

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

JOE SERNA JR.
CAL/EPA HEADQUARTERS BUILDING
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SIERRA HEARING ROOM
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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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1 left.

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

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

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

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

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

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

1 David Griffin -- Geffen Medical School.

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

5 MS. OSHITA: Sure. Good morning. We have --
6 OEHHA has administratively added 21 chemicals to the Prop
7 65 list since the Carcinogen Identification Committee met
8 last September 2010. Eighteen were listed as known to
9 cause cancer, and three were listed as known to cause
10 reproductive toxicity.

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

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

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

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

1 these chemicals and they are currently under review.

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

7 DR. SANDY: Etoposide.

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

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

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

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

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

7 Thank you.

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

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

12 (Laughter.)

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

16 Carol.

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

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

20 ACTING DIRECTOR ALEXEEFF: Can you move the
21 microphone

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

1 members are all parties to that case.

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

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

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

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

12 The last case I was going to mention is a new one
13 that was filed since your last meeting. And that was
14 filed on behalf of a number of beverage organizations.
15 And it has to do with the recent listing of the chemical
16 4-MEI, 4-methylimidazole. And we listed that
17 administratively, and there are challenging our ability to
18 do that. And that is in the trial court right now. It's
19 been briefed and argued. And we're just waiting for an
20 opinion from the court. There's a fair likelihood that
21 the case will also be appealed.

22 Do you have any questions on any of those cases?

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

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

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

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

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

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

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

17 Dave.

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

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

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

1 ACTING CHAIRPERSON LANDOLPH: Any other questions
2 on that issue?

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

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

14 (Thereupon an overhead presentation was
15 Presented as follows.)

16 ACTING DIRECTOR ALEXEEFF: Okay. The item we're
17 discussing now, Procedures For Presentation of Public
18 Comments. This item had its origin in a letter that Dr.
19 Denton received from several non-governmental
20 organizations, or NGOs. And she received it on July 22nd
21 2009. And that was the week after the Developmental and
22 Reproductive Toxicity Committee meeting in 2009. The
23 letter contained several specific criticisms of the way
24 that the meeting was held, and OEHHA met with Dr. Burk,
25 the chair of the DART Committee, and met with

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

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

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

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

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

1 procedures.

2 Thank you.

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

6 (Thereupon and overhead presentation was
7 presented as follows.)

8 CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.

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

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

24 Next slide.

25 --o0o--

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

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

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

20 Next slide.

21 --o0o--

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

1 slide?

2 Yes.

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

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

14 COMMITTEE MEMBER HAMBURG: So far so good.

15 (Laughter.)

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

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

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

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

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

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

1 discussion, you know, just for content.

2 And lastly, the -- next slide.

3 --o0o--

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

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

23 --o0o--

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

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

4 Any questions on this?

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

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

16 ACTING CHAIRPERSON LANDOLPH: Dave.

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

1 they were sequential.

2 CHIEF COUNSEL MONAHAN-CUMMINGS: Right.

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

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

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

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

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

5 ACTING CHAIRPERSON LANDOLPH: Yes.

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

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

22 ACTING CHAIRPERSON LANDOLPH: Other comments from
23 the Committee?

24 Sol, Darryl, Anna?

25 No.

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

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

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

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

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

22 COMMITTEE MEMBER EASTMOND: I would agree with
23 that.

24 ACTING CHAIRPERSON LANDOLPH: Other comments from
25 the Committee?

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

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

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

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

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

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

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

17 ACTING CHAIRPERSON LANDOLPH: Anybody else?
18 Dave.

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

22 ACTING CHAIRPERSON LANDOLPH: Darryl.

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

25 ACTING CHAIRPERSON LANDOLPH: Anna.

1 COMMITTEE MEMBER WU: I'm fine.

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

7 Okay

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

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

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

1 way of voting over the other?

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

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

8 Everybody seems to be reasonably satisfied.

9 Okay. So shall we move to our break --

10 (Laughter.)

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

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

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

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

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

25 There are times when we have, as members of the

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

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

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

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

1 your comments are.

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

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

13 ACTING CHAIRPERSON LANDOLPH: Dave.

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

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

1 point across efficiently.

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

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

13 No.

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

24 Any other discussion on that issue?

25 Please.

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

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

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

21 Thank you.

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

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

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

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

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

13 Thank you.

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

17 Thank you.

18 (Thereupon a recess was taken.)

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

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

25 CHAIRPERSON MACK: It's not working?

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

3 CHAIRPERSON MACK: Is that better?

4 MEMBERS OF THE AUDIENCE: No.

5 CHAIRPERSON MACK: No, not better.

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

8 CHAIRPERSON MACK: All right. Now is that
9 better?

10 MEMBERS OF THE AUDIENCE: Yes.

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

13 DR. SANDY: The TSA.

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

19 (Laughter.)

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

23 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

22 Do you have any questions on that?

23 All right.

24 COMMITTEE MEMBER EASTMOND: Never mind.

25 CHAIRPERSON MACK: Change your mind?

1 COMMITTEE MEMBER EASTMOND: Yes.

2 CHAIRPERSON MACK: Okay.

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

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

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

14 --o0o--

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

23 --o0o--

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

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

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

8 --o0o--

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

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

24 --o0o--

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

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

6 However, the results of the studies were not
7 published in the open literature until the year 2000 by
8 Freudenthal and Henrich. So briefly these studies were
9 conducted in male and female Sprague-Dawley rats. The
10 rats received TDCPP in their diets for two years at
11 concentrations that resulted in doses of 0, 5, 20, or 80
12 milligrams per kilogram day. The dose groups consisted of
13 60 animals of each sex per dose, 10 of which were
14 sacrificed after 12 months of exposure.

15 --o0o--

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

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

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

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

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

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

13 --o0o--

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

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

1 --o0o--

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

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

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

16 --o0o--

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

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

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

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

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

14 --o0o--

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

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

25 --o0o--

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

6 --o0o--

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

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

16 Other metabolites have included
17 1,3-dichloropropanol or 1,3-DCP; 3-monochloropropanediol
18 3-MCPD, and the monoester has also been identified as a
19 metabolite and the structures are all presented on this
20 slide.

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

1 the hazard identification documents last year.

2 --o0o--

3 DR. FAUST: 1,3-DCP and 3-MCPD undergo metabolic
4 processes that can ultimately result in the formation of
5 carbon dioxide cystein derivative oxalic acid, as well as
6 1,3-dichloroacetone.

7 --o0o--

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

12 --o0o--

13 DR. FAUST: So on the next slide we've put a
14 tumor comparison for some of these metabolites in terms of
15 the carcinogenic endpoints. So as we've seen TDCPP
16 produces tumors of the liver, kidney, and testes in rats.
17 1,3-DCP also produces liver and kidney tumors in rats as
18 well as thyroid tumors. Epichlorohydrin has been shown to
19 cause forestomach and nasal cavity tumors. And glycidol
20 causes tumors at multiple sites in rats and mice. And
21 each of these chemicals is on the Proposition 65 list.

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

25 --o0o--

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

9 --o0o--

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

17 --o0o--

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

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

1 well as benign kidney tumors.

2 --o0o--

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

10 So several metabolites of concern for
11 carcinogenicity have been identified. And these include
12 1,3-DCP and 3-MCPD, both recently listed as causing
13 cancer. These compounds are on a metabolic path that also
14 leads to the formation of epichlorohydrin and glycidol,
15 both of which are also listed as carcinogens.

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

19 So that concludes the presentation.

20 CHAIRPERSON MACK: Thank you. John and Laura.

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

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

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

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

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

14 (Thereupon an overhead presentation was
15 presented as follows.

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

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

23 DR. O'MALLEY: I'm sorry.

24 CHAIRPERSON MACK: David.

25 COMMITTEE MEMBER EASTMOND: I have a question.

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

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

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

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

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

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

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

6 Okay. Please continue.

7 COMMITTEE MEMBER EASTMOND: Thanks, John

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

10 CHAIRPERSON MACK: Did you have a comment?

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

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

1 effects on the nutrition and health of the test animals.

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

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

14 CHAIRPERSON MACK: Okay. Anymore questions of
15 staff?

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

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

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

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

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

4 Next slide.

5 --o0o--

6 DR. O'MALLEY: Just a summary of some of the
7 information that has already been discussed from your
8 staff. There have been previous assessments of TDCPP by
9 authorities. None have concluded that there is clear
10 evidence of carcinogenicity for TDCP. And as mentioned by
11 your legal staff, there is a process in order to assess
12 data in evaluating material for listing under Proposition
13 65.

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

20 Next slide.

21 --o0o--

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

1 evidence.

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

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

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

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

25 In structure activity relationships, TDCPP,

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

5 Thank you for changing the slide to the next one.

6 --o0o--

7 DR. O'MALLEY: To the previous slide.

8 Can I have the previous -- there we go.

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

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

20 Next slide.

21 --o0o--

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

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

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

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

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

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

1 Again going back to the CIC -- next slide.

2 --o0o--

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

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

12 Next slide.

13 --o0o--

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

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

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

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

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

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

16 CHAIRPERSON MACK: Two more slides.

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

18 --o0o--

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

1 water solubility of about 18 milligrams for liter. TCP
2 1,080 milligrams per liter, TCEP 7,820 milligrams per
3 liter. This will make things a lot different on how the
4 body sees this material.

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

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

19 Thank you.

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

21 The next speaker will be Andy Wang.

22 (Thereupon an overhead presentation was
23 Presented as follows.)

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

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

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

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

12 Next slide.

13 --o0o--

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

21 Large margins of safety, the ratio is more than
22 2,000 has been concluded by the European Union. And the
23 risk assessment has included all exposure routes.

24 Next slide.

25 --o0o--

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

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

14 Next slide, please.

15 --o0o--

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

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

1 2,000 times higher than the reference dose. Therefore,
2 the European Authority has concluded that there is no
3 concern for consumers from exposure to TDCP treated foam
4 used in furniture, and in the automotive industry.

5 Next slide.

6 --o0o--

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

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

11 DR. WANG: Okay. Next slide.

12 --o0o--

13 DR. WANG: Inhalation. EU risk assessment took
14 the worst case scenario and used a 3.8 micrograms per
15 cubic meter, which represents a 20-fold higher
16 concentration than what has actually been measured. For
17 the air concentration of 3.8, a daily intake inhalation is
18 0.0011, which I just showed.

19 Next slide.

20 --o0o--

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

1 daily dermal intake was assumed equal to the inhalation
2 exposure.

3 Next slide.

4 --o0o--

5 DR. WANG: In addition to the intake of TDCP by
6 inhalation or skin contact, young children may ingest dust
7 containing TDCP. The European authorities used a value of
8 12 milligrams per kilo dust to calculate the worst case
9 scenario. And, the 0.002 milligrams per kilo body weight
10 has been concluded.

11 Next slide.

12 --o0o--

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

18 Next slide.

19 --o0o--

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

25 CHAIRPERSON MACK: You're also a minute and a

1 half now over. If you can

2 DR. WANG: Just one more.

3 CHAIRPERSON MACK: If you can --

4 DR. WANG: Just one more statement.

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

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

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

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

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

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

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

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

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

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

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

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

6 DR. HEIMBACH: Thank you very much.

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

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

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

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

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

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

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

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

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

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

10 Thanks.

11 CHAIRPERSON MACK: Thank you, Dr. Sutton.

12 The next speaker is Sarah Janssen.

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

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

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

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

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

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

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

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

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

7 Thank you.

8 CHAIRPERSON MACK: Thank you, Dr. Janssen.

9 And finally Arlene Blum from UC Berkeley.

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

18 We, at that time, found TDCPP to be weakly
19 positive in the Ames test and the metabolite
20 1,3-dichloropropane to be strongly positive. And that
21 chemical has been recognized under Proposition 65 as a
22 carcinogen.

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

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

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

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

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

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

3 And just to say in our study of baby products, we
4 found TDCPP at high levels in most baby products we
5 studied, at least three to five percent of most types of
6 baby products. So there is a potential for 24-hour a day
7 exposure to infants. They're in mattresses, baby
8 positioners, car seats, changing tables, at levels up to
9 12.5 percent.

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

13 Thank you.

14 CHAIRPERSON MACK: Thank you, Dr. Blum.

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

17 CHAIRPERSON MACK: You didn't your card in.

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

20 Back to the tox again.

21 ACTING DIRECTOR ALEXEEFF: Introduce yourself.

22 DR. LAWYER: Thank you, George.

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

25 It had to do with the kidney adenomas, the

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

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

10 CHAIRPERSON MACK: Thank you.

11 DR. SANDY: Dr. Mack?

12 CHAIRPERSON MACK: Martha.

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

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

17 DR. SANDY: Thank you. I'll talk about the
18 reviews and conclusions of other agencies. And I'd like
19 to point you to page 25 and 26 of the hazard
20 identification document, just to remind you that on page
21 25 we have reported that the National Research Council in
22 2000 reviewed TDCPP and concluded that the available
23 animal data provides sufficient evidence of
24 carcinogenicity in rats following chronic oral exposure.
25 So that's the NRC.

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

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

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

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

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

1 1,3-DCP.

2 And as I said before, in vivo studies have also
3 shown that a certain fraction, about 20 percent, is
4 eliminated in exhaled air as CO₂. So clearly, there is a
5 fraction other than urinary metabolites that is the
6 product of the breakdown of the compound. And I think
7 each of these studies were done in -- with a radiolabeled
8 compound.

9 CHAIRPERSON MACK: Thank you, John.

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

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

14 MEMBERS OF THE AUDIENCE: Microphone.

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

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

19 COMMITTEE MEMBER EASTMOND: I think Joe is.

20 COMMITTEE MEMBER LANDOLPH: Yes.

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

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

1 together.

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

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

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

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

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

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

7 CHAIRPERSON MACK: Thank you, Joe.

8 Sol.

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

14 DR. FAUST: Yes, that's correct.

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

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

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

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

24 CHAIRPERSON MACK: David.

25 COMMITTEE MEMBER HUNTER: Darryl.

1 CHAIRPERSON MACK: Then we'll go to Darryl.

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

4 CHAIRPERSON MACK: Go ahead, Darryl.

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

7 CHIEF COUNSEL MONAHAN-CUMMINGS: Mic.

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

10 It's on.

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

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

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

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

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

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

14 CHAIRPERSON MACK: Anything further, Darryl?

15 COMMITTEE MEMBER HUNTER: (Shakes head.)

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

23 CHAIRPERSON MACK: Joe.

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

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

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

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

15 CHAIRPERSON MACK: David.

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

25 Apparently, the people when they wrote it up

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

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

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

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

1 consider.

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

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

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

23 CHAIRPERSON MACK: Anybody else have any
24 comments?

25 My own view is weighted heavily on the presence

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

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

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

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

20 (Hands raised.)

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

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

24 (Hand raise.)

25 CHAIRPERSON MACK: One.

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

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

7 Martha.

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

11 (Thereupon an overhead presentation was
12 Presented as follows.)

