shown to cause cancer. Tris(2,3-dibromopropyl) phosphate, also known as TDBPP or tris, has been shown to cause liver, kidney, lung, and forestomach tumors in experimental animals. Tris(2-chloroethyl) phosphate, or TCEP, causes tumors of the kidney and thyroid. And both of these chemicals are on the Prop 65 list.

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DR. FAUST: So with respect to possible mechanisms of action, the available evidence suggests that genotoxicity is likely to play a role. TDCPP has also tested positive in a number of short-term tests for mutagenicity and DNA damage as we heard before. It's also possible that other mechanisms of carcinogenicity are operative, but none has been specifically identified.

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DR. FAUST: So in summary, the animal evidence for carcinogenicity comes from long-term studies in male and female rats, exposed to TDCPP. In male rats, the studies show increases in the incidences of malignant and combined malignant and benign liver tumors, benign kidney tumors and testicular interstitial cell tumors.

In female rats, the studies show increased incidence of combined malignant and benign liver tumors as

well as benign kidney tumors.

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DR. FAUST: Multiple tests were positive for genotoxicity, including tests in multiple strains of salmonella, findings of chromosomal aberrations and sister chromatid exchange in mouse lymphoma cells, as well as chromosomal aberrations in hamster fibroblasts. And as we heard earlier, TDCPP is also positive for malignant transformation of cells in vitro.

So several metabolites of concern for carcinogenicity have been identified. And these include 1,3-DCP and 3-MCPD, both recently listed as causing cancer. These compounds are on a metabolic path that also leads to the formation of epichlorohydrin and glycidol, both of which are also listed as carcinogens.

And finally, TDCPP is structurally similar to other halogenated phosphotriester carcinogens, including both tris, TDBPP and TCEP.

So that concludes the presentation.

CHAIRPERSON MACK: Thank you. John and Laura.

Now, usual spiel before we start the parade of comments from the regulated community, and the people on both sides of the issue. We're here to discuss the carcinogenicity of these compounds, not the net benefit and net liability. We don't want to hear a lot of

discussion of why they're very valuable or why they're very nasty in other ways. And we'd prefer not to hear a lot of repetitive discussion.

So we'd like you very much to try and modify your comments to things which have not been previously said, which bear on the carcinogenicity of the compounds.

That shouldn't be too hard with tris. And I hope it won't be too hard with the other compounds we're looking at, but we'll begin with tris. And we'd like you to try and make it within five minutes if you possibly can, each.

So the first person to speak is Nancy O'Malley on behalf of Albemarle Corporation.

(Thereupon an overhead presentation was presented as follows.

DR. O'MALLEY: I'm Dr. Nancy O'Malley. I'm a toxicology advisor for Albemarle Corporation. We are one of the two manufacturers.

CHAIRPERSON MACK: Move the mic closer. As usual, I've screwed up already. I should ask you if there are any questions on the part of the Committee of the people who gave the presentations.

DR. O'MALLEY: I'm sorry.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: I have a question.

This might come up. John. Now, one of the key elements of these kidney adenomas, you mentioned benign tumors. These due to tend to progress to carcinomas, this particular tumor type?

DR. FAUST: Yes. This type of tumor can progress. Although, we did not observe carcinomas in the -- at the end of the study or in the study at all. So these were -- there was a fairly high incidence within the study, but no carcinomas were reported.

COMMITTEE MEMBER EASTMOND: One of the other comments had to do with issues about excessive toxicity at the high dose, and even lethality and decreased body weight gain. Can you comment on that a bit.

DR. FAUST: Yeah. As we noted in the report, there was a significant decrease in body weight in the male rats as well as the female rats, about 20 percent below the control animals. And in male rats as well, there was a significant decrease in mortality or increase in mortality.

COMMITTEE MEMBER EASTMOND: Just, one of the public comments I thought it was even 20 percent decrease in body weight gain in one sex species. The other one I think was as much as 38 percent, was that -- did you see that in the --

DR. O'MALLEY: The mortality was 38 percent.

CHAIRPERSON MACK: Just to outline the procedures, in general, which I think we probably should follow, is questions to the staff a matter of what they've said, next the public comments and public remarks, then we go to the two of you to see what you say.

Okay. Please continue.

COMMITTEE MEMBER EASTMOND: Thanks, John

DR. SANDY: John has some more to respond to your question.

CHAIRPERSON MACK: Did you have a comment?

COMMITTEE MEMBER LANDOLPH: Yeah, along the lines of what Dave was asking, follow on. At what point do you think -- what doses do you think the toxicity becomes excessive? Is all the data compromised by the toxicity or is there a point at which the data is usable in your opinion?

DR. FAUST: Well, we did gather a little of information that you might find helpful in thinking about this particular compound related to adequate dosing in long-term studies. And the maximum tolerated dose. So we have a couple of statements up from the U.S. EPA's 2005 guidelines for cancer risk assessment, basically saying adequate high dose would generally be one that produces some toxic effects without unduly affecting mortality from effects other than cancer or producing significant adverse

effects on the nutrition and health of the test animals.

So it's certainly not unusual to see a certain amount toxicity and even desirable to make sure that the adequate dosing has been achieved. And in this case, we basically want to make sure that we don't have so much mortality that we wouldn't be able to discern a cancer effect.

So in this case, we felt there were adequate numbers of animals surviving to the end of the study, you know, between those that survived to the end, as well as the unscheduled deaths that occurred that we were able to discern that there was, in fact, an increase in tumors at the various endpoints that we described.

CHAIRPERSON MACK: Okay. Anymore questions of staff?

If not, let's continue with Dr. O'Malley.

DR. O'MALLEY: Thank you. If I could have the first slide.

(Thereupon an overhead presentation was Presented as follows.)

DR. O'MALLEY: As I mentioned, I'm Dr Nancy O'Malley. I'm a toxicology advisor for Albemarle Corporation. We are one of the two manufacturers of TDCP that participated in the EU risk assessment process to evaluate TDCP and two other phosphorus flame retardants in

the fourth priority reviews. This was the most recent and in-depth assessment of these phosphorus flames retardants to date.

Next slide.

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DR. O'MALLEY: Just a summary of some of the information that has already been discussed from your staff. There have been previous assessments of TDCPP by authorities. None have concluded that there is clear evidence of carcinogenicity for TDCP. And as mentioned by your legal staff, there is a process in order to assess data in evaluating material for listing under Proposition 65.

And as the CIC guidance outlines, in order to meet the listing criteria, the weight of evidence must clearly show that a certain chemical causes invasive cancers in humans or that causes invasive cancer in animals, unless the mechanism of action has been shown not to be relevant to humans.

Next slide.

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DR. O'MALLEY: Using further guidance in the CIC prioritization as to the types of data, data can be summarized as either direct or indirect evidence in assessment. And there's a hierarchy in how you value this

evidence.

For example, the highest priority of data is human and animal studies. And those can be considered direct evidence of carcinogenic potential. And as mentioned, there is no human data that supports the listing.

There is only a single animal study, and that also does not support the listing, because there is limited evidence of carcinogenicity in that study.

Indirect evidence of carcinogenicity can also be used in the weight of evidence evaluation of data for carcinogenicity listing, for example, genotoxicity data that was mentioned. Also, you can look at structurally similar compounds. The data for TDCP, for example, all of the in vivo genotoxicity data is negative.

The in vitro genotoxicity, although there are some positive studies, particularly in some of the older studies, there is a mixed picture on some of these studies, and there are some quality concerns. So the in vitro genotoxicity data really does not support listing. And as indicated in the guidance on hierarchy of the value of data, the in vitro data is impertinent -- is less pertinent than data generated from whole animals or in vivo studies.

In structure activity relationships, TDCPP,

although it is structurally similar to other phosphate ester flame retardants, there are differences both in physical chemical properties, metabolism, and target organs.

Thank you for changing the slide to the next one.

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DR. O'MALLEY: To the previous slide.

Can I have the previous -- there we go.

Just to go back as far into the direct evidence that was stated for TDCP, there is no evidence that TDCPP causes cancer in humans. The epidemiological data is limited. Again, a single study was mentioned, but there was no data that there was evidence of causation of cancer of any type, particularly invasive cancer.

This study that was generated by Stauffer involved manufacturing personnel that would have been exposed to dermal contact with the material in manufacturing or possibly inhalation, even though the material is not particularly volatile.

Next slide.

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DR. O'MALLEY: In the single animal carcinogenicity study, there are no relevant invasive tumors that were indicated. This is what I was saying is limited evidence of carcinogenicity. These studies --

this study was generated prior to the good laboratory practices requirements that are used to document an adequate study and to evaluate the validity of a study.

It was not conducted to current EPA guidelines. And again, you brought up the question of maximum tolerated dose. Generally, when the maximum tolerated dose is exceeded, the stress on the animals will cause an effect of increased mortality and increased -- decreased weight gain. You mentioned that as effect.

These are confounders, because they can stress an already susceptible animal and cause target organ effects that normally would not be seen.

Again, the tumors were reported at several sites. That's agreed. There is limited data. Many of the tumors were not invasive, that is they weren't malignant. They weren't unusual for the strain of animal. The time of appearance was not shortened. Some of them were misclassified by modern histological protocols. For example, the neoplastic nodules that were mentioned in the original study we do not have the slides to go back and separate those into hyperplasia and adenoma as would the current classification scheme.

And many of these that were increased in number were only observed at a dose well above the maximum tolerated dose.

Again going back to the CIC -- next slide.

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DR. O'MALLEY: -- the CIC weight of evidence guidance on how to evaluate studies. If there is only a single study in one species, CIC guidance indicates that might be sufficient if the malignant tumors occurred at an unusual degree with respect to frequency, type, location, age of onset, at low dosage, or in a strain not otherwise prone, or if heavily supported by indirect evidence.

We'll discuss a little bit now about indirect evidence.

Next slide.

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DR. O'MALLEY: TDCP, the weight of evidence indicates that TDCP is not genotoxic. As mentioned, all of the in vivo tests were negative. In the EU risk assessment process, and as was reevaluated by the European chemical agency in 2010, the statement is made, "Regarding notably the five negative in vivo assays, it is considered the TDCPP is not genotoxic in vivo, and thus no classification for mutagenicity is proposed in the EU".

In the in vitro studies, there were problems in evaluating this during the EU risk assessment process because many of these old studies were either not by standard guidelines, there was not enough documentation

for these studies to fully evaluate. Some of these studies the test article purity could not be identified, so there was -- there were questions on to the value of these studies.

In our comments, we submitted an evaluation of these studies using the Klimisch codes, which investigation how closely these studies were conducted to valid protocols and how useful these studies are. In the process for the EU risk assessment, industry generated some new studies.

CHAIRPERSON MACK: Dr. O'Malley, you're already into about seven minutes and you've only done about a third of your slides.

DR. O'MALLEY: I'm sorry. Could I take two more slides.

CHAIRPERSON MACK: Two more slides.

DR. O'MALLEY: All right. Next slide.

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DR. O'MALLEY: This is some structural comparisons for TDCP to some of the other phosphorus flame retardants. As mentioned, these structurally are similar, but you have to be careful when using a category classification. For example, some of the physical chemical properties of these materials make them very different on how they behave in the body. TDCP has a

water solubility of about 18 milligrams for liter. TCPP 1,080 milligrams per liter, TCEP 7,820 milligrams per liter. This will make things a lot different on how the body sees this material.

Similarly, on metabolism, although metabolism was discussed in detail, a lot of the metabolites that were being shown were putative metabolites. They have not been identified, and we have conducted a more recent in vitro study using liver slices and microsomal extracts that shows that TDCP is rapidly conjugated so that you don't get the propyl moiety off before conjugation, like you do with TCEP and the ethyl moiety.

So again, there are differences in these materials. It has been pointed out by the EU risk assessment as well as ATSDR in its draft review of phosphorus flame retardants that you can't consider these chemicals across the board as a category for all categories of toxic endpoints.

Thank you.

CHAIRPERSON MACK: Thank you, Dr. O'Malley.

The next speaker will be Andy Wang.

(Thereupon an overhead presentation was Presented as follows.)

DR. WANG: Good morning. My name is Andy Wang. I'm the regulatory affairs manager of ICL-IP America.

ICL-IP manufactures TDCP at its West Virginia plant. Today, I'm on behalf of ICL-IP America, and Albemarle Corporation to give this presentation.

This presentation is to clarify the exposure issues of TDCP. I appreciate that this process is about hazard ID. And that has been the focus of our written comments and the talk that you have just heard from Dr. O'Malley.

But with all that, it will be useful to briefly respond to comments made by others regarding exposure issues.

Next slide.

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DR. WANG: TDCP is used as a flame retardant in flexible polyurethane foams. Polyurethane foams is primarily used in autos and furniture. European authorities have conducted a comprehensive risk assessment of TDCP and published their conclusions in 2008. My presentation will be based on the EU risk assessment findings.

Large margins of safety, the ratio is more than 2,000 has been concluded by the European Union. And the risk assessment has included all exposure routes.

Next slide.

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DR. WANG: The potential exposure for consumers are inhalation, skin contact, hand-to-mouth transfer of dust for young children, and dietary. A number of published studies have measured TDCP indoor air and dust. These measurements were related to homes, offices, factories, automobiles, prisons, shops, airplanes, libraries and various other public places. And this monitoring studies show that the levels of TDCP found indoor are 0 to 0.15 micrograms per cubic meter in air, and 0.4 to 67 milligrams per kilo dust respectively.

A recent paper from Webster shows that TDCP dust concentration in the Boston area is consistent with this range.

Next slide, please.

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DR. WANG: The EU risk assessment has concluded that the worst case daily intake of TDCP by consumers, including young children, are 0.0011 milligrams per kilo per day for inhalation exposure; 0.0011 milligrams per kilo per day for skin contact, and 0.0002 milligrams per kilo per day for dust ingestion.

The reference dose for the two-year carcinogenicity study is five milligrams per kilo per body weight per day was used as the basis for the risk assessment. In this assessment, the margin of safety is

2,000 times higher than the reference dose. Therefore, the European Authority has concluded that there is no concern for consumers from exposure to TDCP treated foam used in furniture, and in the automotive industry.

Next slide.

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DR. WANG: I have a few more slides and details from here, but if you had any comments or --

CHAIRPERSON MACK: You have a minute and a half left.

DR. WANG: Okay. Next slide.

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DR. WANG: Inhalation. EU risk assessment took the worst case scenario and used a 3.8 micrograms per cubic meter, which represents a 20-fold higher concentration than what has actually been measured. For the air concentration of 3.8, a daily intake inhalation is 0.0011, which I just showed.

Next slide.

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DR. WANG: In absence of dermal exposure data, and in the view of the enclosed use of TDCP treated foams, the European authorities assumed that the intake from dermal exposure to TDCP is lower than the inhalation intake. Therefore, as the worst case assumption, that

daily dermal intake was assumed equal to the inhalation exposure.

Next slide.

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DR. WANG: In addition to the intake of TDCP by inhalation or skin contact, young children may ingest dust containing TDCP. The European authorities used a value of 12 milligrams per kilo dust to calculate the worst case scenario. And, the 0.002 milligrams per kilo body weight has been concluded.

Next slide.

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DR. WANG: No published data documenting exposure to food. The TDCP does not bioaccumulate. The BCF is less than 100. The TDCP will be eliminated rapidly in the body. The metabolism has been presented and discussed in the previous slide.

Next slide.

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DR. WANG: The long-term retention study has shown that flame retardants are, for the most part, retained within polyurethane foam and so consumer exposures to flame retardants for these foams is expected to be very low. Hence --

CHAIRPERSON MACK: You're also a minute and a

half now over. If you can

DR. WANG: Just one more.

CHAIRPERSON MACK: If you can --

DR. WANG: Just one more statement.

CHAIRPERSON MACK: The things that you're telling us are telling us things about dose. You're not telling us things about carcinogenicity, and that relates to the issues which we're not dealing with. So you're not helping us at all. In fact, all you're doing is taking time, because we have to judge whether it's a carcinogen at any dose, not whether it's a human -- there's human concern in the home right now.

So if you have one more sentence, go ahead, and I think you cut it off.

DR. WANG: That's it. Okay. Thank you.

CHAIRPERSON MACK: The third speaker is David Heimbach from the University of Washington.

DR. HEIMBACH: Thank you. Dr. Mack, I appreciate your comments that you're not interested at all in the importance of these drugs and what they do, but rather whether they cause cancer.

I am here because I've spent 40 years taking care of burn patients, for which I have been rewarded by being the President of the American Burn Association, International Society for Burn Injury, and given an award

recently by the Dalai Lama for my work in developing countries about burn care.

There is no question that fire retardants are important. The problem that I see with listing this are the consequences of the action here. Unless you are truly convinced that this is a cancer-causing drug, I think the consequences will be important. There is a very large -- well, not a very large, but there's a group of very dedicated, although I think misinformed, individuals that want to ban all fire retardants, of which this is a prominent one, which has clearly been shown to be very effective.

So I will be very brief, and just say please think about what you're doing -- stuff that happens in California is worldwide. So as soon as you list this as a carcinogen, other people are going to get on the band wagon and do that. So I just would hope that you would think carefully before you list a compound that is clearly advantageous for important benefits for perhaps future obscure benefits.

CHAIRPERSON MACK: Thank you, Dr. Heimbach. I would assure you that we do think a lot about not that, because that's for others to think about. And we have had the position we've had to list chemicals which are extremely valuable in medicine in all respects and it just

has to be done, because that's what the people of California have asked us to do.

And I'm sure that the people who do the regulation will think really seriously about the things that you're talking about.

DR. HEIMBACH: Thank you very much.

CHAIRPERSON MACK: A couple more here. Okay. Rebecca Sutton.

DR. SUTTON: Thank you. Can you hear me?

All right. So my name is Dr. Rebecca Sutton. I have a Ph.D. in environmental chemistry, and I'm a senior scientist with Environmental Working Group. We're a national public health research and advocacy nonprofit, and we do have a lot of expertise on a variety of flame retardant chemicals.

So I'm going to thank you first for picking this chemical for your review, because of its widespread and growing use. I know you're not dealing with the exposure question, but the carcinogenicity question, but it's good that you prioritize this particular chemical.

It's a bit of a personal issue for me, because I did find out a few months ago that my couch has tris in it. And it's very frustrating for me as an environmental chemist to know that I brought this piece of furniture into my house with tris.

So obviously I'm glad I'm an adult with this tris couch in my house, because if I were a young child, I would be more highly exposed. We know, as just reported, that tris does partition into dust, even at quite high levels, if you look at those values that we just saw. And young children, with all their hand-to-mouth activity get a lot of dust-related chemicals into their bodies.

And they're also more highly vulnerable to carcinogenic chemicals, because they are going through rapid growth and development, and their systems, their organ system, aren't as efficient at detoxifying chemicals as in adults are.

So we saw from the OEHHA presentation that tris pretty clearly meets the Proposition 65 carcinogen classification criteria. We asked that you list it, because we do see in vitro and in vivo evidence of carcinogenic activity, in particular the rat studies showing tumor site -- tumor activity in multiple organs in both males and females.

We're also very concerned about the metabolism issue, the fact that four of the metabolites are already listed by Proposition 65 listing process. So obviously if this is how we're getting exposure to these already listed chemicals, we really need to look clearly and closely at this one.

Now, tris itself hasn't been evaluated for carcinogenicity by the other authoritative bodies that you all consult when you're listing chemicals. So we think it's a great step for you guys, a step forward in science-based regulation to go ahead and list this chemical. And it would be great if a couch like mine in the future might possibly have a warning label, a Prop 65 label on it, so consumers would be more informed about what they're buying.

Thanks.

CHAIRPERSON MACK: Thank you, Dr. Sutton.

The next speaker is Sarah Janssen.

DR. JANSSEN: Good morning. I'm Dr. Sarah Janssen with the Natural Resources Defense Council. I'll keep my comments brief. We submitted written comments, which I'm sure you've already read.

I just want to reiterate our support for the listing of this chemical as a carcinogen. We believe that it does meet the criteria for listing.

I want to react to a couple of things that have been said earlier this morning, one is the prioritization scheme that was presented to you, is just that. It's the prioritization scheme you use for determining which chemicals will undergo a hazard assessment review. But your criteria for determining listing does not need to

include evidence of human cancer, and you can consider both the preneoplastic and tumors in animal studies, as well as the in vivo and in vitro data from cell lines.

I think it's worth asking the OEHHA staff to clarify the issue of the in vivo genotoxicity testing as they presented data consistent with positive results in those assays. And I'm not at genotoxicity expert, so I think that would be worth hearing about the difference in opinion there.

My other comments are that of course a listing on Prop 65 is not a ban. It would just possibly trigger a warning label. And while it's, I think, very supportive of a listing that there are already four metabolites of TDCPP or tris which are on the Prop 65 list, the metabolites are not going to be present in consumer products.

The will of the California people was that we have warning labels on products that contain chemicals that are known to cause cancer or reproductive harm, and therefore the presence of the parent compound or tris in consumer products is the only thing that would trigger a warning label.

I also have a couch that contains tris in it. It would have been nice to have known that when I bought it, so that I could have made a more informed decision.

And my final statement is that, of course, the European Union is not considered an authoritative body for the listing. That's why the chemical has come up for your review. You are the State's appointed experts, and I ask that you objectively review the data that's in front of you today.

Thank you.

CHAIRPERSON MACK: Thank you, Dr. Janssen.

And finally Arlene Blum from UC Berkeley.

DR. BLUM: I'm Dr. Arlene Blum, and I'm a visiting scholar in chemistry at UC and also the executive director of the Green Science Policy Institute. And I have had long experience with TDCPP. I was the a co-author in Gold, et al. in 1977 which first reported the mutagenicity of TDCPP. And I noted that the Albemarle ICL report dismissed our paper as a review article, but it was not a review article. It was a short piece in Science.

We, at that time, found TDCPP to be weakly positive in the Ames test and the metabolite 1,3-dichloropropane to be strongly positive. And that chemical has been recognized under Proposition 65 as a carcinogen.

And just to say our study was co-authored by Bruce Ames, carried out in his laboratory. And Dr. Ames, of course, developed the Ames test.

The Albemarle paper admitted -- I read through their paper, just so -- to say that there was a Mortelmans positive genotoxicity result with TDCP, which they admitted. They said there were no positive in vivo genotoxicity studies, but OEHHA mentioned a number.

Their study also said that TDCPP is not a substitute for pentaBDE. So I'm also a co-author of a recent study in Environmental Science and Technology where we found -- and I know this is a little off the point, but since it's been so addressed by others, I think I would like to just say that in our study in ES&T, we found TDCPP levels up to 12.5 percent by weight in 35 percent of baby products tested. And we have another study not yet published where we found TDCPP in 58 percent of 62 couches that were purchased in California in the last five years.

So it is apparently the number one substitute for pentaBDE. So it is very good that you are taking this chemical up.

The Albemarle ICL report also stated the foams are fully enveloped, and there's no significant exposure. But a number of studies, which OEHHA detailed, have found TDCPP and various media particularly in dust. The Webster study was referred to previously, which found similar levels of TDCPP as pentaBDE. And the EU Union report that has been invoked so many times was 2008 and does not have

a lot of the new generation of studies of TDCPP. And it is being studied a lot as the number one flame retardant.

And just to say in our study of baby products, we found TDCPP at high levels in most baby products we studied, at least three to five percent of most types of baby products. So there is a potential for 24-hour a day exposure to infants. They're in mattresses, baby positioners, car seats, changing tables, at levels up to 12.5 percent.

So it's a very important chemical to study. It might have uniquely high levels of human exposure and potential to harm our children.

Thank you.

CHAIRPERSON MACK: Thank you, Dr. Blum.

DR. LAWYER: Dr. Mack, could I have half minute. I'm sorry. I didn't get my card --

CHAIRPERSON MACK: You didn't your card in.

DR. LAWYER: I know. I was taking care of other people. I'm sorry. It's literally just one comment.

Back to the tox again.

ACTING DIRECTOR ALEXEEFF: Introduce yourself.