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

14 ACTING DIRECTOR ALEXEEFF: Turn your mic on.

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

18 --o0o--

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

25 Fluoride can form salts with positive ions, such

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

5 --o0o--

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

11 Could somebody get me some water?

12 Sorry.

13 --o0o--

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

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

1 --o0o--

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

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

13 --o0o--

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

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

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

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

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

18 --o0o--

19 DR. STEINMAUS: The next study, Bassin et al.,
20 2006. This was a case control study of osteosarcoma in
21 people age 19 or younger. It included 103 cases and 215
22 controls selected from 11 hospitals throughout the United
23 States. Controls were other orthopaedic patients from the
24 same hospitals as the cases matched on age and gender.
25 Exposure was primarily based on drinking water fluoride

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

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

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

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

14 Odds ratios were greater than one for other ages
15 of exposure, but most of those were not statistically
16 significant. Odds ratios for females for exposure at age
17 7, again that was above one, but not statistically
18 significant.

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

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

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

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

7 --o0o--

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

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

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

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

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

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

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

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

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

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

25 Also, the participation rate amongst the controls

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

3 So overall, this study is inconclusive.

4 --o0o--

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

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

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

22 --o0o--

23 DR. STEINMAUS: The next study Comber et al.,
24 2011. This was an ecological study of osteosarcoma in
25 fluoride in Ireland in the years 1994 to 2006. Exposure

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

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

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

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

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

3 --o0o--

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

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

14 --o0o--

15 DR. MORRY: Okay. We'll turn now to the animal
16 evidence. There are nine rodent bioassays that were done
17 on fluoride. The first four were done by the NTP and
18 published in 1990. They included a male, male -- three
19 Fischer rats, female rats, a male B6C3F1 mice in female
20 mice.

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

25 There were another study -- set of studies, two

1 studies was done, published by Maurer et al. in 1990. And
2 this one included male rats and female rats. And then in
3 1993, Maurer et al. published two studies on male mice and
4 female mice.

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

8 --o0o--

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

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

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

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

3 --o0o--

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

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

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

21 --o0o--

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

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

3 --o0o--

4 DR. MORRY: The Maurer et al. studies, this was a
5 1993 bioassay in CD-1 males, male and female mice. It was
6 a 97-week diet study in male and female mice. And the top
7 dose was 25 milligrams per kilogram per day by body
8 weight.

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

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

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

4 --o0o--

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

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

13 --o0o--

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

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

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

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

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

8 --o0o--

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

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

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

24 --o0o--

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

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

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

9 --o0o--

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

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

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

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

1 osteosarcoma.

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

10 --o0o--

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

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

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

1 osteosarcomas.

2 --o0o--

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

9 --o0o--

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

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

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

22 There were no tumor findings in female Fischer
23 rats, male or female Sprague-Dawley rates or male or
24 female B6C3F1 mice.

25 --o0o--

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

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

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

17 And that's concludes the summary of the evidence.

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

23 DR. STEINMAUS: Yes, that's true.

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

1 DR. STEINMAUS: Correct.

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

8 Would you elaborate on that or...

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

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

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

19 Does anybody else have any questions for the
20 staff?

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

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

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

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

13 CHAIRPERSON MACK: Anybody else?

14 David, do you have any questions for the staff?

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

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

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

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

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

6 COMMITTEE MEMBER EASTMOND: Yeah.

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

12 CHAIRPERSON MACK: That's very prudent.

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

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

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

1 mortality in that time frame.

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

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

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

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

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

1 fluoride is out there.

2 (Laughter.)

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

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

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

20 At a time when New York State's cancer registry
21 was the largest in the country. New York State was also
22 where we did some of the original field tests for
23 fluoridation of water supplies. It was in the cities of
24 Newburgh and Kingston on the Hudson River back in the
25 1940s.

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

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

16 CHAIRPERSON MACK: Then it was with great
17 difficulty.

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

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

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

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

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

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

23 And as a Department, we recommend fluoride and
24 its salts should not be listed as a chemical under Prop
25 65.

1 Thank you, Mr. Chairman.

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

4 (Laughter.)

5 CHAIRPERSON MACK: Irrespective of your flouting
6 my request.

7 (Laughter.)

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

12 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

5 Thanks.

6 CHAIRPERSON MACK: Thank you, Dr. Sutton.

7 Catherine Hayes.

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

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

16 As an epidemiologist I'd like to focus on the
17 criteria for causality of epidemiologic evidence, first
18 being consistency. I think what we've heard here this
19 morning is that we don't have consistent findings linking
20 fluoride to osteosarcoma, so we really can't satisfy that
21 criteria. We don't -- the strength of association. In
22 the Bassin study there was an odds ratio that was about
23 4.7, which would be considered as an epidemiologist a
24 strong association. However, that's not replicated in
25 other studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

16 I would also like to point out that in the phase
17 2, or the Kim study, we had additional variables that had
18 been shown to be related to osteosarcoma, and that was the
19 height at diagnosis, birth weight, which were in published
20 peer-reviewed literature shown to be associated with
21 osteosarcoma. We included that.

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

25 We selected a dental journal because, as

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

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

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

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

16 DR. HAYES: Yes.

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

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

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

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

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

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

25 CHAIRPERSON MACK: Thank you.

1 DR. HAYES: Thank you.

2 CHAIRPERSON MACK: Anybody else have any
3 questions?

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

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

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

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

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

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

8 COMMITTEE MEMBER EASTMOND: Okay.

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

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

16 CHAIRPERSON MACK: Thank you very much.

17 Richard Adamson.

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

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

22 Dr. Richard Adamson.

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

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

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

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

15 We reviewed all, and underline all, the published
16 scientific literature on fluoride toxicology in English up
17 to that time. The NTP 1990 technical report toxicology
18 and carcinogenesis studies of sodium fluoride and F344/N
19 rats and B6C3F₁ mice, the Maurer et al. studies in mice
20 and rats, and over 100 public submitted documents.

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

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

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

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

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

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

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

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

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

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

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

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

25 This committee has a very high standard. It is

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

5 Thank you for the opportunity.

6 CHAIRPERSON MACK: Thank you, Dick.

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

10 (Laughter.)

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

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

19 CHAIRPERSON MACK: Take much less than five
20 minutes.

21 (Laughter.)

22 DR. MURRAY: All right.

23 CHAIRPERSON MACK: Give us your bottom line, Jay.

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

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

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

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

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

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

24 Thank you.

25 CHAIRPERSON MACK: Thank you, Dr. Murray.

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

3 Next slide.

4 --o0o--

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

8 Next slide.

9 --o0o--

10 DR. POLLICK: The recent report by European
11 Scientific Committee on Health and Environmental Risks
12 concluded that epidemiological studies do not indicate a
13 clear link between fluoride in drinking water and
14 osteosarcoma and cancer in general. There is no evidence
15 from animal studies to support the link. Thus, fluoride
16 cannot be classified as carcinogenic. That's from the
17 16th of May this year.

18 Next slide.

19 --o0o--

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

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

5 --o0o--

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

15 --o0o--

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

20 Thank you for your time.

21 CHAIRPERSON MACK: Thank you.

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

1 David Kennedy is the next speaker.

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

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

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

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

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

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

25 The EPA considers lead a carcinogen as well. So

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

4 For example, the following:

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

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

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

22 It is a poison.

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

1 even been submitted.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Thank you.

1 CHAIRPERSON MACK: Jeff Green.

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

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

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

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

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

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

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

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

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

1 as to whether it's a carcinogen or not.

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

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

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

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

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

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

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

16 CHAIRPERSON MACK: Thank you.

17 Kim Glazzard.

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

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

1 additional concerns today.

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

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

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

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

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

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

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

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

22 Thank you so much for your time.

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

1 name in agreement with the last couple speakers?

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

4 CHAIRPERSON MACK: You did submit one, right?

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

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

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

18 Okay. My name is Mike Fuller.

19 CHAIRPERSON MACK: One minute would be great.

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

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

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

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

8 I would also like to ask you to take the courage
9 to do what is right for the population of California and
10 its children. And that will take great courage, because
11 you'll be bucking a very powerful, very strong
12 establishment that has been supporting fluoride for over
13 70 years in this country. I don't need to tell you that.
14 You already know that.

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

22 Thank you.

23 CHAIRPERSON MACK: Thank you, Mr. Fuller.

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

1 in the record?

2 CHAIRPERSON MACK: I would presume so --

3 MR. FULLER: For the record.

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

6 MR. FULLER: Thank you very much.

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

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

11 (Thereupon a recess was taken.)

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

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

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

1 carcinogenicity in humans.

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

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

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

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

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

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

1 viruses as well.

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

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

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

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

23 CHAIRPERSON MACK: Who else would like to
24 comment?

25 Anna, Darryl?

1 Joe?

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

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

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

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

17 COMMITTEE MEMBER HAMBURG: Nothing at all.
18 Thank you.

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

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

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

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

6 (No hands raised.)

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

9 (Hands raised.)

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

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

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

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

22 (Laughter.)

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

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

5 (Laughter.)

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

8 (Laughter.)

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

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

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

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

18 (Thereupon a lunch break was taken.)

19

20

21

22

23

24

25

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

9 So next slide, please.

10 --o0o--

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

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

21 Next slide, please.

22 --o0o--

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

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

9 Next slide, please.

10 --o0o--

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

14 Next slide, please.

15 --o0o--

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

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

6 --o0o--

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

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

21 --o0o--

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

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

4 And let's go to the next slide.

5 --o0o--

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

12 You can go to the next one.

13 --o0o--

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

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

23 So that's it for now. Thank you.

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

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

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

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

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

15 CHAIRPERSON MACK: Dr. Wu.

16 COMMITTEE MEMBER WU: Medium.

17 CHAIRPERSON MACK: Medium priority. All right.

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

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

1 bear with me.

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

8 CHAIRPERSON MACK: David, do you want to respond?

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

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

22 So that was my --

23 CHAIRPERSON MACK: Other people on the Committee
24 weigh in?

25 Joe.

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

9 CHAIRPERSON MACK: Sol.

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

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

20 COMMITTEE MEMBER EASTMOND: I'm okay with medium.

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

24 Next drug is acetaminophen.

25 I was one of the reviewers on this. And because

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

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

6 No.

7 COMMITTEE MEMBER EASTMOND: I don't think so.

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

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

12 CHAIRPERSON MACK: Oh, yes. Three people did it.
13 Yes, Joe.

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

20 CHAIRPERSON MACK: Anna?

21 COMMITTEE MEMBER WU: High.

22 CHAIRPERSON MACK: High also.

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

25 Are you going to speak against high?

1 DR. KOCHANOWSKI: Yes, sir.

2 CHAIRPERSON MACK: Okay.

3 DR. KOCHANOWSKI: For one minute --

4 CHAIRPERSON MACK: You have one minute.

5 DR. KOCHANOWSKI: -- or less.

6 As we submitted in our written comments, I'd just
7 like the Committee to be aware of the new drug application
8 that was approved by FDA, Ofirmev, which is an IV,
9 intravenous acetaminophen formulation, which included a
10 very, very in-depth review of all the carcinogenicity
11 data, where they came out with no evidence of concern.
12 And we wanted to make sure that the Committee was aware of
13 that, in addition of course to the two IARC reviews.

14 So thank you for considering that when you
15 prioritize.

16 CHAIRPERSON MACK: Thank you.

17 Now, I guess I should ask if anybody wishes to
18 change their rating on that basis?

19 Hearing none, we continue with high.

20 Third drug is a biggie, Bisphenol A.

21 I also had that drug. And I'm going to defer to
22 the other reviewer first, but my prioritization was also
23 high.

24 The other reviewer is David Eastmond.

25 COMMITTEE MEMBER EASTMOND: Me. Before I make my

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

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

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

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

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

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

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

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

8 Anybody else wish to weigh in?

9 Joe.

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

19 CHAIRPERSON MACK: Sol.

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

24 CHAIRPERSON MACK: Darryl.

25 COMMITTEE MEMBER HUNTER: I agree with medium.

1 CHAIRPERSON MACK: Medium.

2 Anna.

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

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

7 COMMITTEE MEMBER LANDOLPH: Good enough.

8 CHAIRPERSON MACK: Okay, medium it is.

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

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

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

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

15 CHAIRPERSON MACK: Okay.

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

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

1 CHAIRPERSON MACK: Thank you.

2 Steven Hentges.

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

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

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

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

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

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

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

1 rapidly eliminated from the body.

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

7 CHAIRPERSON MACK: Thank you.

8 Kathleen Roberts.

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

14 I would just simply like to reiterate what Steve
15 said about the organizations, the government reviews that
16 have already done it, including the World Health
17 Organization that just completed it November 2010; and the
18 Japanese Research Institute of Science for Safety and
19 Sustainability, which just completed its review in July
20 2011. So we're talking very recent reviews that looked at
21 in vivo, in vitro, epi, genome, and mutatox, and the
22 carcinogenic assay. So there's been some recent ones.
23 And I would agree that perhaps there's other things that
24 you all might want to focus on.

25 Thank you.

1 CHAIRPERSON MACK: Thank you.

2 Does anybody wish to switch to low?

3 DR. JANSSEN: Can I make a comment please?

4 Sorry, I didn't submit a card.

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

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

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

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

1 forms of breast cancer.

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

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

17 Thank you.

18 CHAIRPERSON MACK: Thank you very much.

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

20 CHAIRPERSON MACK: Oh, all right.

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

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

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

6 Thank you.

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

10 So does anybody want to change?

11 No.

12 Next compound is BBP, butyl benzyl phthalate.

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

15 Landolph.

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

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

20 I looked in the wrong line. Sorry about that.

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

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

24 CHAIRPERSON MACK: Yeah.

25 COMMITTEE MEMBER EASTMOND: Okay.

1 CHAIRPERSON MACK: Just a sentence or two of
2 rationale.

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

12 There were some other increases seen.

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

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

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

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

24 CHAIRPERSON MACK: Does anybody wish to offer an
25 alternative?

1 Hearing none, we go with medium from the
2 committee.

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

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

10 CHAIRPERSON MACK: Thank you.

11 Dr. Janssen.

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

22 Thank you.

23 CHAIRPERSON MACK: Thank you.

24 John Butala.

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

1 toxicologist. I represent FERRO, a manufacturer.

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

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

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

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

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

1 phthalate is clearly not estrogenic in vivo.

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

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

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

15 Thank you.

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

19 So --

20 COMMITTEE MEMBER HAMBURG: Mack? Yeah, I would
21 like to push this to high as well. I think the
22 availability, the access, the exposure rates are so high,
23 that even if we don't list it, it would be great to get it
24 off the table so that we can clarify what the issue is.

25 So I would recommend high on this one.

1 CHAIRPERSON MACK: Joe.

2 COMMITTEE MEMBER LANDOLPH: Yeah, I agree with
3 Sol. I would recommend high because the estrogenic
4 activity. There's also transformation of human breast
5 cells with this and the peroxisomal proliferator activity
6 in the bladder and the pancreatic cancer site. I would
7 argue for high too.