DR. LAWYER: Thank you, George.

Dr. Arthur Lawyer, Technology Sciences Group, Davis, California.

It had to do with the kidney adenomas, the

cortical adenomas and whether they are -- they progress. When we submitted our documents, we were supplied -- some of the data that was developed about a decade later in the early 1990s, Kurata et al., is the one. It's a sodium barbital study that was the one that we cited.

In general, what they found when they looked more and more at those study types with that particular species, that they do not progress. I think that was a question from Dr. Eastmond.

CHAIRPERSON MACK: Thank you.

DR. SANDY: Dr. Mack?

CHAIRPERSON MACK: Martha.

DR. SANDY: I'd like to make a couple clarifying points, if I may.

CHAIRPERSON MACK: I think we'd love to hear them.

DR. SANDY: Thank you. I'll talk about the reviews and conclusions of other agencies. And I'd like to point you to page 25 and 26 of the hazard identification document, just to remind you that on page 25 we have reported that the National Research Council in 2000 reviewed TDCPP and concluded that the available animal data provides sufficient evidence of carcinogenicity in rats following chronic oral exposure. So that's the NRC.

And then on page 26 we report that the U.S. Consumer Product Safety Commission concluded that TDCPP exposure also induced tumors at multiple doses in the kidneys and liver of both male and female rats. Therefore, TDCPP may be considered a probable human carcinogen based on sufficient evidence in animals.

And I would also like to ask Dr. John Faust to clarify referring to the information in the hazard identification document the information on metabolism of TDCPP, and perhaps a few other issues.

DR. FAUST: Yeah, sure. Thank you. Yeah. So in the public comments that we received, one of the items was an unpublished study looking into the metabolism. This was the Fabian and Landsiedel recent study. And that study looked at metabolism of TDCPP in liver slices as well as S9 fractions.

So I think, you know, the implication that's trying to be made is that this compound is essentially conjugated and then eliminated unchanged.

And I just call your attention to a few things that we did discuss in the hazard identification document. We do have two in vivo studies in which the compound was administered, and in which 1,3-DCP was measured in the urine. And we also have other in vitro studies that have looked at the metabolism and identified 3-MCPD, as well as

1,3-DCP.

And as I said before, in vivo studies have also shown that a certain fraction, about 20 percent, is eliminated in exhaled air as CO_2. So clearly, there is a fraction other than urinary metabolites that is the product of the breakdown of the compound. And I think each of these studies were done in -- with a radiolabeled compound.

CHAIRPERSON MACK: Thank you, John.

Let's now go to the Committee. We begin with Anna, did you look at the epidemiology?

COMMITTEE MEMBER WU: There was very little, but I did look --

MEMBERS OF THE AUDIENCE: Microphone.

COMMITTEE MEMBER WU: I don't think I have anything to add to what the staff has discussed.

CHAIRPERSON MACK: Okay. David, were you the principal or was Joe?

COMMITTEE MEMBER EASTMOND: I think Joe is.

COMMITTEE MEMBER LANDOLPH: Yes.

CHAIRPERSON MACK: Joe, let's hear from you then.

COMMITTEE MEMBER LANDOLPH: I looked at the genotoxicity database. I want to congratulate Dr. Faust and Dr. August and OEHHA staff. I think they did a great job in putting this hazard identification document

together.

Clearly, this compound is mutagenic in salmonella bacteria, causing base substitution and frameshift mutations. And there's an extensive database there.

It also causes mutations in L5178Y mouse lymphoma cells forward mutations. It causes chromosome aberrations, as they pointed out, in mouse lymphoma cells, and Chinese hamster cells. So it is a mutagenic and clastogenic compound. It provokes unscheduled DNA synthesis. I'm sorry, it doesn't provoke unscheduled DNA synthesis. It binds to the DNA, as they already pointed out, of mouse liver, kidney, and muscle. So it's a DNA-binding, mutagenic, clastogenic compound.

I looked through the animal data, and my opinion is pretty much consistent with the NRC. I see a lot of very beautiful data that's dose dependent, the trend tests are positive. There's hepatocellular adenomas and carcinomas in male and female rats. There's the renal adenocortical adenomas, and the adrenal gland tumors.

And I noticed also, from the nice hazard ID document, that some of these tumors can progress on to malignant tumors. So I guess having thought about this pretty carefully, from my opinion, I would vote in the affirmative that it's a mutagenic, clastogenic chemical that can also provoke tumors in rats, both males and

females, at many different organ sites. And I put great weight on the dose dependence of the data, even though there are confounders, as Dr. O'Malley pointed out.

And, in fact, that the trend tests are positive and statistically significant. So I'm in the affirmative that this has been clearly shown to be carcinogenic.

CHAIRPERSON MACK: Thank you, Joe.

Sol.

COMMITTEE MEMBER HAMBURG: I think Joe, Dr. Landolph, summarized this very well. I don't have anything really to add. I have a question for staff though. Did you mention that the original data was generated in 1981 and published in 2000, is that correct?

DR. FAUST: Yes, that's correct.

COMMITTEE MEMBER HAMBURG: Was there a reason for the delay in the publication that was mentioned in the publication?

DR. FAUST: I'm not aware of any information.

COMMITTEE MEMBER HAMBURG: I mean it's hard to understand why there would be a 19 year delay in the publication of this kind of data.

Okay. Having said that, I would vote in the affirmative.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER HUNTER: Darryl.

CHAIRPERSON MACK: Then we'll go to Darryl.

COMMITTEE MEMBER HUNTER: No. No. I'm sorry. I didn't realize you were --

CHAIRPERSON MACK: Go ahead, Darryl.

COMMITTEE MEMBER HUNTER: I was just curious if there's any comments from staff regarding --

CHIEF COUNSEL MONAHAN-CUMMINGS: Mic.

COMMITTEE MEMBER HUNTER: Any comments -- can you hear me now?

It's on.

Are there any comments with regard to the statement, one of our speakers referred to the standards changing since the data of 1981 in assessing the cancer-causing effects. Were there any comments to that?

DR. FAUST: Yeah. We do have a little bit of information on that I can tell you. This is about the pathological diagnosis for the liver tumors.

Yeah, in the original study reports, the liver tumors were described as neoplastic nodules, which was not an uncommon designation for liver lesions seen in studies conducted at that time.

And so what I have here is some of the information that was actually provided in one of our comments, a publication by Maronpot that just talks about how the diagnostic criteria over the period from the

eighties or in the early eighties changed, such that the term neoplastic nodule fell out of favor, and they -- as it says here, "Pathologists have become increasingly uncomfortable about including hepatoproliferative lesions that they believe to be hyperplasia rather than benign neoplasia under the term neoplastic nodule.

So, you know, we can't rule out the possibility that some of the lesions that were described as adenomas may have included some hyperplastic responses. But I would add that in the publication of the study Freudenthal and Henrich in 2000, they did go ahead and assume that these were hepatocellular adenomas. And the number of the reviews have also reached that conclusion.

CHAIRPERSON MACK: Anything further, Darryl?

COMMITTEE MEMBER HUNTER: (Shakes head.)

DR. FAUST: I might also add that as we noted in the hazard identification document, there was an increase in altered hepatocellular foci. This increase was observed in high dose male rats with marginal significance as well as high dose female rats. And these particular types of lesions are considered to be on the continuum from the proliferative lesions to full neoplasia.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Dr. Blum, did I hear you say that there was in vivo genotoxicity?

DR. BLUM: Well, I just cited in the OEHHA document. OEHHA said there was.

ACTING DIRECTOR ALEXEEFF: Maybe -- there was an apparent disagreement between the statement by Dr. O'Malley and the staff report. So maybe that can be clarified about in vivo genotoxicity.

DR. FAUST: Yeah. We do have the summary table for the in vivo genotoxicity data. And, you know, there are a number of studies that have looked for either sex-linked lethal mutations, chromosomal aberrations and so forth in in vivo studies. And these are largely negative, with the exception of the in vivo exposures that resulted in the DNA binding. So that's the limit of the in vivo data.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: I appreciate the comments that have been made. I find this one actually much more of a judgment call and fairly problematic. And the reason being is were outlined in essentially the public comments, but you have a very definite dose-related increase in these essentially hepatocellular nodules, neoplastic nodules, which are combinations apparently of both hyperplastic nodules and adenomas, because it's not entirely clear.

Apparently, the people when they wrote it up

assumed they were adenomas. And so that strengthens the case. So you've got this sort of diagnostic interpretation a little confusing.

There's also an issue of maximum tolerated dose. And I haven't really been able to come to a personal conclusion of what constitutes exceeding a maximum tolerated dose in these studies. We went through this a couple of years ago. The earliest definitions were at greater than 10 percent decrease in body weight gain, but was largely focused on subchronic studies in which they were picking a dose for the chronic study.

And that's -- and so what really constitutes exceeding a maximum tolerated dose in a chronic study, I'm not entirely sure how one weighs in on that, but that's one of the comments that came out in the public comment period is the high dose, the 80 milligram per kilogram dose was such where there was significant toxicity seen, as well as significant decrease in body weight gain, 20 percent in both the males and the females.

There were -- the adenomas, certainly in the kidney adenomas are apparently dose related. Again, those were benign. And I understand there's no evidence within this study they could progress, but these are the type of tumors that can progress on to become malignant. So ordinarily we would weigh that as an important factor to

consider.

The other part of this, the comment was made about the difference in the structure activity relationships. And for me one of the key points of this is that we do have definite metabolism into metabolites, which have been listed. And so -- and I thought the table that OEHHA put together comparing the different Prop 65 carcinogens and essentially the tumor types, which were identified and comparing that with what seemed for this compound was actually fairly effective.

So although I've had to wrestle with this, I don't think it's as clear cut, simple for me. I still probably lean on the direction of listing. I mean, one other point I should mention, and this always comes to me when you have a study, which is, in this case, now 30 years old, the original study, and there's severe limitations with it, I ask myself, why haven't follow-up studies been conducted to either -- to address these questions?

I mean, I still wonder about it, because it's been a 30-year period of time, and nothing's been done in the interim. And I just wonder about that.

CHAIRPERSON MACK: Anybody else have any comments?

My own view is weighted heavily on the presence

of the metabolites which are already listed. It seems to me that it's difficult to avoid listing, because of that and because of the evidence that there is some metabolism, and there are some metabolites that are produced, which we think are going to be carcinogenic.

But liver tumors are always a real problem. I can recall the issue of the contraceptive pills and the liver adenomas, which were -- they produced in humans, which we thought went on to carcinomas, and which very rarely do, but do sometimes. So because of the metabolites, I think I would go along with that too.

So unless there are more comments, we will call for a vote.

So vote will go as follows, has tris(1,3-dichloro-2-propyl) phosphate been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer? Would everybody who votes yes to that proposition please raise their hand?

(Hands raised.)

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

Would everybody who votes no to that proposition, raise their?

(Hand raise.)

CHAIRPERSON MACK: One.

So the vote is 5 to 1. Four yes votes are required to add a chemical to the list. So tris(1,3-dichloro-2-propyl) phosphate will be listed as a carcinogen under the Prop 65 process.

We then move on to the next topic which was fluoride and its salts.

Martha.

DR. SANDY: Thank you, Dr. Mack. So now we'll present a short presentation by Drs. David Morry and Craig Steinmaus on fluoride and its salts.

(Thereupon an overhead presentation was Presented as follows.)

DR. MORRY: Good afternoon. I'm David Morry.

ACTING DIRECTOR ALEXEEFF: Turn your mic on.

DR. MORRY: I'm David Morry, and with me is Dr. Craig Steinmaus. We'll be discussing the evidence regarding the carcinogenicity of fluoride and its salts.

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DR. MORRY: Let's begin by talking about what fluoride is. It's the monovalent anion that's derived from the element fluorine. Fluorine is the most electronegative of all the halogens. So it's more -- Fluorine compounds are more reactive than chlorine compounds and bromine compounds.

Fluoride can form salts with positive ions, such

as sodium and tin. Fluoride salts are highly soluble in water. And most of them dissociate completely releasing the fluoride ion. There are also other fluoride-releasing compounds that are used for fluoridating drinking water.

--o0o--

DR. MORRY: Fluoride often occurs naturally in drinking water sources. And it occurs in some foods and beverages naturally. It's obtained from a number of naturally occurring minerals, such as calcium, fluoride, fluoroapatite and cryolite.

Could somebody get me some water?

Sorry.

--o0o--

DR. MORRY: So human exposure to fluoride comes from a variety of sources, drinking water fluoridation in California and elsewhere results in very widespread exposures to fluoride.

As we all know, fluoride is also added to dental products such as toothpaste and mouthwashes and so forth. And as I mentioned, it occurs in some foods and beverages. So the exposure -- human exposure is made up of the sum of all of these sources of exposure. And the human exposure varies quite a bit geographically, which makes possible the -- some kinds of epidemiological studies, which Dr. Steinmaus will now talk about.

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DR. STEINMAUS: Hello. So most of the studies on fluoride and cancer, most of the human epidemiological studies, were reviewed by the NRC in its 2006 report. At the time, the NRC concluded that the epidemiological data on fluoride and cancer were inconclusive.

In the next few slides, I'll review a couple of studies that reported some evidence of an association between fluoride intake and osteosarcoma in young males. And I'll also review a few other studies that have been published since the 2006 NRC report. So the first study I'll talk about is Cohn 1992.

--o0o--

DR. STEINMAUS: This is one of the earliest studies to look at fluoride and osteosarcoma. It compared the incidence rate of osteosarcoma in New Jersey municipalities with and without fluoride in their drinking water for the period of 1979 or 19 -- yeah, '79 to '87. In comparing fluoridated to non-fluoridated municipalities, the rate ratio for osteosarcoma, in males less than age 20 was 3.4. And it was statistically significant. There was no clear increase in females and no clear increase in older males.

Potential limitations of this study are the facts that, number one, it was an ecological study. So in other

words, whether a person was considered exposed or not for this study was based solely on the municipality in which they lived. But there was no date on actual -- whether they actually drank the municipal water, how much they drank, whether or not they had been exposed to other sources of fluoride. And there was no data on fluoride levels that passed residences.

I think it's important to note that most of these potential biases that I just listed were probably biased results towards the null for finding no effect, but the bias could occur in either direction.

I think it's also important to note that this was a government report, and it wasn't reported in the -- or published in the peer-reviewed scientific literature. And also the number of cases was relatively small. For males less than age 20, there was only 12 exposed cases and eight unexposed cases. So relatively small.

--o0o--

DR. STEINMAUS: The next study, Bassin et al., 2006. This was a case control study of osteosarcoma in people age 19 or younger. It included 103 cases and 215 controls selected from 11 hospitals throughout the United States. Controls were other orthopaedic patients from the same hospitals as the cases matched on age and gender. Exposure was primarily based on drinking water fluoride

levels at both the current residence as well as past residences.

The odds ratios were calculated based on whether the fluoride levels were above or below recommended levels in drinking water. And that's approximately one part per million. And odds ratios were calculated for each age of exposure from the time of birth to the time of diagnosis.

So the odds ratio in males for having a drinking water fluoride level above the recommended levels, again, about one part per million, was 5.46. And it was statistically significant.

Odds ratios -- I'm sorry. That was for fluoride exposure above recommended levels at age seven.

Odds ratios were greater than one for other ages of exposure, but most of those were not statistically significant. Odds ratios for females for exposure at age 7, again that was above one, but not statistically significant.

Potential problems with this study, a couple of things I noted. It's unclear if the researchers were blinded to the case control status when they were assessing people's past fluoride exposure and the fluoride levels at their past residences.

Also, the authors did a logistic regression analysis and didn't actually present the raw data, in

other words, the number of exposed cases -- exposed and unexposed cases and controls. So it's hard to compare the logistic regression results with the crude results.

So overall, this study does seem to find some evidence of an association, but the results are inconsistent with most other epidemiological studies.

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DR. STEINMAUS: The next study is Kim et al. That was published in 2011. It's also a case control study of osteosarcoma, and fluoride levels in bone samples.

Cases and controls were recruited from nine of the same 11 hospitals that were used in the Bassin study, but the Kim et al. study was done after the Bassin study.

Kim et al. included 137 cases of all ages, 57 controls, who were people with other malignant bone tumors recruited from the same hospitals. Fluoride levels were measured in the bones -- in bone taken from samples from -- that were adjacent to the tumor. So I assume it was -- the tumor was being removed. They had the clear edges, so they took the fluoride levels from the clear edges, but they didn't specifically state that. They just said fluoride levels in tumor-adjacent bones.

And they assessed fluoride in bone under the hypothesis that fluoride does accumulate in bone, so maybe

bone fluoride levels are a valid indicator of true long-term exposure.

Overall, they found no association between fluoride levels in bone and osteosarcoma, either in all subjects combined or in subjects less than 45 years old.

Potential limitations are the study was too small to look at other specific age groups, specifically males, less than age 20, like the Bassin et al. study.

Also, it is unknown whether fluoride levels in tumor-adjacent bone are truly an accurate and valid measure of past fluoride intakes. There's really not much referencing done in this particular article.

And it's also possible that fluoride levels differ in different bones or fluoride levels may differ in different parts of bones. And it's unknown whether the cases had tumor-adjacent bone from the same bones or same parts of bones as the controls. So we don't know if we're comparing like to like.

There's also major age differences between the cases controls. Median age in the cases was 17.6. The Median age in controls was 41 years old. They adjusted for this, but as many of you know, adjusting for a factor like that with major difference, you'll lose statistical power.

Also, the participation rate amongst the controls

was only 48 percent. So we don't know if they truly represent the population from which they got the cases.

So overall, this study is inconclusive.

--o0o--

DR. STEINMAUS: The next study, Sandhu 2009. Another case control study. This was done in India, and it's on osteosarcoma and fluoride levels in serum. Controls included people with other bone tumors and people with musculoskeletal pain.

Overall, they did find higher fluoride level in cases, compared to controls. But the major problem is that this was -- was that serum fluoride levels were assessed at the time that osteosarcoma was diagnosed.

So this is essentially a cross-sectional study. And the problem with a lot of cross-sectional studies is the issue of temporality. We don't know which came first. In other words, did the increase fluoride levels cause or lead to osteosarcoma or did osteosarcoma lead to increasing serum fluoride levels? So we have an issue of temporality on this study.

--o0o--

DR. STEINMAUS: The next study Comber et al., 2011. This was an ecological study of osteosarcoma in fluoride in Ireland in the years 1994 to 2006. Exposure

was based on very broad geographical categorizations. In other words, it was based on population density and whether or not a person lived in northern Ireland versus the Republic of Ireland.

Specifically, people that lived in the Republic of Ireland in high population density areas were considered exposed, because most of the cities in the Republic Ireland, at that time, had fluoridated drinking water. And it was felt that outside of the cities in low population density areas, there wasn't fluoride in the private wells or in the drinking water.

So overall they found no difference in osteosarcoma rates between fluoridated and non-fluoridated areas in this study. There was an elevated risk -- or rate ratio, I should say. There was an elevated rate ratio in females age 0 to 14. That rate ratio was 1.43, statistically significant. But that was only when they use Northern Ireland as their comparison group. If they used Northern Ireland and unexposed Republic of Ireland as the comparison group, they didn't see an elevated risk ratio.

So overall, the major problem with this study, it had a very broad -- it was ecological. It had a very broad definition of exposure, thus a high potential for exposure misclassification. And that will most likely

cause bias towards finding no effect, which use exactly what they found.

--o0o--

DR. STEINMAUS: So to summarize the human epidemiological studies, in 2006, the NRC said the combined literature does not clearly indicate that fluoride, either is or is not carcinogenic to humans.

Studies published since that time were the Bassin study, Sandhu study, Kim study, and Comber et al. study. Taking the NRC report and their evaluation and taking these more recent studies into account, our scientific judgment is that the current body of human epidemiological evidence remains inconclusive.

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DR. MORRY: Okay. We'll turn now to the animal evidence. There are nine rodent bioassays that were done on fluoride. The first four were done by the NTP and published in 1990. They included a male, male -- three Fischer rats, female rats, a male B6C3F$_1$ mice in female mice.

There was another study by the NTP in 1992 that was also a drinking water study, that included a higher dose of fluoride. And this was also done in the male Fischer rats.

There were another study -- set of studies, two

studies was done, published by Maurer et al. in 1990. And this one included male rats and female rats. And then in 1993, Maurer et al. published two studies on male mice and female mice.

So notice that we count male and female rats and mice all as separate studies. And it makes a total of nine rodent bioassays.

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DR. MORRY: So let's begin with the NTP bioassays in the male rats. This was published in 1990. It was a drinking water bioassay. And the top dose was 175 parts per million. In this study, there was a significant increase in a rare osteosarcomas. The P value is less than 0.05. This is for the trend. We'll see the actual data on a coming slide. And this was in the male Fischer rats.

Osteosarcomas are rare malignant bone tumors. The NTP judged that the osteosarcoma data was equivocal evidence of carcinogenic activity. There was also, in the same male rats, a significant increase in thyroid adenomas and carcinomas.

Now, in 1992, the NTP published another drinking water bioassay in -- also in Fischer rats in the same rats -- kind of rats. And this one the high dose was higher. It was up to 250 parts per million. And in this

one, there was no increase in osteosarcomas or any other malignant tumors.

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DR. MORRY: So this is the data from the NTP 1990 study. The osteosarcomas increased from zero in the controls to one in the 100 parts per million and four all together at the high dose. These four osteosarcomas include three that are skeletal and one that was an extra skeletal osteosarcoma that was in a subcutaneous part of the rats flank.

So the P values here. The P value is not significant by pairwise comparison, but it is significant by trend.

Now the thyroid tumors, which I mentioned earlier, followed went from 1 to 1 in the 2 intermediate doses and then 4 in the top dose. And this also was not statistically significant by pairwise comparison, but is significant by trend. So there was a significantly increasing trend in thyroid follicular adenomas and carcinomas combined in this study of male rats.

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DR. MORRY: Now, let's go through the negative findings. There were no significant increases in tumors in the 1990 NTP study in the female rats, in the male or female CD-1 mice. And the NTP 1992 study, the one that

was done at a higher dose, the male rats showed no increase in tumors. So those were all negative findings.

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DR. MORRY: The Maurer et al. studies, this was a 1993 bioassay in CD-1 males, male and female mice. It was a 97-week diet study in male and female mice. And the top dose was 25 milligrams per kilogram per day by body weight.

There was a significant increase in osteomas in the male mice and also in the female mice. Osteomas are benign bone tumors. They're not considered to be related to the malignant osteosarcomas. They don't progress to osteosarcomas. One evidence for this is that the osteosarcomas generally occur inside the bone in the epiphyseal plates near the joints. And the osteomas occur in -- on the surface of the bone in the subperiosteal space, which is just on the surface of the bone below the connective tissue layer that covers the bone. Also, they're different histologically. So they're not considered to be part of the same series.

Now, a complicating factor was that the osteomas in this study all of them -- both the ones in the controls and the ones in the treated animals showed retrovirus infection. And this was determined by electron microscopy. So they sectioned the tumors and you see

these electron microscope pictures that are evidence that there was a retrovirus that could have been the cause of the osteo -- osteomas.

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DR. MORRY: I want to emphasize on the footnote here that there's been some clinical reports of osteomas progressing to malignant osteoblastomas in humans, but osteoblastomas are a different type of tumor from osteosarcomas.

Okay. The Maurer et al. 1990 bioassay in rats, there was no significant increase in any malignant tumors in either the male rats or the female rats.

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DR. MORRY: And so that concludes the animal evidence. Let's turn to some other mechanistic and other kinds of evidence.

Pharmacokinetic studies show that fluoride is taken up and incorporated into bones and teeth. Rodents have been shown to need a much higher exposure to fluoride in order to achieve the same bone levels as humans. So this should be considered when you're considering how the animal data might apply to human exposures.

Fluoride has been shown, both in vivo in live animals and in vitro in test tube type experiments with cells to stimulate cell division in osteoblasts.

Osteoblasts are the cells that form bone and they're also the cell of origin for all of the bone tumors that we discussed.

So this increase in cell division caused by fluoride could be taken as an early indicator of transformation. Also stimulating cell division can facilitate progression of an initiated clone of cells.

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DR. MORRY: In vitro genotox data. So there's both positive and negative findings with and without S9 stimulation. It was positive in the mouse lymphoma assay, which is a single gene assay. Sister chromatid exchange was positive in Chinese hamster ovary cells both with and without S9. It was positive for chromosome aberrations also in Chinese hamster ovary cells, and that was without S9.

And then it was found to cause unscheduled DNA synthesis, which is indicative of DNA damage, in human oral keratinocytes. And those were cells in culture.

It was negative in all strains of salmonella typhimurium with or without S9. And it was also negative for chromosome aberrations in the Chinese hamster ovary cells with S9 stimulation.

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DR. MORRY: I don't know if stimulation is the

right word -- supplemented with S9.

In vivo genotox data. Again, we have some positive and some negative results. The positive results include some studies in humans reported from India and from China, which showed increase in various chromosomal effects, chromosomal aberrations, sister chromatid exchanges and other things.

There were also some studies of chromosomal effects in rats and mice that were positive in vivo. There was also negative in vivo findings, some studies. Also, other studies reported from India and China showed -- did not show the chromosomal effects. And a studies of chromosomal effects in rats and mice were more often negative than positive.

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DR. MORRY: Recent genetox studies that were positive include Drosophila somatic mutation and recombination tests. And in vitro sister chromatid exchange and comet assay in cultured human lymphocytes and an in vitro chromosome aberration comet assay in human peripheral blood lymphocytes, and an in vivo chromosome aberration experiment in mouse bone marrow cells.

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DR. MORRY: Some recent in vitro cell transformation assays. Syrian hamster -- oh, these are

cell transformation assays. So we're talking about morphological transformation of the cells that's indicative of a change towards a neoplastic state.

In Syrian hamster embryo transformation assays, it was positive in three different laboratories. There was also a report of BALB/c 3T3 mouse transformation assay. In that assay, it was positive in the promotion assay but not in the standard focus assay.

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DR. MORRY: So very mixed results in genotox testing in general.

Some other effects of fluoride that might be related to the question of carcinogenicity has to do with its effects on thyroid and parathyroid function. So fluoride level -- fluoride exposure elevates thyroid-stimulating hormone and parathyroid hormone and calcitonin levels. And it also alters T3 and -- the two thyroid hormones T3 and T4 levels.

The reason I use the word "alters" is because some of the reports say it increases, some say it decreases. So it's a very complicated field.

So changes in these thyroid hormones can affect the rate of growth of bone tissue. That's how the rate of growth of bone tissue is controlled. An increase in the rate of bone growth could increase the risk of

osteosarcoma.

Osteosarcomas have been seen to occur more often in adolescents, where -- who have, you know, rapidly growing bones and more often in males than in females. Osteosarcomas arise in the metaphysis or metaphyseal plates of long bones near the joints. So it's the growing area. It's the area where the bone is growing where these tumors occur. And they occur more frequently in periods of rapid bone growth.

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DR. MORRY: Fluoride also has some effects on the immune response. It can either stimulate or inhibit cellular immune response in humans, rats, and mice. It decreases the cellular immune response, and may reduce the immune surveillance of nascent cancer cells. It increases -- there were increases in cellular immune response, which may lead to inflammation. And this is known -- inflammation is known to be involved in carcinogenesis.

Osteosarcomas are often found near the joints of long bones, which is where inflammation would be the most common.

So in all of these things, I'm looking for plausible mechanisms that might relate fluoride to carcinogenesis, and particularly to the carcinogenesis of

osteosarcomas.

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DR. MORRY: So to summarize all the evidence we've talked about, the human evidence we have mostly negative findings in many studies, but some findings of increased osteosarcomas, particularly in young males. And overall, the evidence has been summarized as being inconclusive.

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DR. MORRY: To summarize the animal evidence, there's been -- there are increased osteosarcomas in male rats in one study, which -- and also a trend, an increasing in the thyroid tumors, both of those are by trend.

There were no tumor findings in the later study of male rats, where they were exposed to a higher dose. This is a drinking water study.

There were increased benign osteomas in male and female mice, but this was possibly caused by retroviral infection. And the osteomas are not malignant tumors and they're not believed to progress to malignant tumors.

There were no tumor findings in female Fischer rats, male or female Sprague-Dawley rates or male or female $B6C3F_1$ mice.

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DR. MORRY: And to summarize the mechanistic evidence, there were some findings of genotoxicity including in exposed humans and findings of rearrangement of the genetic material.

I might mention that the kinds of tests that fluoride more likely is positive in are these clastogenicity or tests involving rearrangement of genetic material. Osteosarcomas are -- have quite -- they have quite aneuploid karyotypes. So all malignant tumors aneuploid karyotypes, but osteosarcomas are among the most aneuploid of malignant tumors.

Fluoride stimulates bone growth, and it has affects on the immune system, and effects on the thyroid and parathyroid functions, both of which could be plausibly connected with carcinogenesis for -- particularly for osteosarcomas.

And that's concludes the summary of the evidence.

CHAIRPERSON MACK: I have a question or two for you. Is it fair so say that Cohn is always the study that comes up first because it was a positive ecological study? Is it not true that there were a whole bunch of negative ecological studies of similarly bad quality?

DR. STEINMAUS: Yes, that's true.

CHAIRPERSON MACK: So that there's no reason to pick it out first, in terms of the quality of the study.

DR. STEINMAUS: Correct.

CHAIRPERSON MACK: Okay. My second question relates to the Bassin, or whatever her name was, study. You didn't really comment on the curious state of that study, in which the thesis advisor wrote a letter to the editor in the same issue of the journal suggesting that one shouldn't take the results too seriously.

Would you elaborate on that or...

DR. STEINMAUS: Yeah, I didn't comment on that because I thought it was irrelevant because the thesis advisor said that, yeah, they had -- are doing -- were in the process of doing a follow-up study that had found no effects, but that was the Kim et al. study. So that study was published, the follow-up study by thesis advisor.

DR. MORRY: He's one of the co-authors on the Kim et al. study.

CHAIRPERSON MACK: Oh, I had a little different take on it.

Does anybody else have any questions for the staff?

COMMITTEE MEMBER HAMBURG: Osteosarcomas are relatively rare tumors. I take care of a few of them over the years. Their peak incidence is actually in the teenage years. Is there any SEER data to look at a change in the incidence of osteosarcoma over the last few decades

to tell us that, in fact, there is an increasing incidence as the utilization of fluoride has gone up in drinking water?

My understanding is that the SEER data shows that it's relatively stable and is really unchanged over the past 30 years, but I'd like to confirm that. Maybe staff could help me with that.

DR. STEINMAUS: Yeah. I certainly haven't seen anything published recently, you know, since the NRC report, so I can't tell you if -- you know, more recently in the last 5 or 10 years whether it's increasing or not. But, yeah, that's an interesting question.

CHAIRPERSON MACK: Anybody else?

David, do you have any questions for the staff?

COMMITTEE MEMBER EASTMOND: Not -- well, I should say I have a -- I also noticed this interesting thing between the thesis advisor and the student, and the fact that the thesis advisor's name wasn't on the publication.

However, in the follow-up, the one that was published, if you look at basically the conflict of interest statements, the thesis advisor has all sorts of potential conflicts. So, I mean, it's not just 1 or 2, I men, there's lists of things.

So there's some other stuff going on behind the scenes that I certainly am not aware of, but there's some

funny stuff going on. Let's put it that way. And it may or may not be relevant, so I think the approach you took was probably the best way to do with it, but I was reading between the lines.

DR. STEINMAUS: Yeah. Can I comment on that?

COMMITTEE MEMBER EASTMOND: Yeah.

DR. STEINMAUS: I agree with you. That whole situation was very strange. But I think if we're trying to guess what happened in that situation, it would be a complete guess, so that's why I felt it was just more important to stick with the actual published studies.

CHAIRPERSON MACK: That's very prudent.

So nobody else has any comments. I notice a very familiar face. And I'm looking forward to hear the comments from the health department.

DR. LYMAN: Thank you Mr. Chairman. I'm Dr. Donald Lyman. I'm with the California Department of Public Health, Division of Chronic Disease and Injury Control. And our mission is to do control of leading causes of illness, death, disability. So we are the strategic parts of your State Health Department.

Cancer is a major part of that activity. And we have been actively successful in the last 20 years. We have seen an 11 percent decrease in cancer mortality -- in cancer incidences and 21 percent decrease in cancer

mortality in that time frame.

This is related to our primary prevention activities, notably tobacco control, which where we've been very successful, and nutrition education, the second risk factor for cancer.

We've also implemented a number of secondary prevention activities, including breast cancer screening, colorectal, cervical. So taken together, we're very happy with what we've done on cancer control. And we see you as very important partners in what we do. We're happy you're here.

And some of you may remember that this panel was created when it was part of the State Department of Health Services, and it happened under my watch. OEHHA was created under my watch. So it is part of the family, and we're happy you're here. We're happy with what you're doing.

I'm here for a couple of reasons. Remind you that I'm also a former president of the American Cancer Society, and former president of the American -- the California Academy of Preventive Medicine. We have both an institutional and a personal dedication to cancer control.

Three reasons to be here. One is to break Dr. Mack's rule and remind you that there is a reason that

fluoride is out there.

(Laughter.)

DR. LYMAN: Fluoridation of water supplies is counted as one of the 10 great accomplishments of public health in the 20th century. When you fluoridate a water supply, you address the leading cause of chronic illness among children, the leading cause of chronic illness among children, both in California and in the world.

And fluoridation reduces the frequency of cavities by 40 percent or more. It is spectacular. Among, the elderly it reduces tooth loss up to 70 percent. As you consider this, you must think of the consequences, and I'd remind you that that's where they sit.

The second reason I'm here is to come back to your question about the cancer registry. Cancer Registry is a resource you have, which I suggest you use more frequently. My previous job was the same job I have in California, but in New York. I did this for New York State.

At a time when New York State's cancer registry was the largest in the country. New York State was also where we did some of the original field tests for fluoridation of water supplies. It was in the cities of Newburgh and Kingston on the Hudson River back in the 1940s.

Since that time, while I was in New York, we kept an eye on the cancer registry to see if there were differences, geographic differences, in fluoridated, non-fluoridated areas. We didn't see them. I'm now in California. We now have the largest cancer registry in the country, and we, until recently, were about half of the national SEER registry data. We account for a lot of what's there.

And the oldest parts of that are 2 regional registries. One is the Los Angeles regional registry, which the good Dr. Mack used to run for a number of years. The other is the Bay Area, San Francisco Bay Area. It's very nice for this exercise, because the Bay Area was fluoridated back in the fifties. Los Angeles was not fluoridated until I think about 8 years ago.

CHAIRPERSON MACK: Then it was with great difficulty.

DR. LYMAN: With great difficulty, but it got done.

So there's a comparison there that's quite attractive. You asked whether there's SEER data on osteosarcoma. We rake through these data with some frequency looking for differences. We don't publish them in peer-reviewed things which would pop up on your radar screen here, but the registries are there. And we have

been raking through these with great frequency looking for exactly the things that you're describing.

We did a report about 2 years ago on osteosarcoma in California. I have the report right here, which I'm happy to share with you, and it does not show any trend differences. That's what's there. That's the bottom line. So I'd encourage you to use cancer registries, and you've got the resident expert right here as your Chair, which is very, very nice.

The third reason I'm here is to congratulate the OEHHA staff, our children from not too long ago, for doing another superb job in your technical work, and we thank you for doing that.

The residual staff -- once you moved over to CalEPA, the residual staff at the California Department of Public Health has gone through this report from OEHHA, and we concur with what you found and how you have interpreted it. And based on what you have produced with the scientific literature, we agree with the report and the additional peer-reviewed study release. Subsequently to the report, the evidence is not persuasive or doesn't meet the standard for listing.

And as a Department, we recommend fluoride and its salts should not be listed as a chemical under Prop 65.

Thank you, Mr. Chairman.

CHAIRPERSON MACK: Thank you, Don, for all of your comments.

(Laughter.)

CHAIRPERSON MACK: Irrespective of your flouting my request.

(Laughter.)

CHAIRPERSON MACK: Okay. We have 4 or 5 people who wish to speak. I would repeat my cautionary note, and of course Don is the exception, but everybody else they will damn well mind it.

(Laughter.)

CHAIRPERSON MACK: Because we can spend a lot of time. So, first, we will repeat hearing from Dr. Rebecca Sutton.

DR. SUTTON: I'll reintroduce myself. Dr. Rebecca Sutton, environmental chemist and senior scientist with Environmental Working Group.

We've been looking at the fluoride science for a few years now, and we see it's rapidly changing at this point. Actually, just this year, CDC has lowered its recommended guidelines for water fluoridation, and that's triggering a more in-depth reevaluation of potential problems that this chemical might have consequent from long-term chronic exposure.

Now the targeted epidemiological studies, including Cohn and Bassin that you've reviewed do seem to indicate that exposure to fluoride in tap water during the mid-childhood growth spurt, ages 5 to 10, is linked to higher levels of osteosarcoma in males age 10 to 19. And we certainly find it intriguing the Sandhu finding that higher levels of fluoride were present in those individuals. Their serum fluoride concentration was higher when they had osteosarcoma.

Now, in contrast, those epidemiological studies that have not found this connection, they do not look at age of exposure or the gender issue. And these are critical issues for fluoride in particular. A little bit unusual compared to some of the other chemicals that we've reviewed.

Now, we've also seen a lot of the biological evidence to support the carcinogenic activity of this chemical. We know that half the ingested fluoride goes into our bones, and it can act as mitogen at the bone endings, and that's just where the osteosarcoma occurs.

We've also seen that fluoride can produce DNA damage, including sister chromatid exchange. And that suggests a genotoxic effect on bone cells.

We've also seen a lot of animal studies. And two in particular do seem to indicate fluoride causes cancer,

particularly bone cancer, and particularly in the males of the species.

I'm really pleased that OEHHA's presentation and identify -- hazard identification document highlighted this fact that humans seem to accumulate higher levels of fluoride when compared to lab animals. So that means that an oral or an ingestion exposure that we receive might trigger a health effect where we wouldn't see that exposure in a lab animal, because they simply don't accumulate as much, and therefore, there's less at the site that we're most concerned about, those bones.

While I think we'd all conclude that the evidence for carcinogenicity is not conclusive, this is a pressing concern, and we are often forced to make conclusions based on incomplete evidence. There's 20 million Californians now drinking fluoridated water. And 10 to 20 percent of children are now getting more fluoride than EPA recommends. That's their reference dose, and that's for dental fluorosis only, not cancer, of course.

So as you weigh this issue, I really want to direct your attention, once again, to the age and gender specific results. This is the critical issue for fluoride, and those epidemiological studies that don't look at these 2 variables and gloss over them are just not as useful in the case of fluoride.

So when you take this into consideration, and then you look at the biological evidence, and the fact that we accumulate so much more in your bones, I'd like to ask that you go ahead and list fluoride.

Thanks.

CHAIRPERSON MACK: Thank you, Dr. Sutton.

Catherine Hayes.

DR. HAYES: Good afternoon. My name is Catherine Hayes. I'm an epidemiologist. I have been invited here today by the Consumer Healthcare Products Association.

I have the advantage of being the thesis advisor for Dr. Kim and also an outside reader for Dr. Bassin. I may be able to clear up some of the confusion that you had earlier and be happy to answer any questions at the end of my comments.

As an epidemiologist I'd like to focus on the criteria for causality of epidemiologic evidence, first being consistency. I think what we've heard here this morning is that we don't have consistent findings linking fluoride to osteosarcoma, so we really can't satisfy that criteria. We don't -- the strength of association. In the Bassin study there was an odds ratio that was about 4.7, which would be considered as an epidemiologist a strong association. However, that's not replicated in other studies.

The plausibility. We've heard about the biologic plausibility about mitogenic activity, and I'm not a geneticist. But what I would also like us to look at is the flip side of that. This is an extremely rare disease. And it's also my understanding that the incidence has not changed over the period of time that fluoride has been increasing in our water supplies. A very, very rare disease about five cases per million, and a very, very common exposure. Intuitively, it's unlikely that the two are related. So that's another of our criteria for causality.

The temporal sequence is a criteria for causality that we often can't evaluate. In this case, the age-specific rates that were just discussed, the one Bassin analysis where she looks at individual age-specific rates, one could argue that that might be evidence toward a temporal sequence, but overall there is no evidence for that.

So I'd like to just spend a couple of minutes talking about the Kim paper - and I'm a second author on that paper, so I'm very familiar with it - and answer some of the questions that were pointed out.

The Kim paper is a case control study. It was really -- we refer to them, instead of Bassin and Kim, as phase 1 and phase 2. The phase 1 study was the initial

study that was started that led to some concerns, which is why the larger study was conducted and funded by NCI.

The Bassin, or phase 1, study involved really identifying residences of the cases and the controls. And I do want to point out that there were many cases. There were 91 cases and controls who were not included in the final analysis because that information was not included.

And that's important for you to understand. That's not a criticism of any author. That's just important for you to understand as Committee members. We don't have full information on that.

Similarly, this is, again, ecological information. We don't have information on the individual exposure. We know where the individual resided. We don't know how much water they drank.

In the Kim study, the cases -- and I should point out that the control groups in both studies were exactly the same. That is, they were tumor controls and orthopaedic controls. I raise that, because I see in some of the written comments that it was said that the control groups are very different. I can assure you they're exactly the same.

In the Kim paper, of course, you can't get bone specimens from a healthy orthopaedic control. That would be unethical. The reason for the fact that we didn't have

a lot of younger children that provided bone specimens is that their parents didn't consent to it. It was just something -- an artifact for the study.

Everyone that had a bone specimen was analyzed, and it was analyzed very carefully. And we saw that there was no association between the level of fluoride in the bone, of individuals with osteosarcoma, and the level of fluoride in the bone of individuals who had a different tumor. And I would point out that none of those tumors have been show to be related to fluoride, which is a very accepted method for case control study design.

We often, in a hospital-based case control study, select controls with another condition that's not related to the exposure under study. That's exactly what was done here.

I would also like to point out that in the phase 2, or the Kim study, we had additional variables that had been shown to be related to osteosarcoma, and that was the height at diagnosis, birth weight, which were in published peer-reviewed literature shown to be associated with osteosarcoma. We included that.

The Kim study was published in a reputable peer-reviewed journal, the Journal of Dental Research, which is a highly reputable journal.

We selected a dental journal because, as

dentists, we've been looking at the issue of fluoride for many, many years, and we felt that that was an audience we wanted to speak to.

I know my time is running out, so I'm just going to wrap up quickly and say that we are continuing the analysis. The analysis has been done by our group and an independent group, because we want to be extremely careful. We have looked at water fluoridation. We have looked at topical rinses. We have looked at fluoride supplements. We have found nothing in any of our analyses to indicate that fluoride is related to osteosarcoma.

Thank you. I'd be happy to answer any questions if you have any.

CHAIRPERSON MACK: I think in the interests of efficiency, could I ask you a couple of questions?

DR. HAYES: Yes.

CHAIRPERSON MACK: You referred to 91 cases that were not included in the original. Does that mean that on those 91, information about the water -- the place of residence and the presumed water consumption was taken, but never included in the paper?

DR. HAYES: They could not discern sufficient information on their residence, and therefore could not make the link between what their likely fluoride exposure was.

CHAIRPERSON MACK: Okay. Let me ask one other question. My experience is that when one is comparing cancer cases at a given hospital to other people who are in the same department, there's very often a big difference in their residential distribution.

Cancer cases tend to be referred from farther away to secondary or tertiary care centers. Whereas, fractures are usually local. Which means that one would expect to be a big difference in the water quality and the water characteristics of the cases in the controls a priori, even though they weren't based on age and other things that are pertinent. And I would presume that that's the case in this study too.

DR. HAYES: Initially, we were using, as a matching factor, a geographic ring to see how far they came. And as you can imagine, as an epidemiologist, that was extremely challenging and inefficient, and frankly didn't add enough to the study that we continued that.

But we did look at their residence, zip code, whether it was urban or rural in the analyses, and didn't -- and I understand what you're saying and I agree with that. We didn't see that that was a factor in the analysis. And I would just like to say that we did age and gender sex analysis very carefully.

CHAIRPERSON MACK: Thank you.

DR. HAYES: Thank you.

CHAIRPERSON MACK: Anybody else have any questions?

COMMITTEE MEMBER HUNTER: Yes. You had talked about you looked at different subsets of folks, including those taking a supplement. How about in patients who've had cancers of head and neck area received high doses of radiation that impact -- that actually destroy salivary gland function? We typically have them institute programs for fluoride supplement through dental trays. And I don't know if there's enough data that we've separated out in any kind of subset analysis? But any look at that population?

DR. HAYES: We could consider that a high dose fluoride. We looked at any type of topical fluoride intake. That particular subset would be very small. But any topical fluoride we found no relationship.

COMMITTEE MEMBER EASTMOND: Can I ask a clarifying question? You'd mentioned that one of the criticisms of your paper was the difference between the ages of the cases of the controls, which is understandable given essentially needing informed consent.

Did you mention that same age difference existed for the Bassin study as well?

DR. HAYES: That's an excellent question. Thank

you for pointing that out. The Bassin study actually had a larger number of cases than were analyzed. They selected from the case group only those that were younger than age 20. So that's why there -- although the -- there was a distribution that was -- there were certainly individuals of a higher age group that was not included in their analysis. They restricted their analysis.

COMMITTEE MEMBER EASTMOND: Okay.

CHAIRPERSON MACK: Was that selection made after they had looked at the data?

DR. HAYES: No. Actually, they -- Dr. Bassin, as part of her thesis topic was really to look at, based on, I believe the Cohn study, to see if there were -- if there was an increased risk of osteosarcoma related to fluoride for individuals under age 20.

CHAIRPERSON MACK: Thank you very much.

Richard Adamson.

DR. ADAMSON: Thank you very much. And I appreciate the opportunity to make some comments.

I'm a pharmacologist and I'm speaking mainly today on the animal studies.

Dr. Richard Adamson.

For 4 decades, I've been familiar with the historical and current peer reviewed scientific literature about the toxicology of fluoride. Therefore, I was asked

to speak on the animal studies today by the Consumer Health Products Association,

I was a scientist at the National Cancer Institute from 1961 to 1994. And beginning in 1980, I was a scientific director and Director of the Division of Cancer Etiology. In this position, I was the NCI representative to the Committee to Coordinate Environmental Health and Related Programs, which was chaired by the Assistant Secretary of Health.

I was also the NCI representative to the Ad Hoc Subcommittee on Fluoride, which produced the review of fluoride benefits and risks, which is referenced in the OEHHA July document under Public Health Service 1991. I will not speak about the benefits.

We reviewed all, and underline all, the published scientific literature on fluoride toxicology in English up to that time. The NTP 1990 technical report toxicology and carcinogenesis studies of sodium fluoride and F344/N rats and B6C3F$_1$ mice, the Maurer et al. studies in mice and rats, and over 100 public submitted documents.

Review by the Committee of the Genotoxicity of Fluoride, and I'll give you the bottom line, found that the genotoxicity studies were inconsistent, often showed contradictory findings, and were highly dependent on the methods used. This same conclusion has also been reached

more recently by others, and those who reviewed recent genotoxicity studies, including the NRC report of 2006.

When the committee reviewed the NTP 1990 rodent studies and the Maurer et al. studies of fluoride in mice and rats, which have been summarized by OEHHA, we came to the conclusion that these animal studies failed to establish an association between fluoride and cancer.

Although the NTP study showed no evidence of carcinogenicity in mice of either sex, or in female rats, there was a small number of "equivocal" osteosarcomas in male rats. However, if one reads the NTP 1990 report, and it's a 447 page report, a case can be made that the conclusion of "equivocal" in male rats is too strong for the following 4 reasons:

First, the number of osteosarcomas in male rats was not statistically significant in pairwise comparison between control and treated rats.