8 CHAIRPERSON MACK: So anybody wish to disagree?
9 Okay. High it is.

10 COMMITTEE MEMBER EASTMOND: I might mention, if
11 it doesn't cause peroxisomal proliferation you would
12 expect liver tumors, which we don't see. So it's kind of
13 unusual. I'm still okay with high. It doesn't matter.

14 CHAIRPERSON MACK: Okay. We come to butylated
15 hydroxytoluene.

16 That's Joe and I.

17 Joe.

18 COMMITTEE MEMBER LANDOLPH: I recommend medium.
19 It's an antioxidant preservative in foods, antioxidant for
20 rubber petroleum plastic products. Genotoxicity in the
21 mouse lymphoma cells mutation assay. Chromosome
22 aberrations in human and CHO cells. That's positive in
23 three out of five studies, giving lung tumors in female
24 mice, liver tumors in male mice, liver tumors in male and
25 female rats.

1 So I would recommend a medium on this.

2 CHAIRPERSON MACK: That's what I put down also.

3 Anybody wish to offer an alternative?

4 Okay. So now we come to James Coughlin.

5 DR. COUGHLIN: Thank you, Dr. Mack.

6 I'm Jim Coughlin, toxicologist consultant for
7 five trade associations. We're calling ourselves the BHT
8 Coalition. I thought I had five slides ready to go, but
9 I'm going to do just one, if I can.

10 The main study, it was a Danish study published
11 in 1986, the Olsen et al. study, was a Wistar rat study
12 with three doses. But it got very famous and very
13 unusual, and we spent years dealing with it in the food
14 industry and in other places.

15 But The study went out for 2 3/4 years, as they
16 sometimes do in European studies. And the only carcinomas
17 were in the males. There was statistically significant
18 increase in male carcinoma but not in the females. It was
19 adenoma only.

20 But the most important feature of this study is
21 that it had -- it got famous as we were doing this 25
22 years ago. And I mentioned in my comments that Gary
23 Williams, who did liver -- he's one of the top liver
24 cancer experts in the world for animals -- has reviewed
25 this and done a lot of studies on it. But the animals

1 lived so long because of the antioxidant BHT that they got
2 the tumors in the last three weeks of the study. And so
3 it became very famous for us because the treated animals
4 lived long enough to get the liver tumors, the males did.
5 And the tumor latencies were much greater.

6 Survival was the most important feature in the
7 males. Only 16 percent of the controls lived to
8 termination, 144 weeks, whereas 44 percent of the treated
9 lived that far.

10 The females, only 17 percent got to termination
11 and 39 percent of the treated.

12 So the animals in a two and three-quarter year
13 study, which we don't usually do - we stop at two years -
14 lived long enough to get liver tumors that they were
15 likely to get. So that's the -- I believe is the main.

16 I would urge a low priority for BHT.

17 CHAIRPERSON MACK: Does that change your mind,
18 Joe?

19 COMMITTEE MEMBER LANDOLPH: No, it's very
20 interesting data. But since this is used as antioxidant
21 preservatives in food, there certainly is widespread use
22 and it is carcinogenic. So I don't change my mind.
23 Medium I've got for that.

24 CHAIRPERSON MACK: Neither do I.

25 So we'll stick with medium.

1 C.I. Disperse Yellow 3.

2 Sol, you're the only remaining person.

3 COMMITTEE MEMBER HAMBURG: The only victim.

4 Yeah, I rate this as high. It is another azo
5 dye. Prop 65 has evaluated a number of other azo dyes and
6 they're all listed. I think there's enough data to
7 support looking at it. And as with other agents similar
8 to that that have been listed, this should be evaluated as
9 quickly as we can.

10 CHAIRPERSON MACK: Anybody have comments on this
11 compound?

12 And there are no public comments. So high is
13 where it stands.

14 Chloroalkyl ethers.

15 I'm one of the reviewers on chloroalkyl ethers.

16 DR. SANDY: And, Dr. Mack --

17 COMMITTEE MEMBER EASTMOND: Martha wanted to make
18 a comment.

19 DR. SANDY: Dr. Mack?

20 CHAIRPERSON MACK: Yeah.

21 DR. SANDY: If I could just quickly --

22 COMMITTEE MEMBER MACK: Oh, I'm sorry. This is a
23 group.

24 DR. SANDY: This is a group. So you're being
25 asked a simple question advising on the chemical group,

1 should it be considered for listing? But as I said
2 before, you have the prerogative if you would like to
3 recommend a subset of this group.

4 CHAIRPERSON MACK: Why don't we consider
5 categorizing for priority the highest of the group. In
6 other words if we think any of the compounds require a
7 high priority, then we put the group in the high priority.
8 Is that reasonable?

9 What do you other members of the Committee think
10 about that?

11 COMMITTEE MEMBER EASTMOND: Well, I have a
12 general comment.

13 As I went through -- I didn't like evaluating
14 these classes because they're all quite -- there are a lot
15 of them very different within these classes. Essentially
16 all the ones at low priority you're going to pull up
17 higher to do that.

18 And, indeed, if -- the way I read Proposition 65,
19 it's for specific chemicals. So the class itself is a
20 funny -- I mean I can see for prioritization doing this
21 for convenience sake. But specifically the actual
22 decision's going to be made on individual chemicals, I
23 would assume.

24 DR. SANDY: So maybe I should clarify. We're
25 putting them in groups for ranking purposes. And then as

1 you -- if you rank something as high, you may decide you'd
2 like us to look at all the chemicals in the group. And
3 for listing you might want to have the ability to list
4 only certain ones. Or at juncture for prioritization, you
5 may be pretty certain you only want to prioritize a subset
6 of the chemicals in the group or maybe only one. And so
7 we're trying to let you know you have flexibility. Right
8 now it's ranking for hazard identification development.
9 And developing the hazard identification document, you can
10 direct us to look at the entire group or look at a subset.

11 CHAIRPERSON MACK: I would suggest just from my
12 own standpoint that not enough of us know enough to make
13 the decision you're asking us to make. So what I would
14 prefer is to prioritize as a group, but then reserve the
15 option at your discretion to list them individually when
16 we discuss them.

17 ACTING DIRECTOR ALEXEEFF: I think that would be
18 preferable, Dr. Mack, to look -- that way we would -- if
19 we brought the chemical forward, we would bring all the
20 chemical information of that group, so you could see not
21 only that specific chemical, maybe the one that has the
22 most information, but the other ones to draw your
23 conclusions.

24 And to comment on Dr. Eastmond's comment, you
25 know, earlier we were considering fluoride and its salts.

1 So actually it was a group of chemicals.

2 DR. SANDY: But I have been making a distinction
3 that those are related chemicals. The salts dissociate to
4 fluoride. But the group, they're different chemical
5 structures that do not dissociate to the same one.

6 CHAIRPERSON MACK: Is the summary that we do --
7 we can prioritize them as a group, with the presumption
8 that you will actually list them separately when we look
9 at them?

10 Okay. My view is that these are similar to known
11 listed carcinogens and there's a lot of new information on
12 the individual ones, so I would put them in the high
13 category.

14 Joe.

15 COMMITTEE MEMBER LANDOLPH: Yeah. I would
16 support that particularly because bis chloromethyl ether
17 is a member of that group and it causes human lung cancer
18 from the occupational studies decades ago. So, yeah, I
19 think these are pretty strong agents.

20 CHAIRPERSON MACK: Anybody wish to disagree with
21 the high?

22 COMMITTEE MEMBER EASTMOND: Well, I'm the other
23 commenter on this, and I put them as between low and
24 medium. And mainly because if you look at the summary of
25 the data, most of these don't cause any tumors that have

1 been tested. And even the ones that have, you only have
2 one single study that would look to be valid.

3 So if you're saying what's the end result of this
4 going to be, somebody's going to put a lot of work in, and
5 ultimately probably not a lot of data to go forward. Now,
6 they probably can figure that out pretty quickly. But I
7 didn't rank it very high for that.

8 I recognized that some members of this class
9 certainly are Proposition 65 carcinogens. But the
10 residual ones here, I didn't think there was a lot of
11 evidence. I mean you could argue for I guess the first
12 two that are listed and maybe the third one. But you're
13 getting to sort of injection site tumors and, you know,
14 these are not clean chemicals with a lot of evidence. But
15 I'm pretty flexible on it.

16 CHAIRPERSON MACK: Sarcomas in the injection
17 site.

18 COMMITTEE MEMBER EASTMOND: I've seen a lot of
19 these are injection site tumors.

20 I'm hoping you could hear.

21 COMMITTEE MEMBER LANDOLPH: Well, there's -- a
22 CMME is lung adenomas in the male, injection site sarcomas
23 in the females, respiratory tract tumors in males rats.

24 COMMITTEE MEMBER EASTMOND: That's already
25 listed, Joe. You're looking at the wrong table.

1 COMMITTEE MEMBER LANDOLPH: Yeah, yeah. I'm
2 looking at Table 2.

3 But I think their Similarity to BCME would still
4 make me say that these are alkylating agents and they have
5 a strong propensity to cause tumor induction. So I think
6 they should still be high.

7 CHAIRPERSON MACK: Okay. Let's hear other people
8 on the Committee?

9

10 COMMITTEE MEMBER WU: I put in the medium
11 category, I think partly --

12 CHAIRPERSON MACK: Darryl.

13 COMMITTEE MEMBER HUNTER: Medium.

14 CHAIRPERSON MACK: Medium.

15 So we have --

16 COMMITTEE MEMBER HAMBURG: Medium.

17 CHAIRPERSON MACK: Medium.

18 Joe, can I talk you into that?

19 COMMITTEE MEMBER LANDOLPH: Yeah, I can live with
20 it.

21 CHAIRPERSON MACK: Okay. Medium it is.

22 And we have no comments on that.

23 Okay. Chloropicrin.

24 Sol and Darryl.

25 Sol.

1 COMMITTEE MEMBER HAMBURG: I actually put this
2 one as relatively low, low. It is -- the toxicity data
3 doesn't look that significant. And I think there are
4 other agents of the 39 that require listing much sooner
5 than this agent does. So I'm for low on this.

6 CHAIRPERSON MACK: Darryl.

7 COMMITTEE MEMBER HUNTER: Yes, I put a low. The
8 lab studies indicate some trends but only if you throw in
9 the adenomas and the carcinomas. So I put low.

10 CHAIRPERSON MACK: Does anybody disagree with
11 low?

12 Let's see, I have a comment from John Butala
13 again.

14 CHIEF COUNSEL MONAHAN-CUMMINGS: Maybe it would
15 be good if everybody left their mikes on, and then you
16 don't have to -- you know, leave it on and just push it
17 towards your mouth.

18 CHAIRPERSON MACK: Mr. Butala.

19 Don't you have a comment to make on chloropicrin?

20 DR. BUTALA: Chloropicrin manufacturers --

21 THE REPORTER: Can you come forward.

22 COMMITTEE MEMBER EASTMOND: Did you submit -- do
23 you want to make a comment?

24 DR. BUTALA: Are you proposing low?

25 CHAIRPERSON MACK: Yeah.

1 You're happy with that.

2 Thank you. Way to go.

3 (Laughter.)

4 CHAIRPERSON MACK: Clodinafop-propargyl.

5 DR. SUTTON: I'd like to make a quick comment on
6 chloropicrin.

7 CHAIRPERSON MACK: On Chloropicrin?

8 DR. SUTTON: Yeah. I turned in a card. Maybe
9 it's --

10 CHAIRPERSON MACK: You're sneaking in.

11 DR. SUTTON: No, I really did turn in a card.

12 CHAIRPERSON MACK: All right.

13 DR. SUTTON: All right. Real Quick.

14 We would suggest that you raise this a bit
15 because this a soil fumigant. It's used widely in
16 California. We grow lots strawberries here.

17 Air Resources Board tests show that you can
18 inhale this -- you know, a lot of Californians all
19 throughout the state can inhale this pretty far from
20 application sites.

21 And the animal studies, there are about a half
22 dozen of them. And the interesting thing about them is
23 that to evaluate them fully you need to really look at
24 statistical analyses and the relative merits of different
25 analyses. And that's why we would suggest that a group

1 with your expertise would be better able to distinguish
2 between the different measurements this way.

3 CHAIRPERSON MACK: All right. Let's see if you
4 made a hit with Sol.

5 Still low?

6 COMMITTEE MEMBER HAMBURG: Low.

7 CHAIRPERSON MACK: Darryl?

8 COMMITTEE MEMBER HUNTER: Low.

9 CHAIRPERSON MACK: Sorry.

10 Okay. Now we go to the one that I couldn't
11 pronounce. Clodinafop-Propargyl

12 And the people who evaluated that were again Sol
13 and Darryl again.

14 COMMITTEE MEMBER HAMBURG: Darryl, you go first.

15 COMMITTEE MEMBER HUNTER: Sure, man.

16 I gave it a medium. A little bit higher than the
17 other one. The animal data indicated some trends with
18 carcinomas in more than one site as well as in the rat and
19 mice models. So two different animals. And genotoxicity
20 data, some trends as well.

21 So I gave that one a medium.

22 CHAIRPERSON MACK: Sol.

23 COMMITTEE MEMBER HAMBURG: I would agree with
24 that. It's widely used. There's some data to suggest it
25 may be a carcinogen. So I think a medium.

1 CHAIRPERSON MACK: Debbie Stubbs, Syngenta.

2 MS. STUBBS: I would like to propose that this
3 should be a low. This product has been evaluated twice by
4 EPA in two separate occasions and they gave it their
5 lowest level of concern for a compound where there is any
6 tumor formation. And that's suggestive evidence.

7 In addition, there have been other regulatory
8 authorities that have come to the same conclusion, such as
9 the European Food Safety Authority.

10 And the most important reason why this should be
11 a low is this product -- this active ingredient is not
12 registered in California. So there's no exposure to any
13 of the citizens of California. And we have no plan at
14 this moment to register any products with this active
15 ingredient in California.

16 So therefore I believe it should be low.

17 CHAIRPERSON MACK: Well, Sol.

18 COMMITTEE MEMBER HAMBURG: I can be -- I can
19 change my mind. Let's go to low on this.

20 DR. SANDY: I'd like to point out though, as
21 stated in the document you have, the EPA has established
22 tolerances for this chemical on wheat and hay. So that
23 indicates there's some potential for exposure in
24 California, or else we wouldn't have brought it to you.

25 CHAIRPERSON MACK: Trumped.

1 Darryl. Stick with medium?

2 COMMITTEE MEMBER HUNTER: I'm going to stick with
3 medium.

4 CHAIRPERSON MACK: Sol?

5 COMMITTEE MEMBER HAMBURG: All right. Let's go
6 with medium.

7 CHAIRPERSON MACK: Medium it is.

8 Coumarin. And that's -- Joe Landolph is the only
9 available reviewer.

10 COMMITTEE MEMBER LANDOLPH: That's a natural
11 product fragrance in perfumes, cosmetics, personal care
12 products, industrial uses, electroplating, pharmaceutical
13 uses. So there's a lot of use of it.