Second, the percentage of osteosarcomas that occurred in male rats was within the historical control range.

Third, fluoride accumulation was highest in the female rat bone where there were no osteosarcomas.

And fourth, examination of bone in this fluoride study was more comprehensive than in any previous NTP study of any other chemical. And if asked, I can

elaborate on that further, but I will not take the time right now.

Secondly, the NTP report used an even higher dose in male rats, 250 milligrams per liter, compared with the highest dose in the 1990 study of 175 milligrams per liter, did not yield any osteosarcomas.

The PHS report, which was published and is also on the web, stated that the human epidemiologic data to date, that was to 1991, showed that optimal fluoridation of drinking water did not pose a detectable cancer risk. And you recently heard more recent studies commented on by Dr. Hayes.

Finally, I would like to state that no regulatory agency in the United States or in Canada or any credible scientific institution, including those that are listed as authoritative by OEHHA, after review of all the published data, has classified fluoride and its salts as carcinogenic to animals or humans, not the Food and Drug Administration, not the Environmental Protection Agency, not the National Institute for Occupational Safety and Health, not the National Cancer Institute, not the National Toxicology Program, not the National Research Council, not the European Food Safety Authority, and not the International Agency for Research on Cancer.

This committee has a very high standard. It is

not a plausible standard. It is not a possible standard. It is not an equivocal standard. It is a clearly shown standard. Therefore, I ask you to vote that fluoride and its salts should not be listed as causing carcinogenicity.

Thank you for the opportunity.

CHAIRPERSON MACK: Thank you, Dick.

Jay, could you show your assent with those comments or do you have something to add. And if you do, could you do it quickly --

(Laughter.)

CHAIRPERSON MACK: -- since you're representing the same organization.

DR. MURRAY: I am. Thank you, Chairman Mack and members of the CIC. My name is Dr. Jay Murray. And I am here on behalf of Consumer Healthcare Products Association. And I certainly assent with the comments of the 2 previous speakers. So I've -- I will be very brief. I'll take less than 5 minutes.

CHAIRPERSON MACK: Take much less than five minutes.

(Laughter.)

DR. MURRAY: All right.

CHAIRPERSON MACK: Give us your bottom line, Jay.

DR. MURRAY: Well, I'll jump to the bottom line, and because the OEHHA staff did such a wonderful job in

providing you with these background materials, it allows me to jump to the bottom line.

Bottom line is, let me do epidemiology. You saw Dr. Steinmaus's slide. No conclusive evidence after considering all the recent studies, as well as the old studies.

Animal evidence. NTP bioassays. The only evidence in the NTP bioassay was equivocal evidence in male rats. That was not repeated in 2 subsequent studies, including an NTP bioassay in rats at higher doses. So the animal evidence is very, very weak and doesn't amount to clearly shown.

The mechanism of action. You saw all the information in the postulated theories about how this -- how there could possibly be a link. But all those theories regarding possible mechanisms of actions are insufficient to demonstrate that fluoride causes cancer, especially in the absence of human studies or animal studies that shows that fluoride causes cancer.

So in conclusion, you know, when you add it all up, the evidence is really not sufficient and doesn't allow you to conclude that this has been clearly shown to cause cancer.

Thank you.

CHAIRPERSON MACK: Thank you, Dr. Murray.

Howard Pollick.

DR. POLLICK: I have some slides.

(Thereupon an overhead presentation was presented as follows.)

DR. POLLICK: I have some slide that are already loaded there with my name on it.

Good afternoon, Dr. Mack and members of the Committee. My name is Howard Pollick, I'm a full-time Clinical Professor of the University of California at San Francisco. I Chair the Fluoridation Advisory Council for the California Dental Association Foundation. I'm a spokesperson for the American Dental Association. You've had comments from me, written comments. And you've had comments from the American Dental Association.

Next slide, please.

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DR. POLLICK: It's commendable that the OEHHA report considered up-to-date peer-reviewed, as well as non-peer-reviewed evidence relevant to the OEHHA standard of whether fluoride has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

The report in more recent publications provide the evidence that fluoride and its salts do not meet that standard.

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DR. POLLICK: Statements are made in the OEHHA report demonstrating that fluoride and its salts do not clearly cause cancer. For example, on page 5, the current body of epidemiological research on the carcinogenicity of fluoride remains inconclusive.

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DR. POLLICK: Additionally, while there are quote some positive findings in animal carcinogenicity studies, the 2 positive studies lacked replication and quote the possible contribution of retroviral infection reported could not be ruled out.

Next slide.

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DR. POLLICK: Other studies do not clearly show that fluoride causes cancer. With regard to mutagenicity and clastogenicity, the OEHHA report states that a mix of positive and negative results have been reported across test systems with positive findings more often associated with higher concentrations of fluoride.

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DR. POLLICK: The statements of the report on cellular immune response effects of fluoride is only suggestive regarding the influence on inflammation, which

may play a role in carcinogenesis. There are 33 such "may" statements in the report.

Next slide.

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DR. POLLICK: Since the OEHHA report, there have been other publications. And you've heard about the Kim study and Catherine Hayes's testimony.

Next slide.

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DR. POLLICK: The recent report by European Scientific Committee on Health and Environmental Risks concluded that epidemiological studies do not indicate a clear link between fluoride in drinking water and osteosarcoma and cancer in general. There is no evidence from animal studies to support the link. Thus, fluoride cannot be classified as carcinogenic. That's from the 16th of May this year.

Next slide.

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DR. POLLICK: No other authoritative body, as you have heard, has concluded that fluoride is a carcinogen. The OEHHA report states that fluoride was reviewed by the U.S. EPA in 2007 and classified as having inadequate evidence of carcinogenicity. Fluoride has not been classified as to its potential carcinogenicity by the U.S.

FDA, NTP, NIOSH, or IARC. The U.S. FDA has determined that the available data do not support a conclusion that exposure to fluoride in FDA-regulated products causes cancer. And you have their written comments.

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DR. POLLICK: In conclusion, the report states overall the current body of epidemiological evidence on the carcinogenicity of fluoride is considered inconclusive. With regard to mechanistic and other relevant data considerations, no definitive statements are made about the carcinogenicity of fluoride. In vitro and in vivo studies in bacteria, animal and human cells, animals and humans yielded some positive and some negative results.

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DR. POLLICK: In summary, fluoride and its salts has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Thank you for your time.

CHAIRPERSON MACK: Thank you.

Now, we have 3 individuals who still wish to speak. And I would again ask them to address the scientific issues involved and not the liking or disliking of fluoride in general.

David Kennedy is the next speaker.

DR. KENNEDY: And I have written copies of this information for you.

I'm Dr. David Kennedy. I'm the past president of the International Academy of Oral Medicine and Toxicology. And we have reviewed this issue in some detail.

OEHHA correctly states that fluoride stimulates cell division, induces genetic changes, induces cellular changes and alters cellular immune response. That's an accurate statement.

I was appalled when I read this document in the number of errors, factual and statements of fact, that were in error in this document you hear praised today. In fact, here's one sentence. Can you pick out the 3 errors in this sentence?

In the hospital -- no, wrong sentence. Fluoride salts and other fluoride containing compounds such as fluorosilicic acid are used to fluoridate drinking water.

Fluorosilicic acid, hydrofluorosilic acid has been shown to increase lead in the children that drink the water and in rats. So OEHHA has listed lead as a carcinogen. So if you give a substance to a child that increases the blood level of lead, haven't you increased their risk of cancer?

The EPA considers lead a carcinogen as well. So

far, I've counted 15 significant, deceptive, irresponsible misrepresentations in this document. And I don't think that can be by accident.

For example, the following:

In a hospital-based case control study of osteosarcoma in people under the age of 20 in the U.S. by Bassin et al. odds ratios were reported for males and female drinking water levels above the U.S. Food and Drug Administration target dose of 1 part per million.

That wasn't written by a doctor. That was written by a toxicologist. Nobody on this panel thinks a dose is a concentration. And the FDA doesn't have a target dose, does it? It's never approved any fluoride containing substance intended to be ingested, so it doesn't have a target dose. The concentration is not a dose. Furthermore, it misrepresents the position of the FDA.

In addition, in 1979, the FDA published in the Federal Register remove all references to fluoride as a nutrient or a probable nutrient. It doesn't even consider it a nutrient. Where does that leave it?

It is a poison.

The FDA has never approved any systemic ingestion of a fluoride-containing substance for the purpose of reducing tooth decay and hydrofluorosilic acid has never

even been submitted.

The more serious misrepresentations is that the characterization of Bassin as finding bone cancers in young males above 1 part per million. Is that what you think? Did you read the study?

Look at Table 2 and do your calculations. The dose of her very high category was between 0.63 and 0.7 ppm. Actually, below the water here in Sacramento right now. Gee, would we characterize that as high or low?

Bassin summarized her own findings as remarkably robust. Our exploratory analysis described the association of fluoride levels in drinking water and osteosarcoma at specific ages. It suggests that for males less than 20 years old fluoride levels in drinking water during growth is associated with an increased risk of osteosarcoma demonstrating a peak odds ratio from ages 6 to 8 years old, 7.2 odds ratio, 95 percent confidence interval.

All of our models are remarkably robust in showing this effect during the mid-childhood growth birth spurts for which boys occurs at age 7 to 8, and she references that.

Did you hear that? So all these negative findings. Oh, there's lots of studies that don't show that, like Hoover. He found an increase in bone cancer,

but then dismissed it, because it wasn't time dependent. Bassin shows you why it's not time dependent. It's specific. She showed if that child was drinking fluoridated water, at that point, then she got the 7 odds ratio. So if you do a ecological study, which was criticized. Oh, these other studies are ecological studies. Yes, very poorly controlled ecological studies.

If you control like Cohn did, another bee in my bonnet, if you will, it's reported that unadjusted Cohn odds ratio of 3 point something. Well, he adjusted it in the paper. It's closer to 8. Why don't you report that?

Misrepresentations regarding the NTP cancer study. I am tired of this. It has gone through court twice. Two whistleblower lawsuits with punitive damages against the EPA. The guy that got fired was Bill Marcus and here's his memo. You'll all get a copy of that, thank you very much.

But what he said about the -- what we just heard again, ho, ho we have our historical controls. Oh, my, we have to rely upon those. Here's what he says about the historical controls. The historical controls, consisting over 6,000 animals did not have their diet controlled for fluoride.

So, in actuality, they were the low dose, not the no dose control. They were the low dose control. And

when I plotted their dose on a graph, as we do to determine carcinogenicity, it fell exactly where it was supposed to on the line between the low dose and the high dose.

He also says that every single cancer found in that study was downgraded by the very people Congress didn't trust to do the study in the first place. Well, that's why this paper is talking about a osteoblastoma, and osteomas that -- they took the biggest osteosarcoma and threw it out. It couldn't possibly be. It's not attached to the bone. But, you know, slice it up and look at with a microscope. It's an osteosarcoma.

But even more importantly, it had a hepatoangiocholangioma. Well, gee, what's that. That's a rare, rare, rare liver tumor. It only occurs in animals. And that tumor alone makes those significant findings.

CHAIRPERSON MACK: You're into the 7 minutes now, Dr. Kennedy.

DR. KENNEDY: Well, I'm sorry. I will sum up and say that I really hope you remand this back for further investigation. And the next time you decide to have a report, it be of the same quality as all the rest of the reports coming out of OEHHA. This is the only report I've ever read that was so full of gross errors.

Thank you.

CHAIRPERSON MACK: Jeff Green.

MR. GREEN: I was afraid you couldn't read my printing. Any. My name is Jeff Green. I'm the national director for Citizens for Safe Drinking Water. I'm on the Board of California Citizens for Health Freedom that deal with legislation that deals with how doctors are able to legally deal with cancer issues in California.

I ask that you put fluoride and its salts on the list of carcinogens. And I have several things to -- that I'm going to try to clean up rather than spending as much time as David Kennedy did with some of that, so you'll appreciate that part of it.

I do want to start with a rebuke from the very beginning. I'm sorry, but the Department -- you know, and the EPA did not create this. This is a proposition as all of you know. It was a proposition, and I want to make certain that we're really clear about exactly what they did it for. In the initiative that the language that they had, the People of California find that hazardous chemicals pose a serious and potential threat to their health and well-being, that State government agencies have failed to provide them with adequate protection, and that these failures have been serious enough to lead to investigations.

And it goes on and on, and basically says this is

the reason why they're doing it, that there was a right the be protected and have individual protection.

I believe that the report from OEHHA is insufficient. And there are certain areas that I think that are really important. One of them is the mechanism, even though I think I was almost surprised that the mechanism was covered in as much detail as it was. There were actually comments that were made by individuals with tremendous skills in that area, that provided a whole comment period, that basically there were 27 different references were never included in this.

That, to my mind, and what I would like to present to you is that when you look at studies that don't correspond with any kind of a mechanism and you use that as a way of basically the weight of the evidence, saying okay this didn't show that. It seems a little silly to me, because that isn't what you would correlate it to in the first place.

So, to me, looking at the mechanism of the way that fluoride can cause cancer and looking at those studies and seeing what they represent and how they represent it, to me is much more positive and much more available to you.

There's a couple of things that I need to clear up. One, the FDA has never taken a position on fluoride

as to whether it's a carcinogen or not.

Had they done that, they would have provided you the details and I would ask that you get the details from them if they have it, because we've constantly tried to get them to actually take a stronger look at fluoride and have never taken any kind of -- made any decision about that at all.

A second part is we were actually able to get a Congressional investigation on fluoride, which the FDA responded to show that they did not make any -- that they have never approved anything for osteoporosis as well. That's used as a support in OEHHA to support the fact that maybe this was good for bone. And, in fact, what happens is, is that it was -- it's never been approved for that.

In fact, those particular cases where they did review it, what ended up -- when they were actually studying the effect of fluoride on osteoporosis, it turned out that they had so many hip fractures that they had to stop the procedure. So I don't see that as being supportive basically.

I would say, in addition to that, that basically probably the biggest thing I look at basically is an area that, because you're not speaking first, I don't know if you're going to include or not, the FDA letter suggests that, somehow or other, that you would be preempted by FDA

on certain products and so forth. And I believe that that's not only inaccurate, but using some legal terms that they knew, and with reasonable care, should have known, that all the lawsuits have basically said that Proposition 65 could not be preempted by FDA regulations.

And, in fact, if anything, the interest of the FDA would still be supported by some other things. And that is that even on toothpaste that they do basically suggest, and they've actually approved, to be placed in -- fluoride in. They have warning labels. They have poison warning labels. And that's not too much different than what you'd be doing is providing a warning to people so they can make their own decision.

So with that, I'll closes, because of time. And I thank you for your listening to me.

CHAIRPERSON MACK: Thank you.

Kim Glazzard.

MS. GLAZZARD: Good afternoon, Chairman and Committee members. My name is Kim Glazzard. And while I'm an environmental scientist by profession, I am here today on behalf of a community organization Organic Sacramento.

We're requesting that fluoride and its salts be added to the Prop 65 list. I did submit some concerns in writing, but I would also like to highlight some

additional concerns today.

While some of the questions and inconsistencies of the report, the staff report, and about particular -- excuse me.

Some of the questions and inconsistencies of the report about particular studies and introduction of new studies are addressed in written comments and reports by Dr. Paul Connett, Dr. David Kennedy, Dr. Mike Powell, Dr. Glayol Sabha, and Dr. JoAnn Ross are already submitted, I won't go into the details of that information.

I would, however, like to mention that it is incomplete to only look at individual studies and throw them out individually, as there is no way to construct a single study that covers all the variables. We believe that rather than systematically taking apart all of the studies on fluoride carcinogenicity, the preponderance of the evidence and the cumulative studies, which keep increasing each year, points to fluoride being most likely carcinogenic for certain subsets of the population at certain doses.

As fluoride is not only in water in many areas throughout the state, but also in beverages made with fluoridated water, as well as food that has been grown with fertilizers and pesticides containing fluoride, our food is ridden with fluoride as well. So there is no way

to monitor doses of public exposure to fluoride. It is clear that there is potential for harm.

It is important to remember that fluoride is not a nutrient and that the body has not developed a mechanism for dealing with fluoride, so it increases the risk of dealing -- of the body needing to deal with it as a toxin. The body has developed defenses for other elements that are nutrients that the body needs, but there is no need for fluoride for the body to function.

Fluoride also sits on receptor sites of other critical nutrients, such as iodine, thereby inhibiting the access of the body to critical nutrient absorption, and inhibiting -- and also inhibiting the immune response and promoting carcinogenicity in the body.

We believe that it does meet the criteria for determining a listing on the Prop 65 list as a probable carcinogen, that fluoride does. And we are requesting -- we feel that the listing on Prop 65 will help the public know that there are concerns that they can make informed conclusions and decisions as to their level of exposure, and we hope that you will go forward with this.

Thank you so much for your time.

CHAIRPERSON MACK: Thank you. The final person who wishes to the speak is Mike Fuller. If that person is here -- couldn't we not -- can you not just place your

name in agreement with the last couple speakers?

MR. FULLER: I could do so if I'm allowed to submit public comment in writing.

CHAIRPERSON MACK: You did submit one, right?

MR. FULLER: I would like to clarify that I did send in a comment on September 6th. It apparently didn't make your list. I don't know why. There may have been some technical glitch among our computers. I did notice on the list of public comment that there's a couple of people that had letters dated from last week. So I would like to know if you are abiding by the September 6th deadline or not?

CHAIRPERSON MACK: Can we look into that. You should take a break pretty soon. And if you -- can you just state your final summary position.

MR. FULLER: Okay. Sure. I'll make this quick. Can I have one minute?

Okay. My name is Mike Fuller.

CHAIRPERSON MACK: One minute would be great.

MR. FULLER: My name is Mike Fuller. I just retired from First 5 California, a State agency, where I was manager in the Office of Healthy Development responsible for school readiness programs and health initiatives.

I would like to say that I am here on my own

accord and I do not represent First 5 California in that capacity.

Having reviewed the literature and the evidence of the fluoride carcinogenicity of fluoride, I would like to state that I endorse and fully support the comments of Paul Connett, and -- excuse me, I'm looking for his name here, Mark Neurath at the Fluoride Action Network.

I would also like to ask you to take the courage to do what is right for the population of California and its children. And that will take great courage, because you'll be bucking a very powerful, very strong establishment that has been supporting fluoride for over 70 years in this country. I don't need to tell you that. You already know that.

However, there's a margin of safety that always seems to be overlooked by public policy. And that if you look at the full body of science and studies that indicate there are ill-health effects from fluoride, I would hope that you would give very much attention to that safety margin as it affects the children of California. And I urge you to put fluoride on the list for Prop 65.

Thank you.

CHAIRPERSON MACK: Thank you, Mr. Fuller.

MR. FULLER: To clarify what I earlier said, may I submit my earlier public comment that somehow didn't get

in the record?

CHAIRPERSON MACK: I would presume so --

MR. FULLER: For the record.

CHAIRPERSON MACK: We'll figure that out during the break.

MR. FULLER: Thank you very much.

CHAIRPERSON MACK: So let's take a break. How long?

It's up to me. Why don't we take a 15-minute break then.

(Thereupon a recess was taken.)

ACTING DIRECTOR ALEXEEFF: Can we reconvene, please. I just want to mention for Mr. Fuller, the last speaker here. So we did not have your comments, so we apologize. We will add them to the record now. But thank you very much for being here.

CHAIRPERSON MACK: Okay. Now, it comes to discussing on the part of the Committee the issue of fluoride listing.

So I'm the lead on the epidemiology side. And not to make too fine a point on it, I'm not impressed by the Bassin article. I don't think there is any information in the ecologic studies that is really useful, including the Cohn study. I, frankly, believe that there is no information on any -- of any consequence on

carcinogenicity in humans.

So then I will turn to my colleague and ask his opinion about the animal information.

COMMITTEE MEMBER EASTMOND: Sure. I'll give kind of general comments overall. I hope you can hear me.

As Dr. Mack indicated, there have been a large number of studies. Most studies have been negative. There are, however, a number of them, which have given, what I consider to be, intriguing associations between fluoride exposure and osteosarcomas.

In humans, we heard presentations on those. With regards to the animal studies, there was an initial study by the NTP in which there was a sort of what they describe as an equivocal increase in osteosarcomas seen in the male rats, an increase in thyroid tumors seen as well.

That increase was not seen in a follow-up study conducted by the NTP, although at a somewhat higher dose. There is -- again as indicated, there were increases in osteomas, which were seen in male and female mice. These are different. Although, they sound very similar, apparently they don't progress on to become osteosarcomas. And they remain benign tumors, so they're probably less important from our particular Committee's considerations.

I also -- it potentially could have been -- there's some evidence that they may have been caused by

viruses as well.

As far as genotoxicity, mixed results have been seen. Again, there's some positive results, both certainly in vitro and in vivo, to some degree. There have been pretty consistently positive results seen in the SHE cell assay, the Syrian hamster embryo transformation assay.

With regards to mechanism, fluoride has been reported to be mitogenic to osteoblasts, which is intriguing. It's also reported to be immunotoxic and affect thyroid and parathyroid function, which may -- conceivably could play a role. And it's clear that it's incorporated in the bone.

So other experts groups have looked at this and have considered the evidence to be either negative or inconclusive.

My assessment of this is, while I found the evidence to be intriguing, and clearly suggestive, and biologically plausible, but, in my opinion, fluoride has not been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

CHAIRPERSON MACK: Who else would like to comment?

Anna, Darryl?

Joe?

COMMITTEE MEMBER LANDOLPH: Yeah. It's pretty clear the epidemiology is not going anywhere on this one. And the SEER data, I think, is pretty compelling. We're not seeing any big increases. The animal data is confounded. The experiments are not repeatable, and that is a problem in itself.

The genetox data is not really very strong. There is some chromosomal aberrations, but just SHE cell data for transformation and not the other BALB/c 3T3, so there's inconsistency in that database.

I just don't think the evidence rises to the point where we can do anything with it, so I'm probably going to vote no on this one.

CHAIRPERSON MACK: Sol, do you have anything to add?

COMMITTEE MEMBER HAMBURG: Nothing at all.

Thank you.

CHAIRPERSON MACK: Okay. Let's -- and my general opinion is not only is the human data negative, but the only intriguing parts of the animal and in vivo and short-term data that are interesting are good hypothesis generators but not anything that's really conclusive.

So let's take the vote. Let me find the right page here.

Has fluoride and its salts been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer?

Would everybody who votes yes to that proposition, please raise their hand?

(No hands raised.)

CHAIRPERSON MACK: Everybody who votes no to the proposition, please raise their hand.

(Hands raised.)

CHAIRPERSON MACK: So the 1, 2, 3, 4, 5, 6. Seven votes no, 0 votes yes.

We failed to I've got 7. 1, 2, 3, 4, 5, 6, Sorry. I counted you. Six noes and no yeses.

So the vote is to not list fluoride and its salts.

Now having finished that, let's take a one-half hour lunch break and come back and let me tell you how -- what we're going to do when we come back. We're going to go through each of the 39 compounds. We'd like really -- I mean, the State pays us huge amounts of money and why bother to pay us another day.

(Laughter.)

CHAIRPERSON MACK: So we're going to go through each of the compounds. We're going to tell you whether we think it should be high, medium, or low priority. No

priority is not an option, because all of these are going to be reviewed at some time or other. I would presume that anybody who wants to speak will by and large try to upgrade from low higher. So when it's --

(Laughter.)

CHAIRPERSON MACK: No, I mean the other way around, of course.

(Laughter.)

CHAIRPERSON MACK: Anybody who wants to speak will try and decrease the priority. And therefore, when there is a high that's proposed by the Committee, I would welcome people to come up and spend one minute telling us why it should not be so high, but only one minute.

If we decide that it's low, who's to argue?

If anybody really wants to put it up to high, we'll hear that argument also for one minute.

Okay. So we'll see you in a half hour.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON MACK: Okay. Let's get started.

Martha.

DR. SANDY: Thank you. I need some technical help.