14 The genotoxicity is positive in bacteria, SCEs
15 and CHO cells, chromosome aberrations in plants and CHO
16 cells, micronuclei in human hepatoma cells. So it's got a
17 reasonably robust genetox database.

18 Carcinogenicity, it's positive in four assays
19 tested. It has lung tumors, stomach tumors, lumbar tumors
20 in male and female mice, renal adenomas in male and female
21 rats, pulmonary tumors in male mice, liver tumors in
22 female mice, liver tumors in male and female rats.

23 So I ranked it as a high priority.

24 CHAIRPERSON MACK: Do others have opinions about
25 this?

1 COMMITTEE MEMBER EASTMOND: I ranked it high as
2 well.

3 CHAIRPERSON MACK: High as well.

4 COMMITTEE MEMBER EASTMOND: Based on mainly the
5 animal evidence.

6 CHAIRPERSON MACK: Robert Golden from the
7 International Fragrance Association.

8 Bringing a high level of class to this Committee.

9 DR. GOLDEN: Thank you. I'm Dr. Robert Golden.
10 And as Dr. Mack said, I'm with the International Fragrance
11 Association.

12 The animal data are as you stated.

13 There are no human data. In fact it's been used
14 a lot as a pharmacologic agent, and not even any case
15 reports.

16 IARC has determined that it was not a
17 classifiable for human carcinogenicity. And they
18 determined that the animal data were limited.

19 I would also point out that it is now known - and
20 this has been evaluated by the European Food Safety
21 Authority as well as the BFR - the significant differences
22 between animals and humans in the metabolism, with animals
23 metabolizing it to toxic metabolites, humans hydroxylating
24 it and excreting it.

25 So with the -- all of the in vivo genetox data

1 are also negative.

2 So I would argue just the opposite way, that it
3 should be medium or low.

4 CHAIRPERSON MACK: Did that make any impact on
5 you?

6 COMMITTEE MEMBER LANDOLPH: No. It's an
7 articulate argument, but I'd stick with my original
8 position.

9 CHAIRPERSON MACK: Looks like you didn't smell
10 good enough.

11 (Laughter.)

12 COMMITTEE MEMBER LANDOLPH: Now, I didn't say
13 that. You did.

14 CHAIRPERSON MACK: Okay. I guess we stick with
15 high.

16 Dapsone. I was one of the reviewers for Dapsone.
17 Oh, no, I wasn't. I thought I was.

18 (Laughter.)

19 CHAIRPERSON MACK: Yes, I was. Why can't I --
20 yeah, I am.

21 No, It's Anna Wu.

22 COMMITTEE MEMBER WU: Medium.

23 CHAIRPERSON MACK: And the other one is Joe
24 Landolph.

25 COMMITTEE MEMBER LANDOLPH: Yeah, I had high.

1 CHAIRPERSON MACK: Okay. You want to tell us why
2 high.

3 COMMITTEE MEMBER LANDOLPH: It's used to treat
4 leprosy, dermatitis herpetiformis, also coccidioides in
5 cattle. Aneuploidia achromatic gaps are formed in
6 cultured human lymphocytes. In vivo mouse chromosomal
7 aberrations in micronuclei. So it's getting into the in
8 vivo, which makes it stronger as a genetox. And six out
9 of the seven studies were positive for carcinogenicity in
10 animals:

11 Spleen fibromas, fibrosarcomas and sarcomas in
12 males, peritoneal fibrosarcomas and sarcomas in males,
13 spleen fibrosarcomas and angiosarcomas in males, thyroid C
14 cell carcinoma in male and female rats, thyroid C cell
15 carcinoma in female rats, spleen fibrosarcoma, intestinal
16 reticulosarcoma, liver angioma -- some of these tumors are
17 fairly rare.

18 And for the epidemiology, there's some data on
19 bladder and kidney cancer in leprosy patients treated with
20 this, and urinary tract carcinomas, an adenosarcoma of the
21 secum, two lung cancers and Hodgkin's disease.

22 So it's penetrating into the in vivo gene
23 toxicity. There's some epidemiology and the animal
24 database is pretty strong.

25 CHAIRPERSON MACK: Does that convince you?

1 COMMITTEE MEMBER WU: Not entirely. I mean I
2 don't disagree with any of the things that were said. I
3 just thought that the usage was more limited and there
4 were other things that are more probably pressing.

5 COMMITTEE MEMBER HAMBURG: I've seen one case of
6 leprosy in 30 years, and that was 30 years ago. So it's a
7 very uncommonly used agent as compared to other agents,
8 and I think its clinical relevance is very small. So at
9 least at this time I think either a medium or a low. I
10 would not put it as a high priority.

11 CHAIRPERSON MACK: I went to medium actually,
12 thinking that I hadn't, partly because of that, mainly
13 that there are relatively few people who are being
14 treated, and they're not going to be treated with anything
15 else.

16 COMMITTEE MEMBER HAMBURG: Exactly.

17 CHAIRPERSON MACK: So it's not going to change
18 their treatment modality.

19 So can we talk you into medium?

20 COMMITTEE MEMBER LANDOLPH: Yeah, yeah, that's
21 fine.

22 CHAIRPERSON MACK: Okay. Medium it is.
23 Dibenzanthracenes and dibenz[a,c]anthracene.
24 And that is Joe again.

25 DR. SANDY: And if I could just remind you.

1 You've got two questions. You can rank the chemical
2 group. And we'd like you to rank the
3 dibenz[a,c]anthracene, if you are willing to.

4 COMMITTEE MEMBER LANDOLPH: Say that again.

5 DR. SANDY: We're asking the Committee to rank
6 the chemical group Dibenzanthracenes as well as one of the
7 chemicals in the group, the dibenz[a,c]anthracene.

8 CHAIRPERSON MACK: That was pretty sneaky.

9 (Laughter.)

10 COMMITTEE MEMBER LANDOLPH: Yeah, so there's a
11 pretty robust database on these. Dibenz[a,c] is mutagenic
12 in bacteria mammalian cells, V-79 cells. DNA damage in
13 bacillus subtilis. It transforms Syrian hamster embryo
14 cells. So it's pretty robust, cause skin papillomas in
15 mice -- female mice. It's positive in four out of seven
16 animal studies. Liver adenomas in male mice. Skin
17 papillomas in female mice.

18 The dibenz[h,a]anthracene again is mutagenic in
19 salmonella, causes DNA adducts in mouse epidermis, mutates
20 the codon 61 of the Harvey rat's oncogene. Three out of
21 four experiments it's positive. Skin carcinomas in female
22 mice. Skin papillomas in female mice. Skin papillomas in
23 female mice. There's no epidemiology data of course.

24 The dibenz[a,h]anthracene is of course one of the
25 most famous carcinogens, identified around 1930 as a

1 constituent of coal tar. And that's very hot mutation of
2 salmonella, Chinese hamster cells, sex linked recessive
3 lethal gene mutations in Drosophila. Sister chromatid
4 exchanges in CHO cells, DNA adducts, cell transformation,
5 CHO cells and mouse embryo cells and Fischer rat embryo
6 cells. And that one's positive in seven out of seven
7 experiments.

8 And like most of the PAH, it usually causes skin
9 papillomas and carcinomas. Lung adenomas in mice,
10 sarcoma, fibrosarcoma, lung tumors in rats, lung adenoma
11 in mice, forestomach carcinomas, mammary adenocarcinoma,
12 lung tumors, and liver tumors.

13 So I think the whole class is pretty carcinogenic
14 as far as I'm concerned. Dibenz[a,h]anthracene stands out
15 as the most -- it's one of the most famous historical
16 carcinogens. And you would get this through incomplete
17 combustion. And it's kind of a ubiquitous air contaminant
18 because of that. So I would rank this as a high class.
19 And I think the other -- the chemicals within it are
20 probably -- you know, you'll probably rank them later as
21 high, is my guess.

22 CHAIRPERSON MACK: So did you give her an answer
23 to the questions?

24 COMMITTEE MEMBER LANDOLPH: I thought I did. But
25 sharpen it up if I didn't.

1 I would say the class is high, in my opinion.
2 And I would say I think there's a probability that the
3 members will be high too, because they're typical
4 polycyclic aromatic hydrocarbons.

5 DR. SANDY: But we're looking for advice from you
6 on the ranking of the -- one of the two that are not --

7 COMMITTEE MEMBER LANDOLPH: Just the dibenz[a,c],
8 that's all you want to know about?

9 It looks pretty good. It's mutagenic in
10 bacteria, mammalian cells, and it causes skin tumors --

11 CHAIRPERSON MACK: What's the exposure?

12 COMMITTEE MEMBER LANDOLPH: Mostly in the air.
13 You'll get a lot of it in the air. It's like benzpyrene.
14 You know, you get -- it's thermodynamically favored when
15 you combust these molecules in a paucity of oxygen that
16 they form.

17 CHAIRPERSON MACK: Barbecue.

18 COMMITTEE MEMBER LANDOLPH: Yeah, if you burn
19 your steaks black, sure, you'll get that form, and when
20 you burn trash in a paucity of oxygen. So it's an air
21 contaminant. And you get some of it into the water, some
22 of its into the soil, but mostly air.

23 CHAIRPERSON MACK: So it's a high, high.

24 COMMITTEE MEMBER LANDOLPH: I would say so.

25 CHAIRPERSON MACK: Does anybody --

1 COMMITTEE MEMBER EASTMOND: Can I ask a question.

2 CHAIRPERSON MACK: David.

3 COMMITTEE MEMBER EASTMOND: Martha. Apparently,
4 this was reviewed by IARC when they did the PAH recently.
5 Do you know what the outcome of that review was?

6 DR. SANDY: Yes, and you have this other table
7 that was sent to you and was out as a handout which talks
8 about if an authoritative body has reviewed a chemical and
9 when they did it. So it was reviewed in 2010 in the a,c
10 isomer and put in Group 3.

11 COMMITTEE MEMBER EASTMOND: So. Okay.

12 CHAIRPERSON MACK: Okay.

13 COMMITTEE MEMBER LANDOLPH: Tough to see how it
14 could be in 3, because it makes DNA adducts, it's
15 mutagenic. It's carcinogenic. I have -- I would have a
16 problem with that. I don't know why they would do that.

17 COMMITTEE MEMBER EASTMOND: I mean if I can weigh
18 in on this one.

19 CHAIRPERSON MACK: Please do.

20 COMMITTEE MEMBER EASTMOND: I think the challenge
21 is going to be having data that you think is sufficient
22 and robust enough to go forward with it. I mean, a lot of
23 these are very early studies -- studies done very early on
24 by injection, or then you've got these sorts of IP
25 injections in the newborn mouse model, which depends how

1 you want to evaluate that.

2 So I think my take on this is these are probably
3 medium to high, but it may be difficult to list them,
4 because intrinsically they're probably high, but I'm not
5 sure if the evidence will be there in order to make a
6 determination eventually. That's kind of my take.

7 CHAIRPERSON MACK: Won't it just let that play
8 out as it plays out. And if you think it is omnipresent
9 in the air, and it's potentially nasty, then we should
10 call it high and leave it at that.

11 COMMITTEE MEMBER LANDOLPH: And most of them are
12 either skin carcinogens in the classical skin painting
13 experiment. And Dibenz[a,h]anthracene is so, so strong.
14 This is pretty closely related to that.

15 CHAIRPERSON MACK: So let's call it high and go
16 to the next one. 3,3'-dichlorobenzidine-based compounds
17 metabolized to 3,3'-dichlorobenzidine.

18 COMMITTEE MEMBER HAMBURG: It's me.

19 CHAIRPERSON MACK: That goes to Sol and --

20 COMMITTEE MEMBER HAMBURG: I would rank that as
21 high as well for very similar reasons. It's very active.
22 It's got a compound structure that's associated with many
23 changes in DNA in proteins. And there's a significant
24 amount of exposure. So I would rank that as high along
25 with the other ones.

1 CHAIRPERSON MACK: David.

2 COMMITTEE MEMBER EASTMOND: The dichlorobenzidine
3 forming compounds?

4 CHAIRPERSON MACK: Yeah.

5 COMMITTEE MEMBER HAMBURG: Yeah.

6 COMMITTEE MEMBER EASTMOND: I guess the comments
7 I have on this, I actually put this down as sort of medium
8 to low. And the reason essentially is the class is --
9 it's based more on logical argument. If these compounds
10 are metabolized to this dichlorobenzidine derivative, then
11 therefore they should be carcinogenic.

12 But if I recall, the only chemical that's
13 actually been tested was this pigment yellow 12, which had
14 been negative in both mice and rats.

15 Now, the public comments they did mention that
16 they believed there was an error in the classification,
17 that there was combining of both dyes and pigments. And
18 the idea is pigments were not bioavailable, and so
19 therefore, they shouldn't -- they aren't going to be
20 converted into the -- essentially a dichlorobenzidine.

21 Whereas, the dyes could be, but a lot of these
22 were pigments. So they made that distinction in their
23 public comments.

24 So, I mean, it comes down to kind of a logical
25 argument. If, indeed, those are metabolized and they form

1 the dichlorobenzidine, then you would say sure, we should
2 make them a higher priority. But apparently, a lot of
3 members of this class aren't converted, and so they'd be
4 pulled forward on some ways almost without a lot of
5 evidence. So I put medium as kind of my highest
6 assessment on that.

7 COMMITTEE MEMBER HAMBURG: I can live with
8 medium.

9 CHAIRPERSON MACK: You can live with medium?

10 COMMITTEE MEMBER HAMBURG: Yes, sir.

11 CHAIRPERSON MACK: All right. Medium it is.

12 COMMITTEE MEMBER EASTMOND: Martha has a comment.

13 CHAIRPERSON MACK: Martha has a comment.

14 DR. SANDY: I wondered if it would be helpful to
15 you if I read something that IARC said when they reviewed
16 colorants. They did not make a decision -- any decision
17 on this particular class. But they said, "It was
18 concluded that all azo colorants, whose metabolism can
19 liberate a carcinogenic aromatic amine are potentially
20 carcinogenic. It has therefore been recommended that the
21 colorants be dealt with as if they were classified in the
22 same categories as a corresponding carcinogenic or
23 suspected carcinogenic amine".

24 They go on to say, "There are some colorants that
25 have been claimed to be insoluble and that may not

1 contribute to be amine exposure, and this can tested by
2 use of biomarkers".

3 And the conclusion is, "When the contribution of
4 a benzidine-based dye to cancer risk is claimed to be low
5 or negligible the bioavailability of the carcinogenic
6 component should be excluded e.g. by use of biomarkers of
7 exposure of biomarkers of effect. However, if this is not
8 the case, it does not seem justified to classify
9 benzidine-based dyes differently from benzidine".

10 So they're sort of mixing between the larger
11 class of azo colorants and benzidine-based dyes, but
12 they're implying that you want to look and see if there's
13 are biomarkers of exposure. And we've tried to provide
14 you with that information in here.

15 COMMITTEE MEMBER EASTMOND: Yeah, that's fine. I
16 mean, I just looked at -- the only one of this class
17 that's actually been tested was negative in both the mice
18 and rats. So that's at least what I got out of the
19 screen.