(Thereupon an overhead presentation was presented as follows.)

DR. SANDY: So this is the third year that we've brought chemicals to you as a Committee to rank. And I'm just going to quickly go through for the benefit of the audience what we're doing. So this is the update for 2011.

Next slide, please.

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DR. SANDY: The prioritization process, I want to review the purpose. It's to identify chemicals for evaluation by the CIC for listing at some future date. The goal of the prioritization process is to focus the efforts of the CIC on chemicals that may pose significant hazards to Californians. And I really want to emphasize the prioritization is a preliminary appraisal of the evidence of hazard.

Next slide, please.

--o0o--

DR. SANDY: So this slide shows the flowchart of

the prioritization process. We have a tracking database. And then from among the chemicals that we're tracking, we have a subset that are called candidate chemicals. And those are chemicals with some data suggesting they cause cancer and some data suggesting there's exposure potential in California. And we apply focused screens to those candidate chemicals. We screen them using focused literature reviews to bring forward candidates.

So next side, please.

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DR. SANDY: So this slide shows you what the screening entails during our current round, that this is again the third year of bringing you the results of our current round of prioritization. First, we're reapplying the human data screen, and then we apply an animal data screen. And chemicals caught by either one of those screens we then look at and we conduct a preliminary toxicological evaluation.

And after that, we identify chemicals that we propose for CIC consideration.

Next slide, please.

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DR. SANDY: And again just to refresh folks' memories, the animal data screen that we have applied is that there are either 2 or more positive animal cancer

bioassays or there's one positive animal cancer bioassay with malignant or combined malignant and benign tumors occurring to an unusual degree with regard to incidence, site, type of tumor or age at onset, or; there's one positive study with findings of tumors at multiple sites, or; the one positive study has -- there's also evidence from a second animal study of benign tumors known to progress to malignancy.

Next slide, please.

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DR. SANDY: So you've seen this flowchart. Here, we've highlighted where we are today. We're consulting with the CIC on chemicals for review.

Next slide, please.

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DR SANDY: So this just summarizes what we've done in the last three years. In 2009, we had gone through about half of the database. The candidate chemicals in 2010, about 75 percent. And now we're essentially done, and we've got 39 chemicals we're bringing to you on an ongoing basis. We continue to add chemicals to our tracking database. We actually have screened about 400 or more chemicals in this three-year period. I have 380 plus. But as we find new ones, we are screening them immediately as we enter them in. And as

this new information comes to our attention that's relevant on something that's already in the tracking database, we apply the screen. We expect that we'll be bringing a smaller number of chemicals every now and then to you for consultation in the future.

--o0o--

DR. SANDY: And this year you've probably noticed that some chemicals have been grouped together for consultation. And I've listed the six groups here. And I'm going to say something as we come to each of those. We're taking these chemicals now for ranking in alphabetical order. And as we get to each one, I'd like to just remind you of what we're asking you to do, the question we're posing to you, advice on whether the chemical group should be considered at a future listing date. And then there may be other questions. And of course you as the CIC are able to advise us on even a subset of a group if you'd like.

So that's all I have to say. Oh, no, I don't. I have a few more slides. Sorry.

--o0o--

DR. SANDY: So here's the summary of what you've prioritized in the last two years in either the high, medium or low priority categories. I'm not showing the two chemicals we brought today or the two chemicals we

brought last year in the high priority. They've been removed from there. But this is the list so far. And we'll be adding to that today.

And let's go to the next slide.

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DR. SANDY: So this table, it's a three-page table, and it's been offered as a handout in the back. This table summarizes the exposure characteristics and types of studies providing evidence of carcinogenicity for each of the chemicals to be ranked today. And I don't expect you'd be able to read this on the slide.

You can go to the next one.

--o0o--

DR. SANDY: You'll see here at the top, pimecrolimus and tacrolimus. I wanted to mention that in light of public comments received on tacrolimus, the CIC is not now being asked to provide advice on the ranking of this chemical. And this is because OEHHA is considering the possible listing of tacrolimus via other listing mechanisms.

The Committee's advice is still being sought on pimecrolimus today though.

So that's it for now. Thank you.

CHAIRPERSON MACK: Okay. So I guess we'll go through them in alphabetical order. And what I'll do is

ask the members of the Committee that have been asked to give a prioritization on each one. And then we'll ask members of the regulated community to make a comment if they wish to change that prioritization. Please don't bother if you don't wish to change the prioritization.

If it subsequently gets changed, I'll give you another option -- another opportunity for making a comment. But I don't presume that will be the case.

So let's begin with abacavir and its salts. And the people who are in line to comment are David Eastmond.

David.

COMMITTEE MEMBER EASTMOND: Okay. I listed this as a high priority, somewhat tempered because it's a drug, but just based on the evidence across multiple --

CHAIRPERSON MACK: Dr. Wu.

COMMITTEE MEMBER WU: Medium.

CHAIRPERSON MACK: Medium priority. All right.

So we have to then adjudicate. Why do you consider it medium?

COMMITTEE MEMBER WU: I think there are some animal studies listed. But I think -- at least in the assessment on comparison of some of the other sites -- some of the other compounds, the data did not seem to be as -- there's not as much data in my opinion. So I just put it in the -- sorry, I'm getting over a cold also. So

bear with me.

The reason I put it in the medium category is, even though there are positive studies in both the mice and the rats, I thought that the data that was presented was still -- there was medium amount of data. There was not as compelling as some of the other animal data that were presented for some of the other compounds.

CHAIRPERSON MACK: David, do you want to respond?

COMMITTEE MEMBER EASTMOND: I mean I guess the reason I put it in the high priority was that it's positive in multiple organs in rats, including the preputial gland in male rats. The same target organ was seen in the male mice. And that for me, you have two different studies, two different species, similar target sites, I mean that was a strong evidence, plus the other assays.

It certainly gives mixed results in different genetox tests. It was positive for the micronucleus bone marrow of male mice, which was supportive. And has structure similarities to other Proposition 65 carcinogens.

So that was my --

CHAIRPERSON MACK: Other people on the Committee weigh in?

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I listed it as medium similar to Anna, mainly because the genetox database was a little bit weak. And there is animal data. But I'm a little bit hesitant to bring medicines, which this is - it's an anti-HIV agent - I'm hesitant to bring those to the top because I think there are other things that are more noxious and environmentally important that we need to get rid of, label first.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: Yeah, I would agree with that. As a general statement, I think agents which commonly affect the large population should be listed higher than agents which have a very select small population effect. All of the antivirals are relatively small population effect, and I would suggest that those all be in the medium category and not in the high category.

CHAIRPERSON MACK: So, David, you're willing to go to medium?

COMMITTEE MEMBER EASTMOND: I'm okay with medium.

CHAIRPERSON MACK: Okay. I have no members of the community that wish to comment on this drug, so it will stand at medium.

Next drug is acetaminophen.

I was one of the reviewers on this. And because

it's so commonly used and because there are a substantial number of new studies that have not been reviewed, I would also consider it to be high.

The other reviewer is, again, Dr. Eastmond, I think.

No.

COMMITTEE MEMBER EASTMOND: I don't think so.

CHAIRPERSON MACK: Let's see, where am I? I've got the wrong sheet here.

COMMITTEE MEMBER LANDOLPH: Tom, I did that one too.

CHAIRPERSON MACK: Oh, yes. Three people did it.

Yes, Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree with your high. There's a very strong genetox database. There's animal carcinogenicity. And my lab published a paper on it that it transformed cells. And it's got reactive intermediates that generate oxygen radicals. So I'd go high.

CHAIRPERSON MACK: Anna?

COMMITTEE MEMBER WU: High.

CHAIRPERSON MACK: High also.

Okay. We have one speaker, and that's Barbara Kochanowski. But she's from the Consumer Health Products.

Are you going to speak against high?

DR. KOCHANOWSKI: Yes, sir.
CHAIRPERSON MACK: Okay.
DR. KOCHANOWSKI: For one minute --
CHAIRPERSON MACK: You have one minute.
DR. KOCHANOWSKI: -- or less.
As we submitted in our written comments, I'd just like the Committee to be aware of the new drug application that was approved by FDA, Ofirmev, which is an IV, intravenous acetaminophen formulation, which included a very, very in-depth review of all the carcinogenicity data, where they came out with no evidence of concern. And we wanted to make sure that the Committee was aware of that, in addition of course to the two IARC reviews.
So thank you for considering that when you prioritize.
CHAIRPERSON MACK: Thank you.
Now, I guess I should ask if anybody wishes to change their rating on that basis?
Hearing none, we continue with high.
Third drug is a biggie, Bisphenol A.
I also had that drug. And I'm going to defer to the other reviewer first, but my prioritization was also high.
The other reviewer is David Eastmond.
COMMITTEE MEMBER EASTMOND: Me. Before I make my

comments, I do need to make a disclosure on this. I don't think it's significant. But about eight years ago I was asked by American Plastics Council at that time to do a review of one of the studies on Bisphenol A. And so it's been sufficiently long that usually that's not a problem, but I thought I should at least mention it. I haven't done follow-up work on that.

I have a lot of thoughts about Bisphenol A. But boiling it down to -- I have vacillated between high and medium.

High because there's so much interest and it's very much in the public eye. There's a lot of studies that are suggestive.

On the flip side, most of these -- many of these use routes of exposure that are probably not relevant to humans, and so that has to be tempered in the consideration.

What probably has pushed me more towards medium is because this has been - and this was in part of the public comments - but it's been reviewed by quite a few regulatory bodies recently, probably five or six different regulatory bodies, from the FDA, European Commission, Japanese Agency, et cetera, and none of them have flagged this as a carcinogenic risk. So I'm thinking, okay, there's a concern here, but -- exposure is very high, but

on the other hand I'm not sure what we're going to see that's going to be that much different. Some of these were actually done last year or this year.

So that puts me more in the medium category, but I'm flexible on that.

CHAIRPERSON MACK: Actually I will defer to you and go down to medium.

Anybody else wish to weigh in?

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I went high on it because of the human exposure, stuff that's in children's toys. It's widespread human exposure. The genetox database is reasonable robust. There's also estrogenic activity, peroxisomal proliferation activity. And the carcinogenicity studies, five out of the six of them are positive. And there's pancreatic tumors, bladder carcinomas, and some leukemias. It's a weaker endpoint. So I pushed it up a little bit to high on that one.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: I would suggest we stay at a medium. I think what Dr. Eastmond mention about it's been reviewed thoroughly, I think we have other things that we can prioritize a little higher.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: I agree with medium.

CHAIRPERSON MACK: Medium.

Anna.

COMMITTEE MEMBER WU: I am on the fence between medium and high. So I think, you know, either way.

CHAIRPERSON MACK: So if we can talk Joe into coming down to medium, we have a consensus.

COMMITTEE MEMBER LANDOLPH: Good enough.

CHAIRPERSON MACK: Okay, medium it is.

Now, given that it's medium, unfortunately it can work both ways.

So, Dr. Sutton, would you like to make a case for high?

If you wouldn't, I'd welcome that.

DR. SUTTON: I'll be really, really fast.

CHAIRPERSON MACK: Okay.

DR. SUTTON: We're of course most concerned about the high levels of exposure. And so that's really why we want you to direct your attention to certain chemicals, the ones that we Californians and in the U.S. are most exposed to.

Actually Dr. Sarah Janssen and Gina Solomon presented you guys with a nice little scientific summary of some of the evidence. So I would defer to her for the science part of this. I'm more concerned -- or want to talk more to you guys about exposure.

CHAIRPERSON MACK: Thank you.

Steven Hentges.

DR. HENTGES: Due to popular demand, I'm up here.

I'm Dr. Steve Hentges with the American Chemistry Council. I represent the manufacturers -- global manufacturers of BPA and polycarbonate plastic.

BPA is controversial, for sure, if nothing else. But one thing that it should not be is high priority for your efforts. And the reason, I think we've hit some of it. Dr. Eastmond pointed out it has been recently reviewed by many government agencies worldwide. They've all come to pretty much the same conclusion: Not a carcinogenic -- or significant carcinogenic risk.

Are you going to find anything new? Well, I won't judge your conclusion, but many have looked at it and none have found it a significant risk.

There is an NTP bioassay. No compelling evidence of carcinogenicity there in that study.

A lot of genotox data. And all of those agencies that have looked at that data concluded basically the same, not a significant genotoxic risk in vivo.

And final point is that BPA is very efficiently metabolized, phase 2 metabolism converted to glucuronide primarily, which is rapidly excreted from the body. So it doesn't -- the bioavailability of BPA is very low, very

rapidly eliminated from the body.

So all of those things together would suggest to us that this isn't a high priority for your attention. I would agree you've got -- almost certainly you've got better things to do. BPA has been looked at very carefully.

CHAIRPERSON MACK: Thank you.

Kathleen Roberts.

MS. ROBERTS: Good afternoon. I'm the Executive Director of the North American Metal Packaging Alliance. My members represent the value chain involved with metal packaging. They are interested in BPA because it is used in the epoxy resin coating that's used on metal packaging.

I would just simply like to reiterate what Steve said about the organizations, the government reviews that have already done it, including the World Health Organization that just completed it November 2010; and the Japanese Research Institute of Science for Safety and Sustainability, which just completed its review in July 2011. So we're talking very recent reviews that looked at in vivo, in vitro, epi, genome, and mutatox, and the carcinogenic assay. So there's been some recent ones. And I would agree that perhaps there's other things that you all might want to focus on.

Thank you.

CHAIRPERSON MACK: Thank you.

Does anybody wish to switch to low?

DR. JANSSEN: Can I make a comment please?

Sorry, I didn't submit a card.

DR. JANSSEN: I'll be brief. I'm Dr. Sarah Janssen with the Natural Resources Defense Council. We've submitted comments on this as well. And I would argue that it should be prioritized as high. The reasons being widespread exposure in the human population.

The National Toxicology Program review identified prostate cancer at environmentally relevant levels of exposure as being of some concern, especially when these exposures happen early in development.

Mammary cancer received a somewhat lower rating. But since the time of the NTP review in 2008 there have been a number of studies done on mammary development in both animal studies and human tissues, demonstrating that BPA interferes with development of the mammary gland, predisposing it to increased rates of cancer when challenged with a carcinogen later in life.

Studies done at the California Pacific Medical Center, one that was just published two weeks ago, demonstrate that BPA triggers changes in gene expression pathways that are consistent with the gene pathways that have been linked to highly aggressive uniformly fatal

forms of breast cancer.

And, you know, there's a new study coming out on BPA every week. So I would argue that the reviews that were done last year are already out of date. The World Health Organization review has not been made public. It's not available for public review. I don't know what that review said. But many of the other reviews that were done by other countries were done to determine whether or not it was safe for the chemical to be continued to use in the food supply, and were not specifically looking at evidence of carcinogenicity.

Of course, prioritizing doesn't mean that you're going to rank -- that you're going to list it as a carcinogen on Prop 65, but it does mean that you're going to review it. And I would argue that you're the most qualified body to do that.

Thank you.

CHAIRPERSON MACK: Thank you very much.

DR. ADAMSON: Tom, may I make a comment?

CHAIRPERSON MACK: Oh, all right.

DR. ADAMSON: I'm Richard Adamson, and I'm not representing anybody but science on this compound.

I've looked at this compound for a number of years. And when I was at the NCI, we actually did a study on this compound for carcinogenicity. Although there's

widespread exposure, it's not bioavailable. This compound does not, in my opinion and everything I've seen, does not get into the human system. I would say it's medium priority, not high priority, based on the bioavailability and the fact that it's rapidly metabolized to glucuronide.

Thank you.

CHAIRPERSON MACK: Okay. It sounds like we have a general consensus for medium even if you take an average.

So does anybody want to change?

No.

Next compound is BBP, butyl benzyl phthalate.

And the persons who are speaking to that are Landolph and Mack.

Landolph.

COMMITTEE MEMBER EASTMOND: I think I'm one of them.

CHAIRPERSON MACK: Oh, did I look at the wrong line?

I looked in the wrong line. Sorry about that.

In fact, it's only you, because Hopp is not here.

COMMITTEE MEMBER EASTMOND: Okay. I've put this put this as medium priority. Do you want rationale?

CHAIRPERSON MACK: Yeah.

COMMITTEE MEMBER EASTMOND: Okay.

CHAIRPERSON MACK: Just a sentence or two of rationale.

COMMITTEE MEMBER EASTMOND: Okay. IARC reviewed the data for this and listed as group 3, with limited evidence in animals, no tumors were seen in mice. There was increase in mononuclear cell leukemias seen in female rats. Increase in pancreatic tumors seen in the male rats. NTP considered it some evidence. The other one they saw an increase in pancreatic tumors and bladder tumors in the female rats, which they considered to be equivocal.

There were some other increases seen.

I guess the concern that was mentioned in the public comments -- keep going.

In vitro genotox tests were negative. It was positive for SC's and chromosome aberrations in mouse bone marrow. It has clearly been shown estrogenic activity in multiple studies with human exposure.

Public comments generally said it's not genotoxic. Weak increases in tumors were seen. There was lack of reproducibility in the animal bioassays.

I put all that together and gave it kind of a medium from my point of view.

CHAIRPERSON MACK: Does anybody wish to offer an alternative?

Hearing none, we go with medium from the committee.

And there are -- in fact Dr. Sutton again.

DR. SUTTON: Again, very brief. We would encourage you to go high with this one, because CDC NHANES data show that it's 97 percent of us. So because we're so widely exposed, we just need a definitive answer from you guys, based on the current data, whether or not this thing is a carcinogen.

CHAIRPERSON MACK: Thank you.

Dr. Janssen.

DR. JANSSEN: I would also encourage elevating this to high priority. In addition to the widespread exposure in the human population, butyl benzyl phthalate has the same mode of action as another phthalate already on the Prop 65 list as a carcinogen, which is diethyl hexyl phthalate, DEHP. Both chemicals are peroxisome proliferators, endocrine disrupting chemicals that interfere with the synthesis of testosterone, and in multiple and studies have been linked to altered development of reproductively sensitive organs.

Thank you.

CHAIRPERSON MACK: Thank you.

John Butala.

DR. BUTALA: I'm John Butala. I'm a

toxicologist. I represent FERRO, a manufacturer.

I would argue that many of the cancer bioassays, in fact all five that you represented, in results very much resemble the pattern that you saw just recently with fluoride. For example, the mononuclear cell leukemia that you mentioned, when tested by the NTP, could not be replicated at a higher dose when tested by the NTP at a subsequent test.

Pancreatic tumors that did not appear in the first testing in male rats did appear, and then in a subsequent follow-up to that in a third test, again at a higher dose, appeared only under dietary restriction conditions -- or did not appear under dietary restriction conditions; only appeared in excess diet.

Okay. The urinary bladder tumors that you mentioned in females actually only occurred as a marginally and not statistically significantly increased incidence and, again, in a delayed fashion, out at 32 months and in a restricted study.

NTP, who did those three studies, by the way, did not consider butyl benzyl phthalate as a carcinogen. It's never appeared in their ROC.

I would also say as to the estrogenicity, it's only the in vitro assays, which are fairly nonspecific and not good predictors, that are positive. Butyl benzyl

phthalate is clearly not estrogenic in vivo.

And finally as to the last comment we had on exposure, I think we need to be careful to distinguish that wide exposure. This is according to the CDC's NHANES data, of course, urinary data in the general population. But 97 percent of the population has traces of it. However -- and I want to read this to be sure I get it very, very clear.

"The NHANES population data show that human exposures are five to six orders of magnitude below the lowest BBP effects in rats." So there may be widespread exposure but it's very, very low.

Those are my comments. I think that BBP should not be a medium.

Thank you.

CHAIRPERSON MACK: Sounds like those are comments that really should come up when we actually discuss the carcinogenicity of it more than the prioritization.

So --

COMMITTEE MEMBER HAMBURG: Mack? Yeah, I would like to push this to high as well. I think the availability, the access, the exposure rates are so high, that even if we don't list it, it would be great to get it off the table so that we can clarify what the issue is.

So I would recommend high on this one.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree with Sol. I would recommend high because the estrogenic activity. There's also transformation of human breast cells with this and the peroxisomal proliferator activity in the bladder and the pancreatic cancer site. I would argue for high too.

CHAIRPERSON MACK: So anybody wish to disagree?

Okay. High it is.

COMMITTEE MEMBER EASTMOND: I might mention, if it doesn't cause peroxisomal proliferation you would expect liver tumors, which we don't see. So it's kind of unusual. I'm still okay with high. It doesn't matter.

CHAIRPERSON MACK: Okay. We come to butylated hydroxytoluene.

That's Joe and I.

Joe.

COMMITTEE MEMBER LANDOLPH: I recommend medium. It's an antioxidant preservative in foods, antioxidant for rubber petroleum plastic products. Genotoxicity in the mouse lymphoma cells mutation assay. Chromosome aberrations in human and CHO cells. That's positive in three out of five studies, giving lung tumors in female mice, liver tumors in male mice, liver tumors in male and female rats.

So I would recommend a medium on this.

CHAIRPERSON MACK: That's what I put down also.

Anybody wish to offer an alternative?

Okay. So now we come to James Coughlin.

DR. COUGHLIN: Thank you, Dr. Mack.

I'm Jim Coughlin, toxicologist consultant for five trade associations. We're calling ourselves the BHT Coalition. I thought I had five slides ready to go, but I'm going to do just one, if I can.

The main study, it was a Danish study published in 1986, the Olsen et al. study, was a Wistar rat study with three doses. But it got very famous and very unusual, and we spent years dealing with it in the food industry and in other places.

But The study went out for 2 3/4 years, as they sometimes do in European studies. And the only carcinomas were in the males. There was statistically significant increase in male carcinoma but not in the females. It was adenoma only.

But the most important feature of this study is that it had -- it got famous as we were doing this 25 years ago. And I mentioned in my comments that Gary Williams, who did liver -- he's one of the top liver cancer experts in the world for animals -- has reviewed this and done a lot of studies on it. But the animals

lived so long because of the antioxidant BHT that they got the tumors in the last three weeks of the study. And so it became very famous for us because the treated animals lived long enough to get the liver tumors, the males did. And the tumor latencies were much greater.

Survival was the most important feature in the males. Only 16 percent of the controls lived to termination, 144 weeks, whereas 44 percent of the treated lived that far.

The females, only 17 percent got to termination and 39 percent of the treated.

So the animals in a two and three-quarter year study, which we don't usually do - we stop at two years - lived long enough to get liver tumors that they were likely to get. So that's the -- I believe is the main.

I would urge a low priority for BHT.

CHAIRPERSON MACK: Does that change your mind, Joe?

COMMITTEE MEMBER LANDOLPH: No, it's very interesting data. But since this is used as antioxidant preservatives in food, there certainly is widespread use and it is carcinogenic. So I don't change my mind. Medium I've got for that.

CHAIRPERSON MACK: Neither do I.

So we'll stick with medium.

C.I. Disperse Yellow 3.

Sol, you're the only remaining person.

COMMITTEE MEMBER HAMBURG: The only victim.

Yeah, I rate this as high. It is another azo dye. Prop 65 has evaluated a number of other azo dyes and they're all listed. I think there's enough data to support looking at it. And as with other agents similar to that that have been listed, this should be evaluated as quickly as we can.

CHAIRPERSON MACK: Anybody have comments on this compound?

And there are no public comments. So high is where it stands.

Chloroalkyl ethers.

I'm one of the reviewers on chloroalkyl ethers.

DR. SANDY: And, Dr. Mack --

COMMITTEE MEMBER EASTMOND: Martha wanted to make a comment.

DR. SANDY: Dr. Mack?

CHAIRPERSON MACK: Yeah.

DR. SANDY: If I could just quickly --

COMMITTEE MEMBER MACK: Oh, I'm sorry. This is a group.

DR. SANDY: This is a group. So you're being asked a simple question advising on the chemical group,

should it be considered for listing? But as I said before, you have the prerogative if you would like to recommend a subset of this group.

CHAIRPERSON MACK: Why don't we consider categorizing for priority the highest of the group. In other words if we think any of the compounds require a high priority, then we put the group in the high priority. Is that reasonable?

What do you other members of the Committee think about that?

COMMITTEE MEMBER EASTMOND: Well, I have a general comment.

As I went through -- I didn't like evaluating these classes because they're all quite -- there are a lot of them very different within these classes. Essentially all the ones at low priority you're going to pull up higher to do that.

And, indeed, if -- the way I read Proposition 65, it's for specific chemicals. So the class itself is a funny -- I mean I can see for prioritization doing this for convenience sake. But specifically the actual decision's going to be made on individual chemicals, I would assume.

DR. SANDY: So maybe I should clarify. We're putting them in groups for ranking purposes. And then as

you -- if you rank something as high, you may decide you'd like us to look at all the chemicals in the group. And for listing you might want to have the ability to list only certain ones. Or at juncture for prioritization, you may be pretty certain you only want to prioritize a subset of the chemicals in the group or maybe only one. And so we're trying to let you know you have flexibility. Right now it's ranking for hazard identification development. And developing the hazard identification document, you can direct us to look at the entire group or look at a subset.

CHAIRPERSON MACK: I would suggest just from my own standpoint that not enough of us know enough to make the decision you're asking us to make. So what I would prefer is to prioritize as a group, but then reserve the option at your discretion to list them individually when we discuss them.

ACTING DIRECTOR ALEXEEFF: I think that would be preferable, Dr. Mack, to look -- that way we would -- if we brought the chemical forward, we would bring all the chemical information of that group, so you could see not only that specific chemical, maybe the one that has the most information, but the other ones to draw your conclusions.

And to comment on Dr. Eastmond's comment, you know, earlier we were considering fluoride and its salts.

So actually it was a group of chemicals.

DR. SANDY: But I have been making a distinction that those are related chemicals. The salts dissociate to fluoride. But the group, they're different chemical structures that do not dissociate to the same one.

CHAIRPERSON MACK: Is the summary that we do -- we can prioritize them as a group, with the presumption that you will actually list them separately when we look at them?

Okay. My view is that these are similar to known listed carcinogens and there's a lot of new information on the individual ones, so I would put them in the high category.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. I would support that particularly because bis chloromethyl ether is a member of that group and it causes human lung cancer from the occupational studies decades ago. So, yeah, I think these are pretty strong agents.

CHAIRPERSON MACK: Anybody wish to disagree with the high?

COMMITTEE MEMBER EASTMOND: Well, I'm the other commenter on this, and I put them as between low and medium. And mainly because if you look at the summary of the data, most of these don't cause any tumors that have

been tested. And even the ones that have, you only have one single study that would look to be valid.

So if you're saying what's the end result of this going to be, somebody's going to put a lot of work in, and ultimately probably not a lot of data to go forward. Now, they probably can figure that out pretty quickly. But I didn't rank it very high for that.

I recognized that some members of this class certainly are Proposition 65 carcinogens. But the residual ones here, I didn't think there was a lot of evidence. I mean you could argue for I guess the first two that are listed and maybe the third one. But you're getting to sort of injection site tumors and, you know, these are not clean chemicals with a lot of evidence. But I'm pretty flexible on it.

CHAIRPERSON MACK: Sarcomas in the injection site.

COMMITTEE MEMBER EASTMOND: I've seen a lot of these are injection site tumors.

I'm hoping you could hear.

COMMITTEE MEMBER LANDOLPH: Well, there's -- a CMME is lung adenomas in the male, injection site sarcomas in the females, respiratory tract tumors in males rats.

COMMITTEE MEMBER EASTMOND: That's already listed, Joe. You're looking at the wrong table.

COMMITTEE MEMBER LANDOLPH: Yeah, yeah. I'm looking at Table 2.

But I think their Similarity to BCME would still make me say that these are alkylating agents and they have a strong propensity to cause tumor induction. So I think they should still be high.

CHAIRPERSON MACK: Okay. Let's hear other people on the Committee?

COMMITTEE MEMBER WU: I put in the medium category, I think partly --

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: Medium.

CHAIRPERSON MACK: Medium.

So we have --

COMMITTEE MEMBER HAMBURG: Medium.

CHAIRPERSON MACK: Medium.

Joe, can I talk you into that?

COMMITTEE MEMBER LANDOLPH: Yeah, I can live with it.

CHAIRPERSON MACK: Okay. Medium it is.

And we have no comments on that.

Okay. Chloropicrin.

Sol and Darryl.

Sol.

COMMITTEE MEMBER HAMBURG: I actually put this one as relatively low, low. It is -- the toxicity data doesn't look that significant. And I think there are other agents of the 39 that require listing much sooner than this agent does. So I'm for low on this.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: Yes, I put a low. The lab studies indicate some trends but only if you throw in the adenomas and the carcinomas. So I put low.

CHAIRPERSON MACK: Does anybody disagree with low?

Let's see, I have a comment from John Butala again.

CHIEF COUNSEL MONAHAN-CUMMINGS: Maybe it would be good if everybody left their mikes on, and then you don't have to -- you know, leave it on and just push it towards your mouth.

CHAIRPERSON MACK: Mr. Butala.

Don't you have a comment to make on chloropicrin?

DR. BUTALA: Chloropicrin manufacturers --

THE REPORTER: Can you come forward.

COMMITTEE MEMBER EASTMOND: Did you submit -- do you want to make a comment?

DR. BUTALA: Are you proposing low?

CHAIRPERSON MACK: Yeah.

You're happy with that.

Thank you. Way to go.

(Laughter.)

CHAIRPERSON MACK: Clodinafop-propargyl.

DR. SUTTON: I'd like to make a quick comment on chloropicrin.

CHAIRPERSON MACK: On Chloropicrin?

DR. SUTTON: Yeah. I turned in a card. Maybe it's --

CHAIRPERSON MACK: You're sneaking in.

DR. SUTTON: No, I really did turn in a card.

CHAIRPERSON MACK: All right.

DR. SUTTON: All right. Real Quick.

We would suggest that you raise this a bit because this a soil fumigant. It's used widely in California. We grow lots strawberries here.

Air Resources Board tests show that you can inhale this -- you know, a lot of Californians all throughout the state can inhale this pretty far from application sites.

And the animal studies, there are about a half dozen of them. And the interesting thing about them is that to evaluate them fully you need to really look at statistical analyses and the relative merits of different analyses. And that's why we would suggest that a group

with your expertise would be better able to distinguish between the different measurements this way.

CHAIRPERSON MACK: All right. Let's see if you made a hit with Sol.

Still low?

COMMITTEE MEMBER HAMBURG: Low.

CHAIRPERSON MACK: Darryl?

COMMITTEE MEMBER HUNTER: Low.

CHAIRPERSON MACK: Sorry.

Okay. Now we go to the one that I couldn't pronounce. Clodinafop-Propargyl

And the people who evaluated that were again Sol and Darryl again.

COMMITTEE MEMBER HAMBURG: Darryl, you go first.

COMMITTEE MEMBER HUNTER: Sure, man.

I gave it a medium. A little bit higher than the other one. The animal data indicated some trends with carcinomas in more than one site as well as in the rat and mice models. So two different animals. And genotoxicity data, some trends as well.

So I gave that one a medium.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: I would agree with that. It's widely used. There's some data to suggest it may be a carcinogen. So I think a medium.

CHAIRPERSON MACK: Debbie Stubbs, Syngenta.

MS. STUBBS: I would like to propose that this should be a low. This product has been evaluated twice by EPA in two separate occasions and they gave it their lowest level of concern for a compound where there is any tumor formation. And that's suggestive evidence.

In addition, there have been other regulatory authorities that have come to the same conclusion, such as the European Food Safety Authority.

And the most important reason why this should be a low is this product -- this active ingredient is not registered in California. So there's no exposure to any of the citizens of California. And we have no plan at this moment to register any products with this active ingredient in California.

So therefore I believe it should be low.

CHAIRPERSON MACK: Well, Sol.

COMMITTEE MEMBER HAMBURG: I can be -- I can change my mind. Let's go to low on this.

DR. SANDY: I'd like to point out though, as stated in the document you have, the EPA has established tolerances for this chemical on wheat and hay. So that indicates there's some potential for exposure in California, or else we wouldn't have brought it to you.

CHAIRPERSON MACK: Trumped.

Darryl. Stick with medium?

COMMITTEE MEMBER HUNTER: I'm going to stick with medium.

CHAIRPERSON MACK: Sol?

COMMITTEE MEMBER HAMBURG: All right. Let's go with medium.

CHAIRPERSON MACK: Medium it is.

Coumarin. And that's -- Joe Landolph is the only available reviewer.

COMMITTEE MEMBER LANDOLPH: That's a natural product fragrance in perfumes, cosmetics, personal care products, industrial uses, electroplating, pharmaceutical uses. So there's a lot of use of it.

The genotoxicity is positive in bacteria, SCEs and CHO cells, chromosome aberrations in plants and CHO cells, micronuclei in human hepatoma cells. So it's got a reasonably robust genetox database.

Carcinogenicity, it's positive in four assays tested. It has lung tumors, stomach tumors, lumbar tumors in male and female mice, renal adenomas in male and female rats, pulmonary tumors in male mice, liver tumors in female mice, liver tumors in male and female rats.

So I ranked it as a high priority.

CHAIRPERSON MACK: Do others have opinions about this?

COMMITTEE MEMBER EASTMOND: I ranked it high as well.

CHAIRPERSON MACK: High as well.

COMMITTEE MEMBER EASTMOND: Based on mainly the animal evidence.

CHAIRPERSON MACK: Robert Golden from the International Fragrance Association.

Bringing a high level of class to this Committee.

DR. GOLDEN: Thank you. I'm Dr. Robert Golden. And as Dr. Mack said, I'm with the International Fragrance Association.

The animal data are as you stated.

There are no human data. In fact it's been used a lot as a pharmacologic agent, and not even any case reports.

IARC has determined that it was not a classifiable for human carcinogenicity. And they determined that the animal data were limited.

I would also point out that it is now known - and this has been evaluated by the European Food Safety Authority as well as the BFR - the significant differences between animals and humans in the metabolism, with animals metabolizing it to toxic metabolites, humans hydroxylating it and excreting it.

So with the -- all of the in vivo genetox data

are also negative.

So I would argue just the opposite way, that it should be medium or low.

CHAIRPERSON MACK: Did that make any impact on you?

COMMITTEE MEMBER LANDOLPH: No. It's an articulate argument, but I'd stick with my original position.

CHAIRPERSON MACK: Looks like you didn't smell good enough.

(Laughter.)

COMMITTEE MEMBER LANDOLPH: Now, I didn't say that. You did.

CHAIRPERSON MACK: Okay. I guess we stick with high.

Dapsone. I was one of the reviewers for Dapsone. Oh, no, I wasn't. I thought I was.

(Laughter.)

CHAIRPERSON MACK: Yes, I was. Why can't I -- yeah, I am.

No, It's Anna Wu.

COMMITTEE MEMBER WU: Medium.

CHAIRPERSON MACK: And the other one is Joe Landolph.

COMMITTEE MEMBER LANDOLPH: Yeah, I had high.

CHAIRPERSON MACK: Okay. You want to tell us why high.

COMMITTEE MEMBER LANDOLPH: It's used to treat leprosy, dermatitis herpetiformis, also coccidioides in cattle. Aneuploidia achromatic gaps are formed in cultured human lymphocytes. In vivo mouse chromosomal aberrations in micronuclei. So it's getting into the in vivo, which makes it stronger as a genetox. And six out of the seven studies were positive for carcinogenicity in animals:

Spleen fibromas, fibrosarcomas and sarcomas in males, peritoneal fibrosarcomas and sarcomas in males, spleen fibrosarcomas and angiosarcomas in males, thyroid C cell carcinoma in male and female rats, thyroid C cell carcinoma in female rats, spleen fibrosarcoma, intestinal reticulosarcoma, liver angioma -- some of these tumors are fairly rare.

And for the epidemiology, there's some data on bladder and kidney cancer in leprosy patients treated with this, and urinary tract carcinomas, an adenosarcoma of the secum, two lung cancers and Hodgkin's disease.

So it's penetrating into the in vivo gene toxicity. There's some epidemiology and the animal database is pretty strong.

CHAIRPERSON MACK: Does that convince you?

COMMITTEE MEMBER WU: Not entirely. I mean I don't disagree with any of the things that were said. I just thought that the usage was more limited and there were other things that are more probably pressing.

COMMITTEE MEMBER HAMBURG: I've seen one case of leprosy in 30 years, and that was 30 years ago. So it's a very uncommonly used agent as compared to other agents, and I think its clinical relevance is very small. So at least at this time I think either a medium or a low. I would not put it as a high priority.

CHAIRPERSON MACK: I went to medium actually, thinking that I hadn't, partly because of that, mainly that there are relatively few people who are being treated, and they're not going to be treated with anything else.

COMMITTEE MEMBER HAMBURG: Exactly.

CHAIRPERSON MACK: So it's not going to change their treatment modality.

So can we talk you into medium?

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

CHAIRPERSON MACK: Okay. Medium it is.

Dibenzanthracenes and dibenz[a,c]anthracene.

And that is Joe again.

DR. SANDY: And if I could just remind you.

You've got two questions. You can rank the chemical group. And we'd like you to rank the dibenz[a,c]anthracene, if you are willing to.

COMMITTEE MEMBER LANDOLPH: Say that again.

DR. SANDY: We're asking the Committee to rank the chemical group Dibenzanthracenes as well as one of the chemicals in the group, the dibenz[a,c]anthracene.

CHAIRPERSON MACK: That was pretty sneaky.

(Laughter.)

COMMITTEE MEMBER LANDOLPH: Yeah, so there's a pretty robust database on these. Dibenz[a,c] is mutagenic in bacteria mammalian cells, V-79 cells. DNA damage in bacillus subtilis. It transforms Syrian hamster embryo cells. So it's pretty robust, cause skin papillomas in mice -- female mice. It's positive in four out of seven animal studies. Liver adenomas in male mice. Skin papillomas in female mice.

The dibenz[h,a]anthracene again is mutagenic in salmonella, causes DNA adducts in mouse epidermis, mutates the codon 61 of the Harvey rat's oncogene. Three out of four experiments it's positive. Skin carcinomas in female mice. Skin papillomas in female mice. Skin papillomas in female mice. There's no epidemiology data of course.

The dibenz[a,h]anthracene is of course one of the most famous carcinogens, identified around 1930 as a

constituent of coal tar. And that's very hot mutation of salmonella, Chinese hamster cells, sex linked recessive lethal gene mutations in Drosophila. Sister chromatid exchanges in CHO cells, DNA adducts, cell transformation, CHO cells and mouse embryo cells and Fischer rat embryo cells. And that one's positive in seven out of seven experiments.

And like most of the PAH, it usually causes skin papillomas and carcinomas. Lung adenomas in mice, sarcoma, fibrosarcoma, lung tumors in rats, lung adenoma in mice, forestomach carcinomas, mammary adenocarcinoma, lung tumors, and liver tumors.

So I think the whole class is pretty carcinogenic as far as I'm concerned. Dibenz[a,h]anthracene stands out as the most -- it's one of the most famous historical carcinogens. And you would get this through incomplete combustion. And it's kind of a ubiquitous air contaminant because of that. So I would rank this as a high class. And I think the other -- the chemicals within it are probably -- you know, you'll probably rank them later as high, is my guess.

CHAIRPERSON MACK: So did you give her an answer to the questions?

COMMITTEE MEMBER LANDOLPH: I thought I did. But sharpen it up if I didn't.

I would say the class is high, in my opinion. And I would say I think there's a probability that the members will be high too, because they're typical polycyclic aromatic hydrocarbons.

DR. SANDY: But we're looking for advice from you on the ranking of the -- one of the two that are not --

COMMITTEE MEMBER LANDOLPH: Just the dibenz[a,c], that's all you want to know about?

It looks pretty good. It's mutagenic in bacteria, mammalian cells, and it causes skin tumors --

CHAIRPERSON MACK: What's the exposure?

COMMITTEE MEMBER LANDOLPH: Mostly in the air. You'll get a lot of it in the air. It's like benzpyrene. You know, you get -- it's thermodynamically favored when you combust these molecules in a paucity of oxygen that they form.

CHAIRPERSON MACK: Barbecue.

COMMITTEE MEMBER LANDOLPH: Yeah, if you burn your steaks black, sure, you'll get that form, and when you burn trash in a paucity of oxygen. So it's an air contaminant. And you get some of it into the water, some of its into the soil, but mostly air.

CHAIRPERSON MACK: So it's a high, high.

COMMITTEE MEMBER LANDOLPH: I would say so.

CHAIRPERSON MACK: Does anybody --

COMMITTEE MEMBER EASTMOND: Can I ask a question.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: Martha. Apparently, this was reviewed by IARC when they did the PAH recently. Do you know what the outcome of that review was?

DR. SANDY: Yes, and you have this other table that was sent to you and was out as a handout which talks about if an authoritative body has reviewed a chemical and when they did it. So it was reviewed in 2010 in the a,c isomer and put in Group 3.

COMMITTEE MEMBER EASTMOND: So. Okay.

CHAIRPERSON MACK: Okay.

COMMITTEE MEMBER LANDOLPH: Tough to see how it could be in 3, because it makes DNA adducts, it's mutagenic. It's carcinogenic. I have -- I would have a problem with that. I don't know why they would do that.

COMMITTEE MEMBER EASTMOND: I mean if I can weigh in on this one.

CHAIRPERSON MACK: Please do.

COMMITTEE MEMBER EASTMOND: I think the challenge is going to be having data that you think is sufficient and robust enough to go forward with it. I mean, a lot of these are very early studies -- studies done very early on by injection, or then you've got these sorts of IP injections in the newborn mouse model, which depends how

you want to evaluate that.

So I think my take on this is these are probably medium to high, but it may be difficult to list them, because intrinsically they're probably high, but I'm not sure if the evidence will be there in order to make a determination eventually. That's kind of my take.

CHAIRPERSON MACK: Won't it just let that play out as it plays out. And if you think it is omnipresent in the air, and it's potentially nasty, then we should call it high and leave it at that.

COMMITTEE MEMBER LANDOLPH: And most of them are either skin carcinogens in the classical skin painting experiment. And Dibenz[a,h]anthracene is so, so strong. This is pretty closely related to that.

CHAIRPERSON MACK: So let's call it high and go to the next one. 3,3'-dichlorobenzidine-based compounds metabolized to 3,3'-dichlorobenzidine.

COMMITTEE MEMBER HAMBURG: It's me.

CHAIRPERSON MACK: That goes to Sol and --

COMMITTEE MEMBER HAMBURG: I would rank that as high as well for very similar reasons. It's very active. It's got a compound structure that's associated with many changes in DNA in proteins. And there's a significant amount of exposure. So I would rank that as high along with the other ones.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: The dichlorobenzidine forming compounds?

CHAIRPERSON MACK: Yeah.

COMMITTEE MEMBER HAMBURG: Yeah.

COMMITTEE MEMBER EASTMOND: I guess the comments I have on this, I actually put this down as sort of medium to low. And the reason essentially is the class is -- it's based more on logical argument. If these compounds are metabolized to this dichlorobenzidine derivative, then therefore they should be carcinogenic.

But if I recall, the only chemical that's actually been tested was this pigment yellow 12, which had been negative in both mice and rats.

Now, the public comments they did mention that they believed there was an error in the classification, that there was combining of both dyes and pigments. And the idea is pigments were not bioavailable, and so therefore, they shouldn't -- they aren't going to be converted into the -- essentially a dichlorobenzidine.

Whereas, the dyes could be, but a lot of these were pigments. So they made that distinction in their public comments.

So, I mean, it comes down to kind of a logical argument. If, indeed, those are metabolized and they form

the dichlorobenzidine, then you would say sure, we should make them a higher priority. But apparently, a lot of members of this class aren't converted, and so they'd be pulled forward on some ways almost without a lot of evidence. So I put medium as kind of my highest assessment on that.

COMMITTEE MEMBER HAMBURG: I can live with medium.

CHAIRPERSON MACK: You can live with medium?

COMMITTEE MEMBER HAMBURG: Yes, sir.

CHAIRPERSON MACK: All right. Medium it is.

COMMITTEE MEMBER EASTMOND: Martha has a comment.

CHAIRPERSON MACK: Martha has a comment.

DR. SANDY: I wondered if it would be helpful to you if I read something that IARC said when they reviewed colorants. They did not make a decision -- any decision on this particular class. But they said, "It was concluded that all azo colorants, whose metabolism can liberate a carcinogenic aromatic amine are potentially carcinogenic. It has therefore been recommended that the colorants be dealt with as if they were classified in the same categories as a corresponding carcinogenic or suspected carcinogenic amine".

They go on to say, "There are some colorants that have been claimed to be insoluble and that may not

contribute to be amine exposure, and this can tested by use of biomarkers".

And the conclusion is, "When the contribution of a benzidine-based dye to cancer risk is claimed to be low or negligible the bioavailability of the carcinogenic component should be excluded e.g. by use of biomarkers of exposure of biomarkers of effect. However, if this is not the case, it does not seem justified to classify benzidine-based dyes differently from benzidine".

So they're sort of mixing between the larger class of azo colorants and benzidine-based dyes, but they're implying that you want to look and see if there's are biomarkers of exposure. And we've tried to provide you with that information in here.

COMMITTEE MEMBER EASTMOND: Yeah, that's fine. I mean, I just looked at -- the only one of this class that's actually been tested was negative in both the mice and rats. So that's at least what I got out of the screen.

CHAIRPERSON MACK: So let's go with medium, if there's no other objections.

So we come to 2,4-D. And 2,4-D is myself. And I judged that high, mostly based on the distribution of exposure.

And Anna.

COMMITTEE MEMBER WU: High, and also because there are new epi data since -- in the last decade that suggest it.

CHAIRPERSON MACK: Any other members of the Committee?

David.

COMMITTEE MEMBER EASTMOND: I went high to medium. High is fine.

CHAIRPERSON MACK: High to medium.

Joe.

COMMITTEE MEMBER LANDOLPH: Hang on one second.

CHAIRPERSON MACK: In the meantime, Sol?

COMMITTEE MEMBER HAMBURG: High.

CHAIRPERSON MACK: And Darryl?

COMMITTEE MEMBER HUNTER: Medium.

CHAIRPERSON MACK: Joe?

COMMITTEE MEMBER LANDOLPH: High.

CHAIRPERSON MACK: Okay. So the Committee, except for Darryl goes for high, and he can live with high.

(Laughter.)

CHAIRPERSON MACK: And we have Jim Gray.

MR. GRAY: Good afternoon. I'm Jim Gray. I'm the Executive Director for the industry task force on 2,4-D research data.

I was not anticipating that I would have to come up here and argue from a high listing on down. But I would draw your attention to the fact that there is a robust and modern database that has been developed for this compound very recently, driven by most of the questions and concerns from the 80s and the 90s on apparent linkages or claims of linkages to non-Hodgkins lymphoma and other carcinogens.

All of these studies have been evaluated very recently by regulatory authorities worldwide including U.S. EPA, Health Canada's PMRA, the World Health Organization, New Zealand, and the European community.

Not one of the regulatory authorities worldwide classified 2,4-D as a animal or human carcinogen. And, in fact, in the 2005 evaluation done by U.S. EPA, the scant epidemiology data was not sufficient to raise the level of concern.

And, in fact, the written comments that we've written or that we've read that were supplied by one of the NGOs to this Committee seemed to have reiterated the select data points that they put in in 2004, and again, in 2005 for EPA's consideration, which EPA considered and then rejected.

And there is a question then about after they have done a complete and thorough evaluation of this why

are we looking at yet another round of no, no, you didn't understand us.

With the overwhelming consistency amongst all the regulatory authorities in their determinations, and such a robust database, we think that it's likely that going through the process of prioritization and consideration that the CIC is likely to arrive at a similar decision, determination. And, in fact, in 2009, OEHHA staff itself did an evaluation for this for public health -- a PHG for drinking water goal, and had documents and determinations on file that it did not rise to the level of being prioritized for carcinogens.