20 CHAIRPERSON MACK: So let's go with medium, if
21 there's no other objections.

22 So we come to 2,4-D. And 2,4-D is myself. And I
23 judged that high, mostly based on the distribution of
24 exposure.

25 And Anna.

1 COMMITTEE MEMBER WU: High, and also because
2 there are new epi data since -- in the last decade that
3 suggest it.

4 CHAIRPERSON MACK: Any other members of the
5 Committee?

6 David.

7 COMMITTEE MEMBER EASTMOND: I went high to
8 medium. High is fine.

9 CHAIRPERSON MACK: High to medium.
10 Joe.

11 COMMITTEE MEMBER LANDOLPH: Hang on one second.

12 CHAIRPERSON MACK: In the meantime, Sol?

13 COMMITTEE MEMBER HAMBURG: High.

14 CHAIRPERSON MACK: And Darryl?

15 COMMITTEE MEMBER HUNTER: Medium.

16 CHAIRPERSON MACK: Joe?

17 COMMITTEE MEMBER LANDOLPH: High.

18 CHAIRPERSON MACK: Okay. So the Committee,
19 except for Darryl goes for high, and he can live with
20 high.

21 (Laughter.)

22 CHAIRPERSON MACK: And we have Jim Gray.

23 MR. GRAY: Good afternoon. I'm Jim Gray. I'm
24 the Executive Director for the industry task force on
25 2,4-D research data.

1 I was not anticipating that I would have to come
2 up here and argue from a high listing on down. But I
3 would draw your attention to the fact that there is a
4 robust and modern database that has been developed for
5 this compound very recently, driven by most of the
6 questions and concerns from the 80s and the 90s on
7 apparent linkages or claims of linkages to non-Hodgkins
8 lymphoma and other carcinogens.

9 All of these studies have been evaluated very
10 recently by regulatory authorities worldwide including
11 U.S. EPA, Health Canada's PMRA, the World Health
12 Organization, New Zealand, and the European community.

13 Not one of the regulatory authorities worldwide
14 classified 2,4-D as a animal or human carcinogen. And, in
15 fact, in the 2005 evaluation done by U.S. EPA, the scant
16 epidemiology data was not sufficient to raise the level of
17 concern.

18 And, in fact, the written comments that we've
19 written or that we've read that were supplied by one of
20 the NGOs to this Committee seemed to have reiterated the
21 select data points that they put in in 2004, and again, in
22 2005 for EPA's consideration, which EPA considered and
23 then rejected.

24 And there is a question then about after they
25 have done a complete and thorough evaluation of this why

1 are we looking at yet another round of no, no, you didn't
2 understand us.

3 With the overwhelming consistency amongst all the
4 regulatory authorities in their determinations, and such a
5 robust database, we think that it's likely that going
6 through the process of prioritization and consideration
7 that the CIC is likely to arrive at a similar decision,
8 determination. And, in fact, in 2009, OEHHA staff itself
9 did an evaluation for this for public health -- a PHG for
10 drinking water goal, and had documents and determinations
11 on file that it did not rise to the level of being
12 prioritized for carcinogens.

13 Thank you.

14 CHAIRPERSON MACK: Well, I based my judgment on
15 the suggestion that there might be a relationship to an
16 NHL, which I did not see dismissed by anybody. So my
17 inclination is not to waiver. And actually, let me first
18 call upon Dr. Janssen who listed 2,4-D as well.

19 DR. JANSSEN: I'll waive my comment and --
20 because I agree with the high prioritization.

21 CHAIRPERSON MACK: Okay. Joe.

22 COMMITTEE MEMBER LANDOLPH: Yeah, Tom. I agree
23 with you on the NHL. I also noticed there's thoughts,
24 ratios for breast and stomach cancer in a couple other
25 studies. And there's micronuclei, sister chromatid

1 exchange, chromosome aberrations, comet assay, endocrine
2 disruption. And there's positive carcinogenicity results
3 in 8 out of 12 studies in rats. And a lot of different
4 types of tumors, so I think this is not an innocuous
5 compound.

6 CHAIRPERSON MACK: Okay. So we're sticking with
7 high.

8 COMMITTEE MEMBER WU: Yes, and I think that the
9 new Epi data are actually based on the case control
10 studies, so I think it's worth taking a look at it.

11 CHAIRPERSON MACK: Right.

12 Dicloran. And that's Darryl, only reviewer.

13 COMMITTEE MEMBER HUNTER: Power.

14 I give it a low.

15 CHAIRPERSON MACK: Low.

16 COMMITTEE MEMBER HUNTER: I gave it a low.

17 CHAIRPERSON MACK: Tell us about it in a sentence
18 or 2.

19 COMMITTEE MEMBER HUNTER: Fungicide does have
20 widespread use. In the animal data, the tumor trends were
21 malignant in -- at least in one of the studies isolated to
22 one gender. Females and the males, it was combined benign
23 and malignant. And so my general feeling was that this
24 was something that we have bigger fish to fry.

25 CHAIRPERSON MACK: Anybody disagree?

1 Joe?

2 COMMITTEE MEMBER LANDOLPH: No, I agree
3 completely.

4 CHAIRPERSON MACK: Agree. So it's low. And
5 there's no public comment.

6 The next one is dinitroaniline pesticides.

7 First of all, let me ask the gentleman down there
8 how he's doing?

9 THE COURT REPORTER: I'm okay.

10 CHAIRPERSON MACK: You're all right. Okay. Wave
11 your hand if you need anything.

12 Dinitroaniline pesticides. That will be David
13 Eastmond and Anna Wu.

14 DR. SANDY: And, Dr. Mack, if I could just remind
15 the Committee, we're looking for groupings -- rankings of
16 the group, as well as 2 individual compounds, prodiamine
17 and trifluralin.

18 Thank you.

19 COMMITTEE MEMBER EASTMOND: I certainly didn't
20 realize that when I was reviewing it.

21 So what are the 2 we are commenting on?

22 Prodiamine and trifluralin.

23 I mean, I guess I'll just give you my general
24 comments overall. I ranked this between medium and high.
25 And it really depends upon the likely significance of the

1 thyroid tumors. I mean, one of the things that happens is
2 that there are some reports in humans, but not very
3 consistent. Mixed reports of cancer in rodents. But
4 fairly consistent increases in thyroid, follicular cell
5 adenomas and/or carcinomas seen for a number of the
6 pesticides. And liver tumors were also seen in mice for a
7 number of the studies as well.

8 They mixed frequently negative gene tox studies.
9 It's been proposed in involved in alteration of thyroid
10 hormone levels. If that's true, then that kind of
11 influences how you interpret the thyroid hormones. So
12 again, I had challenges looking at the class at once, but
13 this was one that I thought might be relevant because of
14 the similarities in the tumors.

15 The public comments were also concerned about
16 listing as a group. And that non-carcinogenic agents
17 would be inappropriately prioritized. They said only --
18 EPA has only considered one of these to be carcinogenic.

19 Anyway, I guess a priori understanding the
20 significance of the thyroid tumors would come in the
21 evaluation. So I'd probably put this in the sort of
22 medium-high category. I could go either way on that.

23 CHAIRPERSON MACK: Anna.

24 COMMITTEE MEMBER WU: I had it in the high-medium
25 category. Maybe not for the same reasons, but because

1 they were -- you know, the description was a mixture and
2 that there was certainly enough information there to
3 suggest that only a medium and maybe high.

4 CHAIRPERSON MACK: Would the 2 of you please
5 agree on whether it's medium or high.

6 COMMITTEE MEMBER WU: I would put it in the high,
7 I actually -- the way I do it is high-medium, that means I
8 lean towards the high first. That's how -- you know,
9 that's how I indicated it.

10 CHAIRPERSON MACK: Let's hear from the regulated
11 community. We'll see if we can be -- either offended
12 enough to make it high or be convinced enough to make it
13 low.

14 So Richard Peffer.

15 DR. PEFFER: I'm Richard Peffer with Syngenta
16 Crop Protection. And I actually was going to just speak
17 to the prodiamine, which was part of the question was to
18 ask were it individually should be rated high, low, or
19 medium.

20 And prodiamine has only thyroid tumors as part of
21 its spectrum. And it's genotox profile is negative,
22 except for one study, an Ames assay that was done with an
23 older production batch that was prior to the modern
24 synthetic technique, when it was repeated with the new
25 synthetic technique, three or four other studies were all

1 negative.

2 And the mode of action for thyroid tumors has
3 been investigated and found to be looking like a classic
4 phenobarbital type profile, where UDP-glucuronyl
5 transferase is induced, which causes increased secretion
6 of thyroid hormone. So for prodiamine, I think it ought
7 to be evaluated separately, and it ought to be medium or a
8 low category.

9 CHAIRPERSON MACK: Thank you.

10 Sabitha Papineni.

11 DR. PAPINENI: Good afternoon. I'm Dr. Sabitha
12 Papineni. I'm a toxicologist here working for Dow
13 AgroSciences.

14 And I'm here to represent the DNA, the
15 trifluralin, benfluralin, ethalfluralin. And the concept
16 is about the thyroid tumors as Dr. Eastmond was
17 mentioning. It has been highly investigated, and we also
18 have published literature on trifluralin to show that the
19 mode of action is not relevant to humans and it's very
20 specific to rodents, especially rats.

21 And the other thing I want to draw your attention
22 to is that trifluralin has been investigated by -- I mean,
23 evaluated by other agencies, IARC, the International
24 Agency for Research on Cancer. And clearly it concluded
25 that trifluralin is not classified both as a carcinogen,

1 based on the epidemiological data and also the animal
2 data, which is overly negative.

3 And coming to the widespread use, the use of
4 trifluralin has been declining over the past 10 years by
5 over 50 percent. And it's mostly used a granules, which
6 minimizes exposure. And it's a pre-emergent herbicide
7 applied directly to the soil.

8 And benfluralin clearly in the write-up of the
9 CIC on the dinitroanilines clearly indicate that there is
10 no use or benfluralin reported in 2009. And it's a very
11 minimum use of benfluralin these days.

12 And coming to ethalfluralin, it's just one study
13 that's in Fischer rats showing mammary fibroadenomas which
14 are benign, non-invasive. And clearly showed that this
15 strain is very prone for these tumors. So considered not
16 biologically relevant to humans.

17 So we would request the CIC to give it a medium
18 or low priority based on these findings.

19 Thank you.

20 CHAIRPERSON MACK: David, do you have any
21 response? I mean, we have two problems here. One is
22 resolving between medium, high, and low. And since we
23 have all three of them that's been induced, you two are
24 resolving between medium and high, and then we have to
25 make some decisions about the individual compounds,

1 because we're asked to most recently.

2 COMMITTEE MEMBER EASTMOND: I can go either way.

3 I mean, I probably --

4 COMMITTEE MEMBER WU: Medium.

5 COMMITTEE MEMBER EASTMOND: -- lean it to medium
6 is fine. Yeah. I mean, I suspect that there -- the
7 thyroid tumors seem to be driving it for me. And it does
8 appear that a number of classes of agents induce thyroid
9 tumors are not believed to be relevant to humans. Now,
10 whether this is a class -- whether it fits in that class,
11 I'm not certain, but that would suggest that it would be
12 medium for me.

13 CHAIRPERSON MACK: So we're going to call it
14 medium for each of the two specific compounds as well?

15 COMMITTEE MEMBER WU: Certainly.

16 COMMITTEE MEMBER EASTMOND: Sure.

17 CHAIRPERSON MACK: Does that make you happy?

18 (Laughter.)

19 CHAIRPERSON MACK: Okay. Entecavir. Darryl.

20 COMMITTEE MEMBER HUNTER: I think I also did that
21 one. This is -- has a medical use. It's an anti-viral
22 drug for hepatitis B, so something very important. I gave
23 this a -- I gave it a medium, shown to -- in animal
24 studies to increase in malignant tumors, in males and
25 females, both in mice and rats. So two different animal

1 models. Widespread use. I felt it was something
2 important because of its medical use that it get a little
3 bit of a priority.

4 CHAIRPERSON MACK: Does anybody have additional
5 comments?

6 COMMITTEE MEMBER HAMBURG: Was it a low or a
7 medium?

8 COMMITTEE MEMBER HUNTER: I gave it a medium.

9 COMMITTEE MEMBER HAMBURG: A medium. I would
10 agree with that.

11 CHAIRPERSON MACK: So we'll go with medium.

12 I committed a sin here. Artie Lawyer wanted to
13 talk about dinitroaniline.

14 DR. LAWYER: I'm fine.

15 COMMITTEE MEMBER EASTMOND: You're okay with it?

16 DR. LAWYER: Medium is fine.

17 CHAIRPERSON MACK: And Fred Hess also did.

18 DR. HESS: Back to dinitroaniline. If I could
19 have a couple of minutes.

20 CHAIRPERSON MACK: You can have one minute.

21 DR. HESS: I have an overhead.

22 CHAIRPERSON MACK: We've settled on medium for
23 both the group and for the two individual compounds.

24 DR. HESS: Yes, I realize that. And I represent
25 a different compound. If you'd rather not get into that

1 now, that would be okay. In other words, I have a third
2 dinitroaniline.

3 CHAIRPERSON MACK: I don't think we needed any
4 judgment on a third.

5 DR. HESS: Thinking it was lumped in with the
6 group, that's why.

7 CHAIRPERSON MACK: Okay. Go ahead, and make your
8 comment.

9 DR. HESS: Okay. Request. It's the one the
10 pointer is on.

11 My name is Frederick Hess from Research Triangle
12 Park and BASF's chemical company.

13 The next slide.

14 --o0o--

15 DR. HESS: This is why we don't think that
16 dinitroaniline should be lumped in together as a single
17 class, they may act similarly in plants, herbicidal
18 activity through their activity in there against
19 pre-emergent crabgrass. They prevent -- or inhibit
20 microtubule assembly in the plant.

21 However, their mammalian tox profiles are very
22 different, and including their differences in tumor
23 induction are very different. EPA also thinks that way,
24 and do not consider the group as a cumulative risk
25 approach for risk assessment. And they have said that

1 numerous times for the various dinitroanilines okay.

2 --o0o--

3 DR. HESS: Genotoxic -- this is for
4 pendimethalin. I won't go into this, but the next slide
5 might help us with the thyroid, benign thyroid tumor type
6 of tumor induction for -- this again is for pendimethalin,
7 but at a high dose that cause 20 to 30 percent decrease in
8 body weight gain.

9 There were just benign thyroid follicular cell
10 adenomas. And this is the -- the cell of origin is the
11 follicular epithelial cell in the thyroid gland. And this
12 is a well known mode of action, which is a secondary or
13 indirect mechanism of feedback. It's not a direct acting
14 on the thyroid or iodide, but it's one that involves
15 enzyme induction, increased glucuronyl transferase in the
16 liver. And that sets into place a whole -- multiple
17 stages of trying to get to homeostasis with T4 thyroxine
18 hormone through TSH through thyroid releasing factors from
19 the hypothalamus.

20 CHAIRPERSON MACK: I think you've made the case
21 that when we consider these, in their medium priority
22 subcategory, they will be taken up individually.

23 Thank you very much.

24 DR. HESS: Okay. You're welcome and thank you.

25 CHAIRPERSON MACK: Let's go to flonicamid.

1 COMMITTEE MEMBER HAMBURG: I reviewed that.
2 That's low for me. It's a relatively minimally used
3 compound. The data does not look very strong. The
4 genotoxicity data is relatively -- is all negative, as far
5 as I can see. Nasolacrimal duct tumors in a single
6 species, single sex at very high doses.

7 So I think the likelihood of finding anything
8 significant is relatively small.

9 CHAIRPERSON MACK: Joe.

10 COMMITTEE MEMBER LANDOLPH: I had it medium. I
11 agree with Sol, there's no genotoxicity. It's a
12 nicotinoid insecticide used on cotton and alfalfa, fruits
13 and vegetables. Agricultural workers and people eating
14 crops with residues are exposed. It's positive in 3 out
15 of 3 animal experiments, nasolacrimal duct, carcinomas in
16 the female rats, lung tumors in male and female mice. So
17 I gave it a medium.

18 CHAIRPERSON MACK: You gave it a medium?

19 COMMITTEE MEMBER LANDOLPH: Yeah.

20 CHAIRPERSON MACK: So would the two of you
21 resolve those.

22 COMMITTEE MEMBER HAMBURG: I'm sticking with low.
23 Joe?

24 COMMITTEE MEMBER LANDOLPH: Given the lack of
25 genetox data, I could move to a low on that.

1 COMMITTEE MEMBER EASTMOND: I actually originally
2 gave it a high.

3 (Laughter.)

4 COMMITTEE MEMBER EASTMOND: But I'd go down to
5 medium. But you've got -- it's clearly that it's
6 reproducible in 2 different studies in mice. You've got
7 alveolar, bronchiolar adenomas or carcinomas.

8 CHAIRPERSON MACK: So could we talk you into a
9 medium, Sol?

10 COMMITTEE MEMBER HAMBURG: Yes, you can.

11 CHAIRPERSON MACK: Fluazinam. That's David and
12 Darryl.

13 David?

14 COMMITTEE MEMBER EASTMOND: I put this between
15 low up to medium.

16 CHAIRPERSON MACK: You seem to have a 5 category
17 system.

18 COMMITTEE MEMBER EASTMOND: I have 5 categories
19 always.

20 (Laughter.)

21 COMMITTEE MEMBER EASTMOND: Essentially, it's not
22 registered for use in California, so it's really --
23 exposure would come through residues in crops registered
24 in other states. And that's driving it. They're
25 certainly positive for thyroid gland follicular cell

1 tumors in male rats and also liver tumors in male and
2 female mice.

3 I guess that's what driving it for me. Again,
4 this mechanism for the thyroid tumors, at least in the
5 public comments, was commented this was probably related
6 to a hormone imbalance associated with increase TSH. So
7 anyway.

8 CHAIRPERSON MACK: So, Darryl.

9 COMMITTEE MEMBER HUNTER: I gave it a medium.

10 CHAIRPERSON MACK: So are we both happy with
11 medium?

12 COMMITTEE MEMBER EASTMOND: Medium is okay with
13 me.

14 Everybody else?

15 Hexythiazox. And that's Darryl and Sol.

16 COMMITTEE MEMBER HAMBURG: All right. I gave
17 this one a low as well. Genotoxicity data is all
18 negative. It's a sparsely used compound. There's no
19 human data. Animal data is old. It doesn't have a great
20 significance in my book.

21 COMMITTEE MEMBER HUNTER: Yeah, I gave it a low.

22 CHAIRPERSON MACK: Everybody happy with low?

23 COMMITTEE MEMBER EASTMOND: I have it medium to
24 high.

25 (Laughter.)

1 COMMITTEE MEMBER EASTMOND: Just so you know.
2 Essentially, this was rated by the EPA. It's considered
3 to be likely to be carcinogenic in humans, but it's --
4 you've got again hepatocellular carcinomas in male and
5 female mice. And then you have benign tumors in the male
6 rats, but if you want to go with low, I'm not --

7 COMMITTEE MEMBER HAMBURG: I mean the question
8 when we do this is not whether it's carcinogenic or not.
9 The question is what is its relevance to Prop 65 in the
10 immediate future. I don't think we're talking about
11 whether these are carcinogenic or not. I think how we
12 prioritize these is what the real issue is.

13 CHAIRPERSON MACK: Basically, whether there's a
14 legitimate hypothesis and whether it's an urgent issue.

15 COMMITTEE MEMBER HAMBURG: And I put the urgency
16 as very low. So I think --

17 COMMITTEE MEMBER EASTMOND: The use is actually
18 very low, so that's probably a reasonable way to go.

19 Joe.

20 COMMITTEE MEMBER LANDOLPH: Yeah. I rated it
21 low, because there's no genetox, and there's no Epi at
22 all. Just the 2 animal studies. I thought this was low
23 probability too.

24 COMMITTEE MEMBER EASTMOND: I'm okay with low.

25 CHAIRPERSON MACK: So we'll call it low.

1 COMMITTEE MEMBER LANDOLPH: Low.

2 CHAIRPERSON MACK: And go to hydralazine and its
3 salts. I judged this one to be low. And the other person
4 was --

5 COMMITTEE MEMBER WU: Anna. I had it low.

6 CHAIRPERSON MACK: Low?

7 COMMITTEE MEMBER WU: Yes.

8 CHAIRPERSON MACK: So we both agree on low. Does
9 anybody have a problem with that?

10 So we'll call hydralazine low.

11 Isophosphamide. That would be David and -- David
12 and David.

13 COMMITTEE MEMBER EASTMOND: I put it in the
14 medium to low category based on limited data. I think
15 it's likely a carcinogen, but I'm not sure there will be
16 sufficient data to spend the time on it. But that's -- if
17 you want to go through my kind of rundown of things.

18 CHAIRPERSON MACK: Do you think the people of
19 California will want us to look at it relatively soon?

20 COMMITTEE MEMBER HAMBURG: Let me make a couple
21 comments. It's commonly used in clinical practice. I use
22 this drug at least once a week. It is likely to be a
23 carcinogen as -- I think I lost my microphone.

24 Again, I would say no higher than a medium, if we
25 want to list it. But I don't think for most patients

1 getting this drug, there are no alternatives.

2 CHAIRPERSON MACK: Shall we go with medium

3 COMMITTEE MEMBER HAMBURG: You can go with
4 medium.

5 COMMITTEE MEMBER EASTMOND: I can go with medium
6 or low.

7 COMMITTEE MEMBER HUNTER: I'd go with low. I
8 mean, there's no alternative. You're using it to treat
9 cancer. Is it really a priority for us to --

10 COMMITTEE MEMBER HAMBURG: No. I would agree.
11 Low is fine.

12 COMMITTEE MEMBER EASTMOND: Low is fine.

13 CHAIRPERSON MACK: Low.

14 COMMITTEE MEMBER LANDOLPH: Yeah, I agree, low
15 too.

16 CHAIRPERSON MACK: Nothing like interaction.
17 Metofluthrin. That's David again, and me.

18 COMMITTEE MEMBER EASTMOND: This was positive in
19 liver tumors in both male and female rats. Negative in
20 mice. Negative essentially in genetox studies.
21 Structurally related to a couple of Proposition 65 other
22 pyrethroids. And indicates that the -- it acts through an
23 induction of cytochrome P450 monooxygenase enzymes. And
24 it's fashioned similar to phenobarbital. Although, that
25 hasn't been clarified. Public comments, exposure is very

1 low. So I put this in the sort of medium-low category,
2 probably more low than medium.

3 CHAIRPERSON MACK: I put it in low actually. I
4 did look at it. And if that means that if we both put it
5 in low, then Christian Volz doesn't need to say anything.

6 MR. VOLZ: You got it.

7 COMMITTEE MEMBER EASTMOND: You okay with that?

8 CHAIRPERSON MACK: Okay. We come to mixtures
9 containing pentabromochlorocyclohexane. And that's David
10 Eastmond and Sol Hamburg.

11 COMMITTEE MEMBER HAMBURG: Dr. Eastmond, are you
12 going to say high? Go ahead say high?

13 (Laughter.)

14 COMMITTEE MEMBER EASTMOND: I'm not going to say
15 high. Go ahead.

16 (Laughter.)

17 COMMITTEE MEMBER HAMBURG: Me either.

18 COMMITTEE MEMBER EASTMOND: Well, essentially
19 you've got some positive animal studies. These are flame
20 retardants in presence in -- use for a variety of
21 different exposures. So I think fairly significant
22 exposures.

23 Negative Ames test. I put this sort of medium to
24 low, driven by limited information. But what do you
25 think, Sol?

1 COMMITTEE MEMBER HAMBURG: Yeah. You know, I
2 would -- medium I think. My concern really about it is
3 that there seems to be a scant amount of data from the
4 screening information. So I don't know that we're going
5 to be able to come to a conclusion about this. So I would
6 put it -- but I think it's a relevant issue. I don't
7 think it's been tested enough. So I would put it in the
8 medium level. I wouldn't put it low.

9 CHAIRPERSON MACK: So medium it is. Next is
10 n-methyl-n-nitroso-1-alkylamines

11 DR. SANDY: Dr. Mack?

12 CHAIRPERSON MACK: Yes, ma'am.

13 DR. SANDY: So I'm asking the Committee on this
14 one, 5 different rankings.

15 CHAIRPERSON MACK: Oh, good, Lord. Well, I'm the
16 only person to do it. And I can't give you 5 different
17 rankings. So I have to appeal to one of my molecular
18 colleagues, one of non-epidemiologic colleagues. And the
19 one to my left is the one I first come to.

20 Have you looked at these?

21 COMMITTEE MEMBER EASTMOND: Have I looked at it?
22 Yeah.

23 CHAIRPERSON MACK: What I said was that I'm
24 incapable of judging the priority of these 5 compounds one
25 by one, because they're all animal data, and no

1 epidemiology. So I'll ask David if he can help me.

2 COMMITTEE MEMBER EASTMOND: I mean, I looked at
3 these. And there's -- these are carcinogenic in animal --
4 in multiple targets sites in animal models. So, for me, I
5 thought they were pretty high. The real concern is what's
6 the exposure.

7 And I would suggest, essentially if you want to
8 prioritize among them, it's really prioritizing based upon
9 exposure and what you think their relevance is. As a
10 class, I think they're fairly. It's one that would be a
11 concern if there's sufficient exposure.

12 CHAIRPERSON MACK: So for a person who demanded
13 individual characterization on five compounds, I see 1X in
14 the exposure category, in the chart that you've given us.

15 So if you want five judgments, you're going to
16 have to give us 5Xs.

17 (Laughter.)

18 COMMITTEE MEMBER HAMBURG: Do we have any
19 information about when what you talk about can be
20 detected, what is the level of detection that you're
21 talking about? Do we have any information to say whether
22 it is one in a billion parts, or one in a million parts or
23 do we have any sense of that?

24 DR. SANDY: I don't think we do. We didn't turn
25 it up during the screening process.

1 COMMITTEE MEMBER HAMBURG: No, no, right, so --
2 because it's really hard to say whether it's a relevant
3 issue or not. I mean, if it's a part per billion, I
4 mean -- yeah.

5 CHAIRPERSON MACK: Yeah. I think that's very
6 true.

7 COMMITTEE MEMBER LANDOLPH: Tom.

8 CHAIRPERSON MACK: Yeah.

9 ACTING DIRECTOR ALEXEEFF: George Alexeeff.
10 Well, if exposure is the question, but if you feel you
11 have some confidence on the other -- you know, the
12 potential carcinogenicity, you could just let us know that
13 and say, well, we should probably look at exposure before
14 we spend a lot of time on it, to see if it's relevant or
15 something like that.

16 COMMITTEE MEMBER HAMBURG: Well, how does that
17 fit into our ranking. I mean, I'm trying to work with the
18 program here.

19 ACTING DIRECTOR ALEXEEFF: Oh, I would rank it as
20 high, if that's what I thought I heard you say. And then
21 with a caveat of check exposure, you know, to be sure.

22 COMMITTEE MEMBER HAMBURG: Yeah, clinical
23 relevance, yeah.

24 COMMITTEE MEMBER LANDOLPH: Tom.

25 CHAIRPERSON MACK: Joe.

1 COMMITTEE MEMBER LANDOLPH: Yeah. I was looking
2 at n-methyl-n-nitroso-1-dodecanamine. And I had a little
3 concern there, because it causes pancreatic islet cell
4 tumors, which are rare. And it also causes increases in
5 angiosarcoma of the liver, which also is very rare. So I
6 think I would pull that one maybe forward in that list,
7 based on those rare tumors.

8 CHAIRPERSON MACK: So does that give us answers.
9 We're going to call all of them high and then deal with
10 them individually.

11 COMMITTEE MEMBER LANDOLPH: Yeah, because the
12 rest of them, they're all organ specific. All the
13 nitrosamines are like that. They're very similar except
14 they vary a little bit in the organ. So I think they're
15 similar.

16 CHAIRPERSON MACK: Which brings to us
17 n-nitroso-n-methylaniline.

18 COMMITTEE MEMBER HAMBURG: That's me.

19 CHAIRPERSON MACK: And Sol.

20 COMMITTEE MEMBER HAMBURG: Let me just review
21 what I wrote.

22 Well, I would reiterate what I said with some of
23 these other compounds. The data is very old. I don't
24 know that there's a significant relevance to evaluating
25 this right now as compared, so I would put it low.

1 CHAIRPERSON MACK: That's what I put it also.

2 COMMITTEE MEMBER EASTMOND: I put it high.

3 (Laughter.)

4 COMMITTEE MEMBER HAMBURG: Well, but we knew that
5 as soon as I said low.

6 (Laughter.)

7 CHAIRPERSON MACK: We sort of assumed that.

8 (Laughter.)

9 COMMITTEE MEMBER EASTMOND: Well, I --

10 CHAIRPERSON MACK: Make a case.

11 COMMITTEE MEMBER EASTMOND: Okay. You've got 3
12 studies in rats. All of them gave malignant esophageal
13 tumors. Three separate studies gave you the same tumor
14 type. And then in hamsters, there was increase in liver
15 tumors and spleen hemangiosarcomas.

16 So for me the animal data is actually much
17 stronger than many. This is found in rubber manufacturing
18 and found in smoked meat. Certainly exposures are
19 potentially there. For me, this would be at least a
20 medium and probably a high.

21 COMMITTEE MEMBER LANDOLPH: Yeah. Tom, I would
22 go along with Dave on that. The nitrosamines are very
23 strong carcinogens.