Thank you.

CHAIRPERSON MACK: Well, I based my judgment on the suggestion that there might be a relationship to an NHL, which I did not see dismissed by anybody. So my inclination is not to waiver. And actually, let me first call upon Dr. Janssen who listed 2,4-D as well.

DR. JANSSEN: I'll waive my comment and -- because I agree with the high prioritization.

CHAIRPERSON MACK: Okay. Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, Tom. I agree with you on the NHL. I also noticed there's thoughts, ratios for breast and stomach cancer in a couple other studies. And there's micronuclei, sister chromatid

exchange, chromosome aberrations, comet assay, endocrine disruption. And there's positive carcinogenicity results in 8 out of 12 studies in rats. And a lot of different types of tumors, so I think this is not an innocuous compound.

CHAIRPERSON MACK: Okay. So we're sticking with high.

COMMITTEE MEMBER WU: Yes, and I think that the new Epi data are actually based on the case control studies, so I think it's worth taking a look at it.

CHAIRPERSON MACK: Right.

Dicloran. And that's Darryl, only reviewer.

COMMITTEE MEMBER HUNTER: Power.

I give it a low.

CHAIRPERSON MACK: Low.

COMMITTEE MEMBER HUNTER: I gave it a low.

CHAIRPERSON MACK: Tell us about it in a sentence or 2.

COMMITTEE MEMBER HUNTER: Fungicide does have widespread use. In the animal data, the tumor trends were malignant in -- at least in one of the studies isolated to one gender. Females and the males, it was combined benign and malignant. And so my general feeling was that this was something that we have bigger fish to fry.

CHAIRPERSON MACK: Anybody disagree?

Joe?

COMMITTEE MEMBER LANDOLPH: No, I agree completely.

CHAIRPERSON MACK: Agree. So it's low. And there's no public comment.

The next one is dinitroaniline pesticides.

First of all, let me ask the gentleman down there how he's doing?

THE COURT REPORTER: I'm okay.

CHAIRPERSON MACK: You're all right. Okay. Wave your hand if you need anything.

Dinitroaniline pesticides. That will be David Eastmond and Anna Wu.

DR. SANDY: And, Dr. Mack, if I could just remind the Committee, we're looking for groupings -- rankings of the group, as well as 2 individual compounds, prodiamine and trifluralin.

Thank you.

COMMITTEE MEMBER EASTMOND: I certainly didn't realize that when I was reviewing it.

So what are the 2 we are commenting on?

Prodiamine and trifluralin.

I mean, I guess I'll just give you my general comments overall. I ranked this between medium and high. And it really depends upon the likely significance of the

thyroid tumors. I mean, one of the things that happens is that there are some reports in humans, but not very consistent. Mixed reports of cancer in rodents. But fairly consistent increases in thyroid, follicular cell adenomas and/or carcinomas seen for a number of the pesticides. And liver tumors were also seen in mice for a number of the studies as well.

They mixed frequently negative gene tox studies. It's been proposed in involved in alteration of thyroid hormone levels. If that's true, then that kind of influences how you interpret the thyroid hormones. So again, I had challenges looking at the class at once, but this was one that I thought might be relevant because of the similarities in the tumors.

The public comments were also concerned about listing as a group. And that non-carcinogenic agents would be inappropriately prioritized. They said only -- EPA has only considered one of these to be carcinogenic.

Anyway, I guess a priori understanding the significance of the thyroid tumors would come in the evaluation. So I'd probably put this in the sort of medium-high category. I could go either way on that.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: I had it in the high-medium category. Maybe not for the same reasons, but because

they were -- you know, the description was a mixture and that there was certainly enough information there to suggest that only a medium and maybe high.

CHAIRPERSON MACK: Would the 2 of you please agree on whether it's medium or high.

COMMITTEE MEMBER WU: I would put it in the high, I actually -- the way I do it is high-medium, that means I lean towards the high first. That's how -- you know, that's how I indicated it.

CHAIRPERSON MACK: Let's hear from the regulated community. We'll see if we can be -- either offended enough to make it high or be convinced enough to make it low.

So Richard Peffer.

DR. PEFFER: I'm Richard Peffer with Syngenta Crop Protection. And I actually was going to just speak to the prodiamine, which was part of the question was to ask were it individually should be rated high, low, or medium.

And prodiamine has only thyroid tumors as part of its spectrum. And it's genotox profile is negative, except for one study, an Ames assay that was done with an older production batch that was prior to the modern synthetic technique, when it was repeated with the new synthetic technique, three or four other studies were all

negative.

And the mode of action for thyroid tumors has been investigated and found to be looking like a classic phenobarbital type profile, where UDP-glucuronyl transferase is induced, which causes increased secretion of thyroid hormone. So for prodiamine, I think it ought to be evaluated separately, and it ought to be medium or a low category.

CHAIRPERSON MACK: Thank you.

Sabitha Papineni.

DR. PAPINENI: Good afternoon. I'm Dr. Sabitha Papineni. I'm a toxicologist here working for Dow AgroSciences.

And I'm here to represent the DNA, the trifluralin, benfluralin, ethalfluralin. And the concept is about the thyroid tumors as Dr. Eastmond was mentioning. It has been highly investigated, and we also have published literature on trifluralin to show that the mode of action is not relevant to humans and it's very specific to rodents, especially rats.

And the other thing I want to draw your attention to is that trifluralin has been investigated by -- I mean, evaluated by other agencies, IARC, the International Agency for Research on Cancer. And clearly it concluded that trifluralin is not classified both as a carcinogen,

based on the epidemiological data and also the animal data, which is overly negative.

And coming to the widespread use, the use of trifluralin has been declining over the past 10 years by over 50 percent. And it's mostly used a granules, which minimizes exposure. And it's a pre-emergent herbicide applied directly to the soil.

And benfluralin clearly in the write-up of the CIC on the dinitroanilines clearly indicate that there is no use or benfluralin reported in 2009. And it's a very minimum use of benfluralin these days.

And coming to ethalfluralin, it's just one study that's in Fischer rats showing mammary fibroadenomas which are benign, non-invasive. And clearly showed that this strain is very prone for these tumors. So considered not biologically relevant to humans.

So we would request the CIC to give it a medium or low priority based on these findings.

Thank you.

CHAIRPERSON MACK: David, do you have any response? I mean, we have two problems here. One is resolving between medium, high, and low. And since we have all three of them that's been induced, you two are resolving between medium and high, and then we have to make some decisions about the individual compounds,

because we're asked to most recently.

COMMITTEE MEMBER EASTMOND: I can go either way. I mean, I probably --

COMMITTEE MEMBER WU: Medium.

COMMITTEE MEMBER EASTMOND: -- lean it to medium is fine. Yeah. I mean, I suspect that there -- the thyroid tumors seem to be driving it for me. And it does appear that a number of classes of agents induce thyroid tumors are not believed to be relevant to humans. Now, whether this is a class -- whether it fits in that class, I'm not certain, but that would suggest that it would be medium for me.

CHAIRPERSON MACK: So we're going to call it medium for each of the two specific compounds as well?

COMMITTEE MEMBER WU: Certainly.

COMMITTEE MEMBER EASTMOND: Sure.

CHAIRPERSON MACK: Does that make you happy?

(Laughter.)

CHAIRPERSON MACK: Okay. Entecavir. Darryl.

COMMITTEE MEMBER HUNTER: I think I also did that one. This is -- has a medical use. It's an anti-viral drug for hepatitis B, so something very important. I gave this a -- I gave it a medium, shown to -- in animal studies to increase in malignant tumors, in males and females, both in mice and rats. So two different animal

models. Widespread use. I felt it was something important because of its medical use that it get a little bit of a priority.

CHAIRPERSON MACK: Does anybody have additional comments?

COMMITTEE MEMBER HAMBURG: Was it a low or a medium?

COMMITTEE MEMBER HUNTER: I gave it a medium.

COMMITTEE MEMBER HAMBURG: A medium. I would agree with that.

CHAIRPERSON MACK: So we'll go with medium.

I committed a sin here. Artie Lawyer wanted to talk about dinitroaniline.

DR. LAWYER: I'm fine.

COMMITTEE MEMBER EASTMOND: You're okay with it?

DR. LAWYER: Medium is fine.

CHAIRPERSON MACK: And Fred Hess also did.

DR. HESS: Back to dinitroaniline. If I could have a couple of minutes.

CHAIRPERSON MACK: You can have one minute.

DR. HESS: I have an overhead.

CHAIRPERSON MACK: We've settled on medium for both the group and for the two individual compounds.

DR. HESS: Yes, I realize that. And I represent a different compound. If you'd rather not get into that

now, that would be okay. In other words, I have a third dinitroaniline.

CHAIRPERSON MACK: I don't think we needed any judgment on a third.

DR. HESS: Thinking it was lumped in with the group, that's why.

CHAIRPERSON MACK: Okay. Go ahead, and make your comment.

DR. HESS: Okay. Request. It's the one the pointer is on.

My name is Frederick Hess from Research Triangle Park and BASF's chemical company.

The next slide.

--o0o--

DR. HESS: This is why we don't think that dinitroaniline should be lumped in together as a single class, they may act similarly in plants, herbicidal activity through their activity in there against pre-emergent crabgrass. They prevent -- or inhibit microtubule assembly in the plant.

However, their mammalian tox profiles are very different, and including their differences in tumor induction are very different. EPA also thinks that way, and do not consider the group as a cumulative risk approach for risk assessment. And they have said that

numerous times for the various dinitroanilines okay.

--o0o--

DR. HESS: Genotoxic -- this is for pendimethalin. I won't go into this, but the next slide might help us with the thyroid, benign thyroid tumor type of tumor induction for -- this again is for pendimethalin, but at a high dose that cause 20 to 30 percent decrease in body weight gain.

There were just benign thyroid follicular cell adenomas. And this is the -- the cell of origin is the follicular epithelial cell in the thyroid gland. And this is a well known mode of action, which is a secondary or indirect mechanism of feedback. It's not a direct acting on the thyroid or iodide, but it's one that involves enzyme induction, increased glucuronyl transferase in the liver. And that sets into place a whole -- multiple stages of trying to get to homeostasis with T4 thyroxine hormone through TSH through thyroid releasing factors from the hypothalamus.

CHAIRPERSON MACK: I think you've made the case that when we consider these, in their medium priority subcategory, they will be taken up individually.

Thank you very much.

DR. HESS: Okay. You're welcome and thank you.

CHAIRPERSON MACK: Let's go to flonicamid.

COMMITTEE MEMBER HAMBURG: I reviewed that. That's low for me. It's a relatively minimally used compound. The data does not look very strong. The genotoxicity data is relatively -- is all negative, as far as I can see. Nasolacrimal duct tumors in a single species, single sex at very high doses.

So I think the likelihood of finding anything significant is relatively small.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: I had it medium. I agree with Sol, there's no genotoxicity. It's a nicotinoid insecticide used on cotton and alfalfa, fruits and vegetables. Agricultural workers and people eating crops with residues are exposed. It's positive in 3 out of 3 animal experiments, nasolacrimal duct, carcinomas in the female rats, lung tumors in male and female mice. So I gave it a medium.

CHAIRPERSON MACK: You gave it a medium?

COMMITTEE MEMBER LANDOLPH: Yeah.

CHAIRPERSON MACK: So would the two of you resolve those.

COMMITTEE MEMBER HAMBURG: I'm sticking with low.

Joe?

COMMITTEE MEMBER LANDOLPH: Given the lack of genetox data, I could move to a low on that.

COMMITTEE MEMBER EASTMOND: I actually originally gave it a high.

(Laughter.)

COMMITTEE MEMBER EASTMOND: But I'd go down to medium. But you've got -- it's clearly that it's reproducible in 2 different studies in mice. You've got alveolar, bronchiolar adenomas or carcinomas.

CHAIRPERSON MACK: So could we talk you into a medium, Sol?

COMMITTEE MEMBER HAMBURG: Yes, you can.

CHAIRPERSON MACK: Fluazinam. That's David and Darryl.

David?

COMMITTEE MEMBER EASTMOND: I put this between low up to medium.

CHAIRPERSON MACK: You seem to have a 5 category system.

COMMITTEE MEMBER EASTMOND: I have 5 categories always.

(Laughter.)

COMMITTEE MEMBER EASTMOND: Essentially, it's not registered for use in California, so it's really -- exposure would come through residues in crops registered in other states. And that's driving it. They're certainly positive for thyroid gland follicular cell

tumors in male rats and also liver tumors in male and female mice.

I guess that's what driving it for me. Again, this mechanism for the thyroid tumors, at least in the public comments, was commented this was probably related to a hormone imbalance associated with increase TSH. So anyway.

CHAIRPERSON MACK: So, Darryl.

COMMITTEE MEMBER HUNTER: I gave it a medium.

CHAIRPERSON MACK: So are we both happy with medium?

COMMITTEE MEMBER EASTMOND: Medium is okay with me.

Everybody else?

Hexythiazox. And that's Darryl and Sol.

COMMITTEE MEMBER HAMBURG: All right. I gave this one a low as well. Genotoxicity data is all negative. It's a sparsely used compound. There's no human data. Animal data is old. It doesn't have a great significance in my book.

COMMITTEE MEMBER HUNTER: Yeah, I gave it a low.

CHAIRPERSON MACK: Everybody happy with low?

COMMITTEE MEMBER EASTMOND: I have it medium to high.

(Laughter.)

COMMITTEE MEMBER EASTMOND: Just so you know. Essentially, this was rated by the EPA. It's considered to be likely to be carcinogenic in humans, but it's -- you've got again hepatocellular carcinomas in male and female mice. And then you have benign tumors in the male rats, but if you want to go with low, I'm not --

COMMITTEE MEMBER HAMBURG: I mean the question when we do this is not whether it's carcinogenic or not. The question is what is its relevance to Prop 65 in the immediate future. I don't think we're talking about whether these are carcinogenic or not. I think how we prioritize these is what the real issue is.

CHAIRPERSON MACK: Basically, whether there's a legitimate hypothesis and whether it's an urgent issue.

COMMITTEE MEMBER HAMBURG: And I put the urgency as very low. So I think --

COMMITTEE MEMBER EASTMOND: The use is actually very low, so that's probably a reasonable way to go.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. I rated it low, because there's no genetox, and there's no Epi at all. Just the 2 animal studies. I thought this was low probability too.

COMMITTEE MEMBER EASTMOND: I'm okay with low.

CHAIRPERSON MACK: So we'll call it low.

COMMITTEE MEMBER LANDOLPH: Low.

CHAIRPERSON MACK: And go to hydralazine and its salts. I judged this one to be low. And the other person was --

COMMITTEE MEMBER WU: Anna. I had it low.

CHAIRPERSON MACK: Low?

COMMITTEE MEMBER WU: Yes.

CHAIRPERSON MACK: So we both agree on low. Does anybody have a problem with that?

So we'll call hydralazine low.

Isophosphamide. That would be David and -- David and David.

COMMITTEE MEMBER EASTMOND: I put it in the medium to low category based on limited data. I think it's likely a carcinogen, but I'm not sure there will be sufficient data to spend the time on it. But that's -- if you want to go through my kind of rundown of things.

CHAIRPERSON MACK: Do you think the people of California will want us to look at it relatively soon?

COMMITTEE MEMBER HAMBURG: Let me make a couple comments. It's commonly used in clinical practice. I use this drug at least once a week. It is likely to be a carcinogen as -- I think I lost my microphone.

Again, I would say no higher than a medium, if we want to list it. But I don't think for most patients

getting this drug, there are no alternatives.

CHAIRPERSON MACK: Shall we go with medium

COMMITTEE MEMBER HAMBURG: You can go with medium.

COMMITTEE MEMBER EASTMOND: I can go with medium or low.

COMMITTEE MEMBER HUNTER: I'd go with low. I mean, there's no alternative. You're using it to treat cancer. Is it really a priority for us to --

COMMITTEE MEMBER HAMBURG: No. I would agree. Low is fine.

COMMITTEE MEMBER EASTMOND: Low is fine.

CHAIRPERSON MACK: Low.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree, low too.

CHAIRPERSON MACK: Nothing like interaction.

Metofluthrin. That's David again, and me.

COMMITTEE MEMBER EASTMOND: This was positive in liver tumors in both male and female rats. Negative in mice. Negative essentially in genetox studies. Structurally related to a couple of Proposition 65 other pyrethroids. And indicates that the -- it acts through an induction of cytochrome P450 monooxygenase enzymes. And it's fashioned similar to phenobarbital. Although, that hasn't been clarified. Public comments, exposure is very

low. So I put this in the sort of medium-low category, probably more low than medium.

CHAIRPERSON MACK: I put it in low actually. I did look at it. And if that means that if we both put it in low, then Christian Volz doesn't need to say anything.

MR. VOLZ: You got it.

COMMITTEE MEMBER EASTMOND: You okay with that?

CHAIRPERSON MACK: Okay. We come to mixtures containing pentabromochlorocyclohexane. And that's David Eastmond and Sol Hamburg.

COMMITTEE MEMBER HAMBURG: Dr. Eastmond, are you going to say high? Go ahead say high?

(Laughter.)

COMMITTEE MEMBER EASTMOND: I'm not going to say high. Go ahead.

(Laughter.)

COMMITTEE MEMBER HAMBURG: Me either.

COMMITTEE MEMBER EASTMOND: Well, essentially you've got some positive animal studies. These are flame retardants in presence in -- use for a variety of different exposures. So I think fairly significant exposures.

Negative Ames test. I put this sort of medium to low, driven by limited information. But what do you think, Sol?

COMMITTEE MEMBER HAMBURG: Yeah. You know, I would -- medium I think. My concern really about it is that there seems to be a scant amount of data from the screening information. So I don't know that we're going to be able to come to a conclusion about this. So I would put it -- but I think it's a relevant issue. I don't think it's been tested enough. So I would put it in the medium level. I wouldn't put it low.

CHAIRPERSON MACK: So medium it is. Next is n-methyl-n-nitroso-1-alkylamines

DR. SANDY: Dr. Mack?

CHAIRPERSON MACK: Yes, ma'am.

DR. SANDY: So I'm asking the Committee on this one, 5 different rankings.

CHAIRPERSON MACK: Oh, good, Lord. Well, I'm the only person to do it. And I can't give you 5 different rankings. So I have to appeal to one of my molecular colleagues, one of non-epidemiologic colleagues. And the one to my left is the one I first come to.

Have you looked at these?

COMMITTEE MEMBER EASTMOND: Have I looked at it? Yeah.

CHAIRPERSON MACK: What I said was that I'm incapable of judging the priority of these 5 compounds one by one, because they're all animal data, and no

epidemiology. So I'll ask David if he can help me.

COMMITTEE MEMBER EASTMOND: I mean, I looked at these. And there's -- these are carcinogenic in animal -- in multiple targets sites in animal models. So, for me, I thought they were pretty high. The real concern is what's the exposure.

And I would suggest, essentially if you want to prioritize among them, it's really prioritizing based upon exposure and what you think their relevance is. As a class, I think they're fairly. It's one that would be a concern if there's sufficient exposure.

CHAIRPERSON MACK: So for a person who demanded individual characterization on five compounds, I see 1X in the exposure category, in the chart that you've given us.

So if you want five judgments, you're going to have to give us 5Xs.

(Laughter.)

COMMITTEE MEMBER HAMBURG: Do we have any information about when what you talk about can be detected, what is the level of detection that you're talking about? Do we have any information to say whether it is one in a billion parts, or one in a million parts or do we have any sense of that?

DR. SANDY: I don't think we do. We didn't turn it up during the screening process.

COMMITTEE MEMBER HAMBURG: No, no, right, so -- because it's really hard to say whether it's a relevant issue or not. I mean, if it's a part per billion, I mean -- yeah.

CHAIRPERSON MACK: Yeah. I think that's very true.

COMMITTEE MEMBER LANDOLPH: Tom.

CHAIRPERSON MACK: Yeah.

ACTING DIRECTOR ALEXEEFF: George Alexeeff. Well, if exposure is the question, but if you feel you have some confidence on the other -- you know, the potential carcinogenicity, you could just let us know that and say, well, we should probably look at exposure before we spend a lot of time on it, to see if it's relevant or something like that.

COMMITTEE MEMBER HAMBURG: Well, how does that fit into our ranking. I mean, I'm trying to work with the program here.

ACTING DIRECTOR ALEXEEFF: Oh, I would rank it as high, if that's what I thought I heard you say. And then with a caveat of check exposure, you know, to be sure.

COMMITTEE MEMBER HAMBURG: Yeah, clinical relevance, yeah.

COMMITTEE MEMBER LANDOLPH: Tom.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. I was looking at n-methyl-n-nitroso-1-dodecanamine. And I had a little concern there, because it causes pancreatic islet cell tumors, which are rare. And it also causes increases in angiosarcoma of the liver, which also is very rare. So I think I would pull that one maybe forward in that list, based on those rare tumors.

CHAIRPERSON MACK: So does that give us answers. We're going to call all of them high and then deal with them individually.

COMMITTEE MEMBER LANDOLPH: Yeah, because the rest of them, they're all organ specific. All the nitrosamines are like that. They're very similar except they vary a little bit in the organ. So I think they're similar.

CHAIRPERSON MACK: Which brings to us n-nitroso-n-methylaniline.

COMMITTEE MEMBER HAMBURG: That's me.

CHAIRPERSON MACK: And Sol.

COMMITTEE MEMBER HAMBURG: Let me just review what I wrote.

Well, I would reiterate what I said with some of these other compounds. The data is very old. I don't know that there's a significant relevance to evaluating this right now as compared, so I would put it low.

CHAIRPERSON MACK: That's what I put it also.

COMMITTEE MEMBER EASTMOND: I put it high.

(Laughter.)

COMMITTEE MEMBER HAMBURG: Well, but we knew that as soon as I said low.

(Laughter.)

CHAIRPERSON MACK: We sort of assumed that.

(Laughter.)

COMMITTEE MEMBER EASTMOND: Well, I --

CHAIRPERSON MACK: Make a case.

COMMITTEE MEMBER EASTMOND: Okay. You've got 3 studies in rats. All of them gave malignant esophageal tumors. Three separate studies gave you the same tumor type. And then in hamsters, there was increase in liver tumors and spleen hemangiosarcomas.

So for me the animal data is actually much stronger than many. This is found in rubber manufacturing and found in smoked meat. Certainly exposures are potentially there. For me, this would be at least a medium and probably a high.

COMMITTEE MEMBER LANDOLPH: Yeah. Tom, I would go along with Dave on that. The nitrosamines are very strong carcinogens.

CHAIRPERSON MACK: Okay. So we go along with high?

COMMITTEE MEMBER LANDOLPH: Yeah.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: Well, I'll go to a medium.

CHAIRPERSON MACK: All right. Let's call it a medium.

COMMITTEE MEMBER EASTMOND: All right. That's fine.

CHAIRPERSON MACK: And let me make sure there's nobody who wants to speak to that. No. Oh, yes there is.

Okay. We're going to NMP now. And that's Joe and I.

And I called it medium.

COMMITTEE MEMBER LANDOLPH: And I gave it a low, based on weak genotoxicity, weak animal studies only. One out of 3 was positive. And there's no epidemiology studies as all on it.

It's an industrial solvent, paint stripper, petroleum refining, industrial refining.

CHAIRPERSON MACK: It's a household -- it's a contaminant -- it's a component of household solvents too. I mean, it's wood -- paint strippers and things, and that's the basis on which I thought maybe it ought to be looked at.

COMMITTEE MEMBER LANDOLPH: Okay.

CHAIRPERSON MACK: Can I talk you into a medium?

COMMITTEE MEMBER LANDOLPH: Yeah. It's weak as a carcinogen, but based on household use, that's fine.

CHAIRPERSON MACK: Okay. Let's go for medium. And we have somebody who -- Kathleen Roberts wanted to speak. She doesn't like a medium.

MS. ROBERTS: I don't. I'm sorry.