24 CHAIRPERSON MACK: Okay. So we go along with
25 high?

1 COMMITTEE MEMBER LANDOLPH: Yeah.

2 CHAIRPERSON MACK: Sol.

3 COMMITTEE MEMBER HAMBURG: Well, I'll go to a
4 medium.

5 CHAIRPERSON MACK: All right. Let's call it a
6 medium.

7 COMMITTEE MEMBER EASTMOND: All right. That's
8 fine.

9 CHAIRPERSON MACK: And let me make sure there's
10 nobody who wants to speak to that. No. Oh, yes there is.
11 Okay. We're going to NMP now. And that's Joe
12 and I.

13 And I called it medium.

14 COMMITTEE MEMBER LANDOLPH: And I gave it a low,
15 based on weak genotoxicity, weak animal studies only. One
16 out of 3 was positive. And there's no epidemiology
17 studies as all on it.

18 It's an industrial solvent, paint stripper,
19 petroleum refining, industrial refining.

20 CHAIRPERSON MACK: It's a household -- it's a
21 contaminant -- it's a component of household solvents too.
22 I mean, it's wood -- paint strippers and things, and
23 that's the basis on which I thought maybe it ought to be
24 looked at.

25 COMMITTEE MEMBER LANDOLPH: Okay.

1 CHAIRPERSON MACK: Can I talk you into a medium?

2 COMMITTEE MEMBER LANDOLPH: Yeah. It's weak as a
3 carcinogen, but based on household use, that's fine.

4 CHAIRPERSON MACK: Okay. Let's go for medium.
5 And we have somebody who -- Kathleen Roberts wanted to
6 speak. She doesn't like a medium.

7 MS. ROBERTS: I don't. I'm sorry.

8 I would reiterate that the -- there were 3
9 cancerous animal -- there were no epidemiology studies
10 mentioned, 3 animal cancer studies mentioned. Only one
11 showed positive effects. That was a dietary study in mice
12 for liver tumors. Those were only seen at very high dose
13 levels over a thousand mgs per kg. And we -- the belief
14 is that that's a consequence of enzyme induction.

15 Of the one positive in vitro genotox result, that
16 actually was considered invalid by OECD when it did its
17 international assessment of this chemical back in 2007.
18 And certainly far outweighed by the 11 negative in vitro,
19 in vivo studies that are valid and available on this.

20 As far as the consumer products, it is in some
21 consumer products, but at low concentrations, and
22 therefore we think a low priority is probably more
23 appropriate.

24 CHAIRPERSON MACK: What's a low concentration?

25 MS. ROBERTS: I'm sorry?

1 CHAIRPERSON MACK: What's a low concentration?

2 MS. ROBERTS: I don't have that data, but I can
3 certainly get it.

4 CHAIRPERSON MACK: But it's in paint strippers,
5 is it not?

6 MS. ROBERTS: It is in some paint strippers, yes.

7 CHAIRPERSON MACK: And since it's household
8 stuff, and it's a scary household stuff to a lot of
9 people, it might be -- make them much happier to know that
10 nobody thinks it's carcinogenic from the State of
11 California.

12 MS. ROBERTS: Yes, sir. I suppose that is your
13 opinion. I would also point out that there's a lot of
14 high and mediums on this list right now. And if we're
15 looking for truly a prioritization process, some will have
16 to go to the low priority.

17 CHAIRPERSON MACK: Okay. Your point is well
18 taken.

19 Shall we go with low?

20 COMMITTEE MEMBER LANDOLPH: Okay. That's where I
21 started.

22 CHAIRPERSON MACK: Okay.

23 COMMITTEE MEMBER HAMBURG: I'm okay with low.

24 COMMITTEE MEMBER EASTMOND: Low.

25 CHAIRPERSON MACK: You called it high?

1 COMMITTEE MEMBER EASTMOND: No. Did we go to
2 low?

3 CHAIRPERSON MACK: Yeah.

4 COMMITTEE MEMBER EASTMOND: Okay.

5 CHAIRPERSON MACK: 6-nitrobenzimidazole.

6 COMMITTEE MEMBER HUNTER: I was one of the two on
7 that one. I gave that one a low. It is compound used as
8 a anti-fogging agent in photographic developing solutions,
9 so there's going to be some occupational exposure. But
10 the animal data was pretty sparse, limited to one study.
11 So I didn't feel it met the priority of being low.

12 CHAIRPERSON MACK: Anna.

13 COMMITTEE MEMBER WU: I agree.

14 CHAIRPERSON MACK: So this one is a low. Does
15 anybody argue with that?

16 COMMITTEE MEMBER EASTMOND: I even agree with
17 that one.

18 CHAIRPERSON MACK: My God.

19 (Laughter.)

20 CHAIRPERSON MACK: Not only did he agree with it,
21 but he only chose one level.

22 COMMITTEE MEMBER EASTMOND: Not on my notes
23 though.

24 (Laughter.)

25 CHAIRPERSON MACK: Pentachloronitrobenzene.

1 COMMITTEE MEMBER HAMBURG: This is of concern to
2 broccoli eaters and golfers. There is some animal data to
3 suggest that there's a malignancy associated with it. And
4 there is some genotoxicity data. However, I think it's
5 relatively of low importance to the citizens of the State
6 of California, and I would keep it as low.

7 CHAIRPERSON MACK: And Joe?

8 COMMITTEE MEMBER LANDOLPH: Yeah. I completely
9 agree. Not much genetox data. There's some animal
10 carcinogenicity data. But I think it's kind of a limited
11 use thing, so I would go with low on this too.

12 CHAIRPERSON MACK: Next, we go with pimecrolimus.
13 We're not dealing with tacrolimus. It sounds like
14 characters out of a Shakespeare. Pimecrolimus is going to
15 be me and Anna.

16 COMMITTEE MEMBER WU: I made it medium.

17 CHAIRPERSON MACK: And I called it medium also.
18 My God.

19 (Laughter.)

20 CHAIRPERSON MACK: That's regression to the mean,
21 if I ever heard it.

22 (Laughter.)

23 CHAIRPERSON MACK: Does anybody disagree with
24 that?

25 COMMITTEE MEMBER HAMBURG: I want to ask you a

1 question about this particular agent. When we are to
2 consider chemical carcinogenesis, this agent, like
3 tacrolimus, is really immunosuppressive. And you may get
4 secondary malignancies related to that. It may not be a
5 direct carcinogen.

6 Are we to include that in our consideration or is
7 it really strict chemical carcinogenesis with induction of
8 changes in DNA, et cetera.

9 CHAIRPERSON MACK: Obviously, that's a logical
10 option, but as an empiricist and an epidemiologist, I
11 would say somebody can always come up with a mechanism.
12 I'm interested in the association and whether it's causal.

13 COMMITTEE MEMBER HAMBURG: But the mandate of
14 Prop 65?

15 CHAIRPERSON MACK: Yeah, and Prop 65 doesn't
16 specify mechanism.

17 COMMITTEE MEMBER HAMBURG: Doesn't specify.
18 Okay.

19 CHAIRPERSON MACK: Pivalolactone.

20 COMMITTEE MEMBER HUNTER: I was one of the two.
21 I gave it a medium.

22 CHAIRPERSON MACK: And the other one was --

23 COMMITTEE MEMBER HAMBURG: And I gave it a low.
24 Poor data or old data, not that clinically relevant as
25 compared to their other agents, so I think we should

1 prioritize this in a low level.

2 COMMITTEE MEMBER HUNTER: I could live with that.

3 CHAIRPERSON MACK: Okay. Low, it is.

4 Pyraflufen ethyl.

5 COMMITTEE MEMBER HUNTER: I also am one of those.

6 I have that one a low.

7 COMMITTEE MEMBER HAMBURG: I gave that one a low

8 also, similar reasons.

9 CHAIRPERSON MACK: Okay. Raloxifen and its
10 salts. I gave that one a low also. And who was the other
11 person?

12 Joe.

13 COMMITTEE MEMBER LANDOLPH: Yeah. I gave it a
14 medium. It's completely negative in the genetox assays.
15 Positive in 2 out 2 animal carcinogenicity assays. Lowers
16 the risk of endometrial cancers, so it's good for that,
17 compared to general population tamoxifen users. So I said
18 low, but, you know, I could be --

19 CHAIRPERSON MACK: I said low also.

20 COMMITTEE MEMBER LANDOLPH: I said medium
21 initially, but I could be moved to low.

22 CHAIRPERSON MACK: Okay. Let's go for low.

23 COMMITTEE MEMBER HAMBURG: Sorry. I would argue
24 this one a little differently.

25 CHAIRPERSON MACK: Okay.

1 COMMITTEE MEMBER HAMBURG: Only in the sense from
2 a clinical standpoint, we often use it similar to
3 tamoxifen, for better or for worse. And since we listed
4 tamoxifen as a Prop 65 carcinogen, and since the IARC
5 listed it as a Group 1 agent, similarly, I think we're
6 obligated to list a similar class of drugs.

7 CHAIRPERSON MACK: We're certainly obligated to
8 look at it at some time.

9 COMMITTEE MEMBER HAMBURG: Look at it, yes.

10 CHAIRPERSON MACK: My understanding was that it
11 is not nearly as strong as --

12 COMMITTEE MEMBER HAMBURG: It is not as strong,
13 definitely.

14 CHAIRPERSON MACK: -- as a estrogen as tamoxifen
15 is

16 COMMITTEE MEMBER HAMBURG: Absolutely true.

17 CHAIRPERSON MACK: So -- and since -- even
18 tamoxifen, while it's widely used -- you'll recall our
19 difficulty with that --

20 COMMITTEE MEMBER HAMBURG: Right.

21 CHAIRPERSON MACK: -- because of all of the
22 eminent oncologists who came in to insist that we
23 shouldn't even be talking about it. Of course, we should
24 be talking about it, but again in the context, because
25 it's not that strong, I would call it a low, but I don't

1 mind going medium if everybody else thinks so. Do you
2 prefer medium.

3 COMMITTEE MEMBER HAMBURG: Medium I would prefer.

4 CHAIRPERSON MACK: Okay.

5 Joe.

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

7 CHAIRPERSON MACK: Okay. Medium it is.

8 Stavudine. That's Joe.

9 COMMITTEE MEMBER LANDOLPH: I said medium on this
10 one. Some genotoxicity, carcinogenicity and 2 experiments
11 in rats and mice, one each. Multiple tumors in males and
12 females. No epidemiology studies. It's a anti-HIV agent.
13 I don't want to push this one too hard, because I don't
14 want to get put in the position of wrecking good drugs
15 that are useful to the public, so that's why I gave it a
16 medium.

17 CHAIRPERSON MACK: You are the only one who
18 reviewed. What do you think, Sol?

19 COMMITTEE MEMBER HAMBURG: Either medium or low.
20 I wouldn't put it high, so medium is fine.

21 CHAIRPERSON MACK: Let's go for medium.

22 COMMITTEE MEMBER EASTMOND: Let me just say I put
23 this as high, but tempered, because it's a drug and very
24 useful. So it would go to medium, but it's kind of a
25 screaming positive in rats. I mean, there's all sorts of

1 tumors that are showing up in these animals. And it's
2 positive in mice. So, you know, it's one of these where I
3 think you do it because of specialized usage, rather than
4 actual data.

5 COMMITTEE MEMBER LANDOLPH: Yeah, I agree with
6 that.

7 CHAIRPERSON MACK: So we conclude medium.

8 COMMITTEE MEMBER EASTMOND: Yeah, let's go
9 medium.

10 CHAIRPERSON MACK: Topoisomerase II inhibitors.

11 COMMITTEE MEMBER WU: I had it.

12 COMMITTEE MEMBER HUNTER: No. I think you have
13 to go to Thiophanate.

14 CHAIRPERSON MACK: Oh, I'm sorry. I missed one.
15 Thiophanate methyl.

16 COMMITTEE MEMBER HUNTER: Yea. I'm one of the
17 two. I gave that one a medium.

18 CHAIRPERSON MACK: Joe.

19 COMMITTEE MEMBER LANDOLPH: I'm the other one of
20 the two. I gave it a medium too.

21 CHAIRPERSON MACK: Okay. That's easy.

22 Now, topoisomerase II inhibitors

23 COMMITTEE MEMBER WU: I gave it a medium.

24 CHAIRPERSON MACK: And she is the only reviewer.

25 And there are no public comments.

1 COMMITTEE MEMBER EASTMOND: I can comment on this
2 one.

3 Again, this is a class, and I feel like these
4 should be reviewed individually. The -- it's kind of
5 indicated in the footnote, etoposide has currently -- has
6 been classified as a Group 2 carcinogen by IARC.

7 Teniposide has been classified as a 2A, so those
8 would be going forward on it through the authoritative
9 body listing.

10 The other ones that are mentioned here, and I
11 should say they're different types of Topo II inhibitors.
12 These are all, what are called, Topo II poisons that you
13 have listed here, which are probably certainly seen
14 historically as the most serious, and they're the ones who
15 are most actively used clinically, but there are quite a
16 few other Topo II poisons out there. And I think they
17 need to be classified individually.

18 The 2 that you have here mitoxantrone and
19 epirubicin I think there's additional data on these.
20 Whether it would be sufficient to list, I'm not sure. But
21 the other thing on these Topo II inhibitors is they're
22 going to be very different, because the animal studies are
23 really not very helpful. I mean, you really come down to
24 human epidemiological studies combined with mechanistic
25 information in order to make a decision will probably be

1 driving them today.

2 So I would probably put them as medium, given
3 simply the idea that these are valuable for clinical use.
4 And they're used in the anti-cancer drugs, so there's --
5 they're being used for a very definite reason.

6 COMMITTEE MEMBER HAMBURG: Yeah, I would concur.
7 We use all of these agents on a daily basis. They're felt
8 to be carcinogenic in general. Certainly, if you look at
9 any of the package inserts, you'll see that these are
10 carcinogenic.

11 I don't know whether we have to review the data
12 though in order to list it. I think -- Dr. Mack, I
13 mean --

14 CHAIRPERSON MACK: I think medium would be a
15 reasonable conclusion. You're okay with that, Anna?

16 COMMITTEE MEMBER WU: Yes. That's what I said.

17 CHAIRPERSON MACK: That's what you said.

18 Okay. Triazole antifungal agents. And that's
19 David again and it's another group.

20 DR. SANDY: It is another group. And you have
21 the option -- well, we'd like you to rank the group or any
22 individual triazoles.

23 COMMITTEE MEMBER EASTMOND: All right. Mine.
24 This is a series of agents, many of which induce liver
25 tumors in male and female mice, but are largely inactive

1 in rats. The mouse liver cancer could be related to
2 halogen substituents, which are found on the molecules.

3 The results of genotoxicity study are mixed.
4 Most negative, but several are certainly genotoxic in
5 vivo. It's been proposed that these act through induction
6 inhibition of cytochrome P450 monooxygenase enzymes,
7 oxidative stress, altered cell signaling, proliferation.

8 As I indicated before, evaluating it as a class
9 is difficult. I think ultimately it will have to come
10 down to an individual ranking. The public comments
11 indicated they act through a number of different
12 mechanisms, so they shouldn't be classified together.

13 I guess then my rankings on this would be
14 probably medium to medium-high for the triadimefon; medium
15 for fenbuconazole; and depending on how you want to go you
16 could go with propiconazole, maybe medium, the others
17 would be low. That's kind of my rankings.

18 CHAIRPERSON MACK: So let's rank the group as
19 medium.

20 COMMITTEE MEMBER EASTMOND: Yeah. That's
21 probably fine.

22 CHAIRPERSON MACK: And Richard Peffer. You
23 unhappy with medium?

24 DR. PEFFER: Yeah. I think I just heard you say
25 that for the whole group you're going to categorize them

1 together as medium for prioritization.

2 CHAIRPERSON MACK: Yes.

3 DR. PEFFER: I was going to speak to the idea
4 that it's not appropriate to consider them all as a class
5 from the standpoint of they don't necessarily have a
6 common mechanism of action. And I think I see nodding
7 heads, and you all agree with that.

8 From the standpoint of some of the individual
9 chemicals that are on the list there. There's one on
10 there, etaconazole, that's in the list that has no
11 registrations anywhere and never did. So that one
12 probably could save you some work. You should strike that
13 one from the list. There's no exposure.

14 And there's -- the others I think I heard what
15 you mentioned was likely medium to high for 3 of the
16 listed chemicals and then low for the others.

17 COMMITTEE MEMBER EASTMOND: Well, there was
18 only -- only one was sort of this -- the others would be
19 medium. The three I listed would be medium and all the
20 rest would be low. And even the propiconazole could
21 actually go to low. It depends how you interpret the
22 mechanistic data. There's been a ton of mechanistic data
23 generated on that. And it depends how you interpret that
24 data.

25 I don't think it's -- it certainly is not a high,

1 high priority from my point of view, but --

2 DR. PEFFER: Yeah. And I would speak to
3 propiconazole as well. Syngenta, my company, is the
4 primary registrant for that. And EPA has done a fair
5 amount of studying on propiconazole and published on it.
6 And the one positive mutagenicity finding that's shown up
7 in the literature was big blue mouse assay that EPA did.

8 But actually a further review of that's been
9 done. It's recently been published in Environmental
10 Molecular Mutagenesis. And it looks like that study had
11 some analytical flaws in that they were comparing two
12 different control groups and two different sets of
13 experiments across time. And the propiconazole group was
14 right within the range of normal historical control.

15 So it's likely not positive in that assay. And I
16 would agree with the rest of its database for
17 mutagenicity.

18 CHAIRPERSON MACK: Okay. So I think with calling
19 them medium, they will be evaluated separately when the
20 time comes. And all of that will be pertinent
21 information.

22 DR. PEFFER: Okay.

23 COMMITTEE MEMBER EASTMOND: I mean, I guess the
24 way I would recommend looking at this is to put them
25 medium as a class. But as you get into that, very quickly

1 you'll see that some of these should actually be lower,
2 and we -- you know, you would put them as low priority as
3 you get into it.

4 CHAIRPERSON MACK: Okay. 2,4,6-T,
5 2,4,6-Trimethylaniline and its Salts.

6 COMMITTEE MEMBER HUNTER: I'm one of the two.

7 CHAIRPERSON MACK: Darryl.

8 COMMITTEE MEMBER HUNTER: Yeah, I gave it a
9 medium.

10 CHAIRPERSON MACK: And Anna?

11 COMMITTEE MEMBER WU: I gave it a low-medium. So
12 but, I mean, I can be swayed to the medium.

13 CHAIRPERSON MACK: Could we hold off on this for
14 a second, because I neglected Dr. Papineni wants to
15 comment on the one of the triazoles.

16 DR. PAPINENI: We concur if it's a medium.

17 CHAIRPERSON MACK: You're happy with medium.

18 DR. PAPINENI: As a group.

19 CHAIRPERSON MACK: Go ahead. So Anna.

20 COMMITTEE MEMBER HUNTER: She said low-medium.

21 COMMITTEE MEMBER WU: Yeah.

22 COMMITTEE MEMBER HUNTER: I said medium.

23 CHAIRPERSON MACK: You say medium too. So we're
24 happy with medium, everybody?

25 COMMITTEE MEMBER LANDOLPH: Yeah.

1 CHAIRPERSON MACK: Okay. And the last one is a
2 tris(2-ethylhexyl)phosphate. That's David and me. And I
3 gave it a medium. I did it based on what it said about
4 animals.

5 COMMITTEE MEMBER EASTMOND: I was medium to low
6 on this. Low was kind of my stronger leaning, but I'd go
7 to medium. That's fine.

8 CHAIRPERSON MACK: Okay. Low and behold
9 comment -- oh, there's a comment on this one.

10 Yes. Dr. Sutton. You get the last word or the
11 penultimate word anyway.

12 COMMITTEE MEMBER EASTMOND: Another flame
13 retardant.

14 DR. SUTTON: Yeah. Well, medium is decent. We
15 might urge you to go a bit higher, because it's a flame
16 retardant, so we have higher exposures in this state. We
17 find it in dust, so you got the young children's exposures
18 again. So you could consider that -- consider maybe
19 edging toward high.

20 CHAIRPERSON MACK: But you don't have that in
21 your sofa.

22 DR. SUTTON: No, just the other one.

23 CHAIRPERSON MACK: Well, it looks like we've done
24 it. Call that a meeting.

25 ACTING DIRECTOR ALEXEEFF: Are you asking me?

1 Ask the group.

2 CHAIRPERSON MACK: Do we have any words we have
3 to use, lawyer?

4 CHIEF COUNSEL MONAHAN-CUMMINGS: I don't think
5 so. You can just close the meeting. But I think that
6 usually Dr. Alexeeff would give a summary of the meeting
7 before you close.

8 CHAIRPERSON MACK: Yes. I was just making sure
9 we hadn't erred in our deliberation methodology.

10 Dr. Alexeeff.

11 ACTING DIRECTOR ALEXEEFF: Well, it's 4:30, and
12 the court reporter is still with us.

13 CHAIRPERSON MACK: I think we should give him a
14 big round of applause.

15 (Applause.)

16 ACTING DIRECTOR Alexeeff: Well, before I
17 summarize the meeting, I really want to thank Dr. Mack and
18 members of the CIC, all the members of the public that
19 testified or looking on line and submitted public comments
20 and such.

21 We had originally planned this as a 2-day
22 meeting. We've completed it in 1 day. I think, at the
23 same time, we did due diligence in terms of considering
24 all of the issues. So, you know, I really compliment the
25 Committee and everyone who participated in this. And I

1 also want to thank the staff for their preparation and
2 their presentations. And I take it that that helped the
3 Committee move to a speedy decision on these items.

4 And, let's see, I don't know if originally, Dr.
5 Mack, before -- when we were discussing the procedures
6 item, I had left a comment that staff could -- that the
7 members could comment on whether there was anything they
8 wanted to mention about the information that was provided
9 to them, any, you know, improvements or suggestions or
10 things like that. I don't know if there are any. I'm not
11 fishing for compliments. I'm simply just -- since we're
12 all here, I thought I'd just give the opportunity if there
13 were any comments that members want to make.

14 CHAIRPERSON MACK: Well, actually I think the
15 staff did a terrific job. I do, however, have one,
16 somewhat negative, comment. I would like members of OEHHA
17 to see if they can find the phone number for OEHHA from
18 411. I have tried on Friday when I realized that I had
19 not received a couple of the papers that I should have
20 received, I tried for a full half hour to try and get --
21 and this was Friday. I was home. I didn't have a number.

22 None of the pieces of stationary that have your
23 heading that says George Alexeeff on top have a phone
24 number. There's no Email address. There's no way to
25 contact you if one is not in the office with previously

1 available information.

2 COMMITTEE MEMBER HAMBURG: This is a secret
3 organization.

4 (Laughter.)

5 CHAIRPERSON MACK: It seems to be a far more
6 secretive organization than it really needs to be. So I
7 would beg you to put the number on the letters or provide
8 the number to -- call 411 and try and see what happens. I
9 couldn't even get EPA. EPA was basically, "I'm not at my
10 phone right now. I'll come back and call you later".

11 (Laughter.)

12 CHAIRPERSON MACK: So that's my only negative.

13 ACTING DIRECTOR ALEXEEFF: I think we can rectify
14 that situation.

15 COMMITTEE MEMBER EASTMOND: If I can comment.
16 Having gone through this prioritization, the summaries
17 that we received this time were far more helpful than in
18 the early stages, which we'd -- when we receive nothing at
19 all but just -- so it's been actually an improvement, I
20 guess, now that we're at the end of it. Hopefully, for
21 the next series it will continue this way.

22 CHAIRPERSON MACK: I think there were really very
23 good. And, in fact, more voluminous than necessary in
24 some instances, but very appreciative, very much
25 appreciated.

1 ACTING DIRECTOR ALEXEEFF: I do want to -- I do
2 really want to compliment Martha Sandy and her staff on
3 the prioritization. And the reason is because we've
4 completed, you know, prioritization of 400 chemicals,
5 which was -- when we started this early on, and I think a
6 suggestion from Dr. Landolph at the time was suggesting
7 let's look at the Epi data. And we had, you know,
8 thoughts of how we would proceed on this. And we've kind
9 of marched through.

10 And having worked with Martha and her staff, I
11 know that I discussed each chemical with the staff on the
12 prioritization. And I know that Dr. Sandy discussed each
13 chemical with her their staff several times. So, I mean,
14 they spent, you know -- for the ones you did not see, they
15 spent a lot of time checking to see what information was
16 there. So it was very hercu -- anyway, it was a great
17 effort on their part I just wanted to say.

18 So, you know, although you've seen, what is it,
19 close to 100 chemicals, there was an equal amount of work
20 on the other 300 that you didn't see. I just want to let
21 you know that. And I really appreciate their work. So I
22 wanted to make that comment.

23 So I think I will go ahead and summarize the
24 decisions here.

25 So the Committee considered 2 chemicals for

1 potential listing today. The first chemical, the
2 Committee concluded that tris(1,3-dichloro-2-propyl)
3 phosphate has been clearly shown through scientifically
4 valid testing, according to generally accepted principles
5 to cause cancer.

6 For the second chemical, the Committee concluded
7 that fluoride and its salts has not been clearly shown
8 through scientifically valid testing, according to
9 generally accepted principles to cause cancer.

10 And then I want to thank the Committee for giving
11 us advice on prioritizing chemicals to bring to the
12 committee. And so there were 39, 38 chemicals?

13 DR. SANDY: Thirty-nine.

14 ACTING DIRECTOR ALEXEEFF: Thirty-nine. Well,
15 plus the groups. And so I thought I would just mention
16 which ones were classified first as high, so -- for us to
17 consider.

18 Acetaminophen, butyl benzyl phthalate, C.I.
19 disperse yellow 3, coumarin, dibenzanthracenes and
20 dibenz[a,c]anthracene, 2,4-dichlorophenoxyacetic acid its
21 salts and esters, n-methyl-n-nitroso-1-alkylamines and
22 some specific ones, depending upon their exposure.

23 That's it, right?

24 And then a number of chemicals were classified as
25 medium. Abacavir and its salts, bisphenol A, butylated

1 hydroxytoluene, chloroalkyl ethers, clodinafop-propargyl,
2 dapsone, 3,3'-dichlorobenzidine, DBZ-based compounds
3 metabolized to 3,3'DBZ, dinitroaniline pesticides,
4 including prodiamine and trifluralin, entecavir,
5 flonicamid, fluazinam, mixtures containing pentachloro --
6 I'm sorry, mixtures containing
7 pentabromochlorocyclohexane, n-nitroso-n-methylaniline,
8 pimecrolimus, raloxifen, stavudine, thiophanate methyl,
9 and the top 2 inhibitors, triazole antifungal agents.
10 Although those should be looked at individually,
11 2,4,6-trimethylaniline and its salts, and tris
12 (2-Ethylhexyl) phosphate.

13 So I want to thank you. Is there anything else
14 that I should consider from any comments from staff?

15 CHIEF COUNSEL MONAHAN-CUMMINGS: Just one
16 follow-up question. When we had our earlier discussion
17 about procedures, we had left the question open whether or
18 not the five minutes with the timer was -- you thought was
19 the useful approach or not, that you could advise the
20 Chair concerning how you felt that went.

21 ACTING DIRECTOR ALEXEEFF: And the question was
22 whether or not -- how they felt about the five-minute time
23 limit that had been utilized today and such, I think that
24 was the question.

25 CHAIRPERSON MACK: Oh, I think it went very well

1 today. I can't -- in fact, I wasn't -- I certainly wasn't
2 very strict, not as strict as I would have wished to have
3 been.

4 (Laughter.)

5 CHAIRPERSON MACK: But I think the information
6 that was provided by the people who spoke was very useful
7 and I thought it went very well. I'd like to congratulate
8 them all actually on being succinct and informative.
9 We've had some past experience with the opposite of that.
10 And nobody here did that today and it was great. And I
11 think it helps us -- it helps us to be succinct and
12 informative, because we've looked at what you've submitted
13 usually.

14 Yes, Joe.

15 COMMITTEE MEMBER LANDOLPH: Just on another
16 issue. You know, quite awhile ago we had random
17 prioritization, which I always rationally revolted
18 against. I hated that, because it was giving us dumb
19 chemicals to study, which was wasting our time. And then
20 we went to the prioritization meetings, the subcommittee
21 with George and myself and Lauren and Martha. I think
22 that cut through a lot. I think we're getting very good
23 chemicals now.

24 And Chief Counsel Carol Monahan-Cummings knows
25 that we have received criticism about wasting quote

1 unquote time on doing that prioritization. And my comment
2 is, I think that criticism is misguided, at best. So I
3 think the prioritization process is working very well.
4 We're getting serious chemicals to deal with now.

5 They all have -- you know, many of them -- some
6 of them have Epi data, most of them have strong animal
7 data. I think it's working very well.

8 CHAIRPERSON MACK: I would add that not just
9 serious chemicals, but they're chemicals people are
10 worried about. And that's perhaps even more important.

11 DR. LAWYER: One more from the public on the
12 timing.

13 It won't take like 10 minutes.

14 CHAIRPERSON MACK: You won't even get five
15 minutes.

16 DR. LAWYER: Arthur Lawyer, Technology Sciences
17 Group, downtown Davis. My only comment, and maybe it's
18 what the staff has in mind, but for the time constraints,
19 the five minutes or if there's ever a time where you think
20 there might be one minute. It would be very beneficial
21 for those that come from out of town and prepare, think
22 they should -- should I prepare slides, should I not, you
23 know, especially for the scientists that come all this way
24 to know the restrictions long in advance would be very
25 helpful, because a lot of people in the audience had to do

1 a lot of rearranging of their life today. So I'd
2 certainly appreciate it.

3 Thanks.

4 CHAIRPERSON MACK: Nobody could disagree with
5 that.

6 DR. LAWYER: And it was short.

7 ACTING DIRECTOR ALEXEEFF: Well, I want to thank
8 everyone again. And I close the meeting right now.

9 Thank you.

10 (Thereupon the Carcinogen Identification
11 Committee adjourned at 4:43 p.m.)

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