I would reiterate that the -- there were 3 cancerous animal -- there were no epidemiology studies mentioned, 3 animal cancer studies mentioned. Only one showed positive effects. That was a dietary study in mice for liver tumors. Those were only seen at very high dose levels over a thousand mgs per kg. And we -- the belief is that that's a consequence of enzyme induction.

Of the one positive in vitro genotox result, that actually was considered invalid by OECD when it did its international assessment of this chemical back in 2007. And certainly far outweighed by the 11 negative in vitro, in vivo studies that are valid and available on this.

As far as the consumer products, it is in some consumer products, but at low concentrations, and therefore we think a low priority is probably more appropriate.

CHAIRPERSON MACK: What's a low concentration?

MS. ROBERTS: I'm sorry?

CHAIRPERSON MACK: What's a low concentration?

MS. ROBERTS: I don't have that data, but I can certainly get it.

CHAIRPERSON MACK: But it's in paint strippers, is it not?

MS. ROBERTS: It is in some paint strippers, yes.

CHAIRPERSON MACK: And since it's household stuff, and it's a scary household stuff to a lot of people, it might be -- make them much happier to know that nobody thinks it's carcinogenic from the State of California.

MS. ROBERTS: Yes, sir. I suppose that is your opinion. I would also point out that there's a lot of high and mediums on this list right now. And if we're looking for truly a prioritization process, some will have to go to the low priority.

CHAIRPERSON MACK: Okay. Your point is well taken.

Shall we go with low?

COMMITTEE MEMBER LANDOLPH: Okay. That's where I started.

CHAIRPERSON MACK: Okay.

COMMITTEE MEMBER HAMBURG: I'm okay with low.

COMMITTEE MEMBER EASTMOND: Low.

CHAIRPERSON MACK: You called it high?

COMMITTEE MEMBER EASTMOND: No. Did we go to low?

CHAIRPERSON MACK: Yeah.

COMMITTEE MEMBER EASTMOND: Okay.

CHAIRPERSON MACK: 6-nitrobenzimidazole.

COMMITTEE MEMBER HUNTER: I was one of the two on that one. I gave that one a low. It is compound used as a anti-fogging agent in photographic developing solutions, so there's going to be some occupational exposure. But the animal data was pretty sparse, limited to one study. So I didn't feel it met the priority of being low.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: I agree.

CHAIRPERSON MACK: So this one is a low. Does anybody argue with that?

COMMITTEE MEMBER EASTMOND: I even agree with that one.

CHAIRPERSON MACK: My God.

(Laughter.)

CHAIRPERSON MACK: Not only did he agree with it, but he only chose one level.

COMMITTEE MEMBER EASTMOND: Not on my notes though.

(Laughter.)

CHAIRPERSON MACK: Pentachloronitrobenzene.

COMMITTEE MEMBER HAMBURG: This is of concern to broccoli eaters and golfers. There is some animal data to suggest that there's a malignancy associated with it. And there is some genotoxicity data. However, I think it's relatively of low importance to the citizens of the State of California, and I would keep it as low.

CHAIRPERSON MACK: And Joe?

COMMITTEE MEMBER LANDOLPH: Yeah. I completely agree. Not much genetox data. There's some animal carcinogenicity data. But I think it's kind of a limited use thing, so I would go with low on this too.

CHAIRPERSON MACK: Next, we go with pimecrolimus. We're not dealing with tacrolimus. It sounds like characters out of a Shakespeare. Pimecrolimus is going to be me and Anna.

COMMITTEE MEMBER WU: I made it medium.

CHAIRPERSON MACK: And I called it medium also. My God.

(Laughter.)

CHAIRPERSON MACK: That's regression to the mean, if I ever heard it.

(Laughter.)

CHAIRPERSON MACK: Does anybody disagree with that?

COMMITTEE MEMBER HAMBURG: I want to ask you a

question about this particular agent. When we are to consider chemical carcinogenesis, this agent, like tacrolimus, is really immunosuppressive. And you may get secondary malignancies related to that. It may not be a direct carcinogen.

Are we to include that in our consideration or is it really strict chemical carcinogenesis with induction of changes in DNA, et cetera.

CHAIRPERSON MACK: Obviously, that's a logical option, but as an empiricist and an epidemiologist, I would say somebody can always come up with a mechanism. I'm interested in the association and whether it's causal.

COMMITTEE MEMBER HAMBURG: But the mandate of Prop 65?

CHAIRPERSON MACK: Yeah, and Prop 65 doesn't specify mechanism.

COMMITTEE MEMBER HAMBURG: Doesn't specify. Okay.

CHAIRPERSON MACK: Pivalolactone.

COMMITTEE MEMBER HUNTER: I was one of the two. I gave it a medium.

CHAIRPERSON MACK: And the other one was --

COMMITTEE MEMBER HAMBURG: And I gave it a low. Poor data or old data, not that clinically relevant as compared to their other agents, so I think we should

prioritize this in a low level.

COMMITTEE MEMBER HUNTER: I could live with that.

CHAIRPERSON MACK: Okay. Low, it is.

Pyraflufen ethyl.

COMMITTEE MEMBER HUNTER: I also am one of those. I have that one a low.

COMMITTEE MEMBER HAMBURG: I gave that one a low also, similar reasons.

CHAIRPERSON MACK: Okay. Raloxifen and its salts. I gave that one a low also. And who was the other person?

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah. I gave it a medium. It's completely negative in the genetox assays. Positive in 2 out 2 animal carcinogenicity assays. Lowers the risk of endometrial cancers, so it's good for that, compared to general population tamoxifen users. So I said low, but, you know, I could be --

CHAIRPERSON MACK: I said low also.

COMMITTEE MEMBER LANDOLPH: I said medium initially, but I could be moved to low.

CHAIRPERSON MACK: Okay. Let's go for low.

COMMITTEE MEMBER HAMBURG: Sorry. I would argue this one a little differently.

CHAIRPERSON MACK: Okay.

COMMITTEE MEMBER HAMBURG: Only in the sense from a clinical standpoint, we often use it similar to tamoxifen, for better or for worse. And since we listed tamoxifen as a Prop 65 carcinogen, and since the IARC listed it as a Group 1 agent, similarly, I think we're obligated to list a similar class of drugs.

CHAIRPERSON MACK: We're certainly obligated to look at it at some time.

COMMITTEE MEMBER HAMBURG: Look at it, yes.

CHAIRPERSON MACK: My understanding was that it is not nearly as strong as --

COMMITTEE MEMBER HAMBURG: It is not as strong, definitely.

CHAIRPERSON MACK: -- as a estrogen as tamoxifen is

COMMITTEE MEMBER HAMBURG: Absolutely true.

CHAIRPERSON MACK: So -- and since -- even tamoxifen, while it's widely used -- you'll recall our difficulty with that --

COMMITTEE MEMBER HAMBURG: Right.

CHAIRPERSON MACK: -- because of all of the eminent oncologists who came in to insist that we shouldn't even be talking about it. Of course, we should be talking about it, but again in the context, because it's not that strong, I would call it a low, but I don't

mind going medium if everybody else thinks so. Do you prefer medium.

COMMITTEE MEMBER HAMBURG: Medium I would prefer.

CHAIRPERSON MACK: Okay.

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, that's fine.

CHAIRPERSON MACK: Okay. Medium it is.

Stavudine. That's Joe.

COMMITTEE MEMBER LANDOLPH: I said medium on this one. Some genotoxicity, carcinogenicity and 2 experiments in rats and mice, one each. Multiple tumors in males and females. No epidemiology studies. It's a anti-HIV agent. I don't want to push this one too hard, because I don't want to get put in the position of wrecking good drugs that are useful to the public, so that's why I gave it a medium.

CHAIRPERSON MACK: You are the only one who reviewed. What do you think, Sol?

COMMITTEE MEMBER HAMBURG: Either medium or low. I wouldn't put it high, so medium is fine.

CHAIRPERSON MACK: Let's go for medium.

COMMITTEE MEMBER EASTMOND: Let me just say I put this as high, but tempered, because it's a drug and very useful. So it would go to medium, but it's kind of a screaming positive in rats. I mean, there's all sorts of

tumors that are showing up in these animals. And it's positive in mice. So, you know, it's one of these where I think you do it because of specialized usage, rather than actual data.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree with that.

CHAIRPERSON MACK: So we conclude medium.

COMMITTEE MEMBER EASTMOND: Yeah, let's go medium.

CHAIRPERSON MACK: Topoisomerase II inhibitors.

COMMITTEE MEMBER WU: I had it.

COMMITTEE MEMBER HUNTER: No. I think you have to go to Thiophanate.

CHAIRPERSON MACK: Oh, I'm sorry. I missed one. Thiophanate methyl.

COMMITTEE MEMBER HUNTER: Yea. I'm one of the two. I gave that one a medium.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: I'm the other one of the two. I gave it a medium too.

CHAIRPERSON MACK: Okay. That's easy.

Now, topoisomerase II inhibitors

COMMITTEE MEMBER WU: I gave it a medium.

CHAIRPERSON MACK: And she is the only reviewer. And there are no public comments.

COMMITTEE MEMBER EASTMOND: I can comment on this one.

Again, this is a class, and I feel like these should be reviewed individually. The -- it's kind of indicated in the footnote, etoposide has currently -- has been classified as a Group 2 carcinogen by IARC.

Teniposide has been classified as a 2A, so those would be going forward on it through the authoritative body listing.

The other ones that are mentioned here, and I should say they're different types of Topo II inhibitors. These are all, what are called, Topo II poisons that you have listed here, which are probably certainly seen historically as the most serious, and they're the ones who are most actively used clinically, but there are quite a few other Topo II poisons out there. And I think they need to be classified individually.

The 2 that you have here mitoxantrone and epirubicin I think there's additional data on these. Whether it would be sufficient to list, I'm not sure. But the other thing on these Topo II inhibitors is they're going to be very different, because the animal studies are really not very helpful. I mean, you really come down to human epidemiological studies combined with mechanistic information in order to make a decision will probably be

driving them today.

So I would probably put them as medium, given simply the idea that these are valuable for clinical use. And they're used in the anti-cancer drugs, so there's -- they're being used for a very definite reason.

COMMITTEE MEMBER HAMBURG: Yeah, I would concur. We use all of these agents on a daily basis. They're felt to be carcinogenic in general. Certainly, if you look at any of the package inserts, you'll see that these are carcinogenic.

I don't know whether we have to review the data though in order to list it. I think -- Dr. Mack, I mean --

CHAIRPERSON MACK: I think medium would be a reasonable conclusion. You're okay with that, Anna?

COMMITTEE MEMBER WU: Yes. That's what I said.

CHAIRPERSON MACK: That's what you said.

Okay. Triazole antifungal agents. And that's David again and it's another group.

DR. SANDY: It is another group. And you have the option -- well, we'd like you to rank the group or any individual triazoles.

COMMITTEE MEMBER EASTMOND: All right. Mine. This is a series of agents, many of which induce liver tumors in male and female mice, but are largely inactive

in rats. The mouse liver cancer could be related to halogen substituents, which are found on the molecules.

The results of genotoxicity study are mixed. Most negative, but several are certainly genotoxic in vivo. It's been proposed that these act through induction inhibition of cytochrome P450 monooxygenase enzymes, oxidative stress, altered cell signaling, proliferation.

As I indicated before, evaluating it as a class is difficult. I think ultimately it will have to come down to an individual ranking. The public comments indicated they act through a number of different mechanisms, so they shouldn't be classified together.

I guess then my rankings on this would be probably medium to medium-high for the triadimefon; medium for fenbuconazole; and depending on how you want to go you could go with propiconazole, maybe medium, the others would be low. That's kind of my rankings.

CHAIRPERSON MACK: So let's rank the group as medium.

COMMITTEE MEMBER EASTMOND: Yeah. That's probably fine.

CHAIRPERSON MACK: And Richard Peffer. You unhappy with medium?

DR. PEFFER: Yeah. I think I just heard you say that for the whole group you're going to categorize them

together as medium for prioritization.

CHAIRPERSON MACK: Yes.

DR. PEFFER: I was going to speak to the idea that it's not appropriate to consider them all as a class from the standpoint of they don't necessarily have a common mechanism of action. And I think I see nodding heads, and you all agree with that.

From the standpoint of some of the individual chemicals that are on the list there. There's one on there, etaconazole, that's in the list that has no registrations anywhere and never did. So that one probably could save you some work. You should strike that one from the list. There's no exposure.

And there's -- the others I think I heard what you mentioned was likely medium to high for 3 of the listed chemicals and then low for the others.

COMMITTEE MEMBER EASTMOND: Well, there was only -- only one was sort of this -- the others would be medium. The three I listed would be medium and all the rest would be low. And even the propiconazole could actually go to low. It depends how you interpret the mechanistic data. There's been a ton of mechanistic data generated on that. And it depends how you interpret that data.

I don't think it's -- it certainly is not a high,

high priority from my point of view, but --

DR. PEFFER: Yeah. And I would speak to propiconazole as well. Syngenta, my company, is the primary registrant for that. And EPA has done a fair amount of studying on propiconazole and published on it. And the one positive mutagenicity finding that's shown up in the literature was big blue mouse assay that EPA did.

But actually a further review of that's been done. It's recently been published in Environmental Molecular Mutagenesis. And it looks like that study had some analytical flaws in that they were comparing two different control groups and two different sets of experiments across time. And the propiconazole group was right within the range of normal historical control.

So it's likely not positive in that assay. And I would agree with the rest of its database for mutagenicity.

CHAIRPERSON MACK: Okay. So I think with calling them medium, they will be evaluated separately when the time comes. And all of that will be pertinent information.

DR. PEFFER: Okay.

COMMITTEE MEMBER EASTMOND: I mean, I guess the way I would recommend looking at this is to put them medium as a class. But as you get into that, very quickly

you'll see that some of these should actually be lower, and we -- you know, you would put them as low priority as you get into it.

CHAIRPERSON MACK: Okay. 2,4,6-T, 2,4,6-Trimethylaniline and its Salts.

COMMITTEE MEMBER HUNTER: I'm one of the two.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: Yeah, I gave it a medium.

CHAIRPERSON MACK: And Anna?

COMMITTEE MEMBER WU: I gave it a low-medium. So but, I mean, I can be swayed to the medium.

CHAIRPERSON MACK: Could we hold off on this for a second, because I neglected Dr. Papineni wants to comment on the one of the triazoles.

DR. PAPINENI: We concur if it's a medium.

CHAIRPERSON MACK: You're happy with medium.

DR. PAPINENI: As a group.

CHAIRPERSON MACK: Go ahead. So Anna.

COMMITTEE MEMBER HUNTER: She said low-medium.

COMMITTEE MEMBER WU: Yeah.

COMMITTEE MEMBER HUNTER: I said medium.

CHAIRPERSON MACK: You say medium too. So we're happy with medium, everybody?

COMMITTEE MEMBER LANDOLPH: Yeah.

CHAIRPERSON MACK: Okay. And the last one is a tris(2-ethylhexyl)phosphate. That's David and me. And I gave it a medium. I did it based on what it said about animals.

COMMITTEE MEMBER EASTMOND: I was medium to low on this. Low was kind of my stronger leaning, but I'd go to medium. That's fine.

CHAIRPERSON MACK: Okay. Low and behold comment -- oh, there's a comment on this one.

Yes. Dr. Sutton. You get the last word or the penultimate word anyway.

COMMITTEE MEMBER EASTMOND: Another flame retardant.

DR. SUTTON: Yeah. Well, medium is decent. We might urge you to go a bit higher, because it's a flame retardant, so we have higher exposures in this state. We find it in dust, so you got the young children's exposures again. So you could consider that -- consider maybe edging toward high.

CHAIRPERSON MACK: But you don't have that in your sofa.

DR. SUTTON: No, just the other one.

CHAIRPERSON MACK: Well, it looks like we've done it. Call that a meeting.

ACTING DIRECTOR ALEXEEFF: Are you asking me?

Ask the group.

CHAIRPERSON MACK: Do we have any words we have to use, lawyer?

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't think so. You can just close the meeting. But I think that usually Dr. Alexeeff would give a summary of the meeting before you close.

CHAIRPERSON MACK: Yes. I was just making sure we hadn't erred in our deliberation methodology.

Dr. Alexeeff.

ACTING DIRECTOR ALEXEEFF: Well, it's 4:30, and the court reporter is still with us.

CHAIRPERSON MACK: I think we should give him a big round of applause.

(Applause.)

ACTING DIRECTOR Alexeeff: Well, before I summarize the meeting, I really want to thank Dr. Mack and members of the CIC, all the members of the public that testified or looking on line and submitted public comments and such.

We had originally planned this as a 2-day meeting. We've completed it in 1 day. I think, at the same time, we did due diligence in terms of considering all of the issues. So, you know, I really compliment the Committee and everyone who participated in this. And I

also want to thank the staff for their preparation and their presentations. And I take it that that helped the Committee move to a speedy decision on these items.

And, let's see, I don't know if originally, Dr. Mack, before -- when we were discussing the procedures item, I had left a comment that staff could -- that the members could comment on whether there was anything they wanted to mention about the information that was provided to them, any, you know, improvements or suggestions or things like that. I don't know if there are any. I'm not fishing for compliments. I'm simply just -- since we're all here, I thought I'd just give the opportunity if there were any comments that members want to make.

CHAIRPERSON MACK: Well, actually I think the staff did a terrific job. I do, however, have one, somewhat negative, comment. I would like members of OEHHA to see if they can find the phone number for OEHHA from 411. I have tried on Friday when I realized that I had not received a couple of the papers that I should have received, I tried for a full half hour to try and get -- and this was Friday. I was home. I didn't have a number.

None of the pieces of stationary that have your heading that says George Alexeeff on top have a phone number. There's no Email address. There's no way to contact you if one is not in the office with previously

available information.

COMMITTEE MEMBER HAMBURG: This is a secret organization.

(Laughter.)

CHAIRPERSON MACK: It seems to be a far more secretive organization than it really needs to be. So I would beg you to put the number on the letters or provide the number to -- call 411 and try and see what happens. I couldn't even get EPA. EPA was basically, "I'm not at my phone right now. I'll come back and call you later".

(Laughter.)

CHAIRPERSON MACK: So that's my only negative.

ACTING DIRECTOR ALEXEEFF: I think we can rectify that situation.

COMMITTEE MEMBER EASTMOND: If I can comment. Having gone through this prioritization, the summaries that we received this time were far more helpful than in the early stages, which we'd -- when we receive nothing at all but just -- so it's been actually an improvement, I guess, now that we're at the end of it. Hopefully, for the next series it will continue this way.

CHAIRPERSON MACK: I think there were really very good. And, in fact, more voluminous than necessary in some instances, but very appreciative, very much appreciated.

ACTING DIRECTOR ALEXEEFF: I do want to -- I do really want to compliment Martha Sandy and her staff on the prioritization. And the reason is because we've completed, you know, prioritization of 400 chemicals, which was -- when we started this early on, and I think a suggestion from Dr. Landolph at the time was suggesting let's look at the Epi data. And we had, you know, thoughts of how we would proceed on this. And we've kind of marched through.

And having worked with Martha and her staff, I know that I discussed each chemical with the staff on the prioritization. And I know that Dr. Sandy discussed each chemical with her their staff several times. So, I mean, they spent, you know -- for the ones you did not see, they spent a lot of time checking to see what information was there. So it was very hercu -- anyway, it was a great effort on their part I just wanted to say.

So, you know, although you've seen, what is it, close to 100 chemicals, there was an equal amount of work on the other 300 that you didn't see. I just want to let you know that. And I really appreciate their work. So I wanted to make that comment.

So I think I will go ahead and summarize the decisions here.

So the Committee considered 2 chemicals for

potential listing today. The first chemical, the Committee concluded that tris(1,3-dichloro-2-propyl) phosphate has been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer.

For the second chemical, the Committee concluded that fluoride and its salts has not been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer.

And then I want to thank the Committee for giving us advice on prioritizing chemicals to bring to the committee. And so there were 39, 38 chemicals?

DR. SANDY: Thirty-nine.

ACTING DIRECTOR ALEXEEFF: Thirty-nine. Well, plus the groups. And so I thought I would just mention which ones were classified first as high, so -- for us to consider.

Acetaminophen, butyl benzyl phthalate, C.I. disperse yellow 3, coumarin, dibenzanthracenes and dibenz[a,c]anthracene, 2,4-dichlorophenoxyacetic acid its salts and esters, n-methyl-n-nitroso-1-alkylamines and some specific ones, depending upon their exposure.

That's it, right?

And then a number of chemicals were classified as medium. Abacavir and its salts, bisphenol A, butylated

hydroxytoluene, chloroalkyl ethers, clodinafop-propargyl, dapsone, 3,3'-dichlorobenzidine, DBZ-based compounds metabolized to 3,3'DBZ, dinitroaniline pesticides, including prodiamine and trifluralin, entecavir, flonicamid, fluazinam, mixtures containing pentachloro -- I'm sorry, mixtures containing pentabromochlorocyclohexane, n-nitroso-n-methylaniline, pimecrolimus, raloxifen, stavudine, thiophanate methyl, and the top 2 inhibitors, triazole antifungal agents. Although those should be looked at individually, 2,4,6-trimethylaniline and its salts, and tris (2-Ethylhexyl) phosphate.

So I want to thank you. Is there anything else that I should consider from any comments from staff?

CHIEF COUNSEL MONAHAN-CUMMINGS: Just one follow-up question. When we had our earlier discussion about procedures, we had left the question open whether or not the five minutes with the timer was -- you thought was the useful approach or not, that you could advise the Chair concerning how you felt that went.

ACTING DIRECTOR ALEXEEFF: And the question was whether or not -- how they felt about the five-minute time limit that had been utilized today and such, I think that was the question.

CHAIRPERSON MACK: Oh, I think it went very well

today. I can't -- in fact, I wasn't -- I certainly wasn't very strict, not as strict as I would have wished to have been.

(Laughter.)

CHAIRPERSON MACK: But I think the information that was provided by the people who spoke was very useful and I thought it went very well. I'd like to congratulate them all actually on being succinct and informative. We've had some past experience with the opposite of that. And nobody here did that today and it was great. And I think it helps us -- it helps us to be succinct and informative, because we've looked at what you've submitted usually.

Yes, Joe.

COMMITTEE MEMBER LANDOLPH: Just on another issue. You know, quite awhile ago we had random prioritization, which I always rationally revolted against. I hated that, because it was giving us dumb chemicals to study, which was wasting our time. And then we went to the prioritization meetings, the subcommittee with George and myself and Lauren and Martha. I think that cut through a lot. I think we're getting very good chemicals now.

And Chief Counsel Carol Monahan-Cummings knows that we have received criticism about wasting quote

unquote time on doing that prioritization. And my comment is, I think that criticism is misguided, at best. So I think the prioritization process is working very well. We're getting serious chemicals to deal with now.

They all have -- you know, many of them -- some of them have Epi data, most of them have strong animal data. I think it's working very well.

CHAIRPERSON MACK: I would add that not just serious chemicals, but they're chemicals people are worried about. And that's perhaps even more important.

DR. LAWYER: One more from the public on the timing.

It won't take like 10 minutes.

CHAIRPERSON MACK: You won't even get five minutes.

DR. LAWYER: Arthur Lawyer, Technology Sciences Group, downtown Davis. My only comment, and maybe it's what the staff has in mind, but for the time constraints, the five minutes or if there's ever a time where you think there might be one minute. It would be very beneficial for those that come from out of town and prepare, think they should -- should I prepare slides, should I not, you know, especially for the scientists that come all this way to know the restrictions long in advance would be very helpful, because a lot of people in the audience had to do

a lot of rearranging of their life today. So I'd certainly appreciate it.

Thanks.

CHAIRPERSON MACK: Nobody could disagree with that.

DR. LAWYER: And it was short.

ACTING DIRECTOR ALEXEEFF: Well, I want to thank everyone again. And I close the meeting right now.

Thank you.

(Thereupon the Carcinogen Identification Committee adjourned at 4:43 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 26th day of October, 2011.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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