

MEETING
STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
PROPOSITION 65
DEVELOPMENTAL AND REPRODUCTIVE TOXICANT
IDENTIFICATION COMMITTEE

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SACRAMENTO, CALIFORNIA

WEDNESDAY, MARCH 19, 2014

10:30 A.M.

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CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

A P P E A R A N C E S

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Laurence Baskin, M.D.

Aydin Nazmi, Ph.D.

Isaac Pessah, Ph.D.

Meredith Rocca, Ph.D., D.A.B.T.

Tracey Woodruff, Ph.D., M.P.H.

STAFF:

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Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

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Dr. Francisco Moran, Reproductive Toxicology and
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Ms. Cynthia Oshita, Proposition 65 Implementation

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

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

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

ALSO PRESENT:

Dr. Arthur Lawyer, Technology Sciences Group

Mr. Dennis J. Naas, Eastman Chemical Company

Mr. Tim Shestek, American Chemistry Council

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1 P R O C E E D I N G S

2 DIRECTOR ALEXEEFF: We're going to go ahead and
3 get started here. I'm George Alexeeff, Director of the
4 Office of Environmental Health Hazard Assessment. And
5 first, I just want to start just to remind you that we
6 have the exit doors here, in case there's a need to
7 evacuate the room in case there's a fire drill or any
8 other reason.

9 So if there's a fire alarm, you know, take your
10 valuables with you. Do not use the elevator. Staff will
11 assist you if need to. We exit down the stairways outside
12 and to a relocation site across the street. Also,
13 drinking fountains and restrooms are out the door and to
14 my left, your right, past the glass sculptures there.

15 Okay. So I would like to go ahead and introduce
16 the Committee. First, I want to welcome you to the
17 meeting of the Developmental and Reproductive Toxicant
18 Identification Committee. And we are meeting today, March
19 19th, in the Sierra Room in Sacramento.

20 So on my left -- on my right is Dr. Ellen Gold,
21 who is the Chair of the Committee. She is professor and
22 Chair, Department of Public Health Sciences at UC Davis.
23 And further to my right is Dr. Aydin Nazmi. And he is
24 assistant professor of Food, Science, and Nutrition at Cal
25 Poly, San Luis Obispo. Now, to my left is Dr. Meredith

1 Rocca. And she's the director of non-clinical toxicology
2 at Janssen Alzheimer Immunotherapy Research and
3 Development. And to her left is Dr. Isaac Pessah, who's
4 professor and chair of the Department of Molecular
5 Biosciences at UC Davis.

6 As you can tell, we are missing a few members of
7 the Committee. They are on their way. Their train was
8 delayed. And when they arrive, I will introduce them.

9 In the meantime, so we can go ahead and proceed,
10 we'll be proceeding with some non -- essentially some
11 non-discussion or decision items, just some informational
12 items from staff. But I -- so I was wondering, Dr. Gold,
13 first, if you wanted to make any comments in the
14 beginning?

15 CHAIRPERSON GOLD: No, thank you. I don't really
16 have any comments, except to welcome everyone here for a
17 good discussion today, and a fuller discussion when the
18 rest of the Committee arrives. But we'll turn it over to
19 the staff now, I think.

20 DIRECTOR ALEXEEFF: Yes. We'll begin with Carol
21 Monahan-Cummings.

22 CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning.
23 Just as a reminder to myself and others that you almost
24 have to swallow the microphones in order for them to work
25 well enough for people to hear, particularly on the

1 webcast. So if you can get right up there, that would be
2 good.

3 So I'm just going to give you a couple of updates
4 on some litigation that we're still involved in, and then
5 some of our regulatory actions that you might be
6 interested in as well.

7 I've given an update on the Sierra Club versus
8 Brown case every year for the last eight years. So right
9 now, the only issue left in that case is the attorney's
10 fees. And so the whole thing has been resolved and that
11 was a case about listings under Prop 65 and the other
12 committee, the CIC, members were sued in their capacity as
13 members of the Committee, but they have been dismissed and
14 the actions resolved except for the fees. So I'm hoping
15 one of these days I can get this off of our agenda.

16 There's two active cases currently in the trial
17 court. We don't have any court of appeal cases. We have
18 an action by the American Chemistry Council against OEHHA
19 for the brief listing of the chemical bisphenol A. It was
20 listed for eight days?

21 CHIEF DEPUTY DIRECTOR HIRSCH: Eight days.

22 CHIEF COUNSEL MONAHAN-CUMMINGS: Yes. Okay. So
23 that action is challenging the basis for the listing of
24 the chemical under the authoritative bodies listing
25 mechanism. It wasn't a committee listing. And in that

1 case, we are in the very early stages, where we're doing a
2 lot of motion practice. It will be really boring for
3 people that aren't lawyers. So we don't have a firm trial
4 date yet, but we do expect that that would be resolved
5 within the next year or so.

6 We also have a case where OEHHA was sued by the
7 Syngenta Crop Protection Company. And that has to do with
8 the establishment of a safe harbor level for a pesticide
9 called chlorothalonil. And the company is suing us
10 because they believe that the number is too low.

11 So that again is in the early stages of
12 litigation in the motion practice, and we are similarly
13 hoping that it will be resolved within a year. We do
14 anticipate that most likely both of these cases will go up
15 on appeal depending on the decisions, but we'll -- I'll
16 let you know that later.

17 So that's all the active litigation. Of course,
18 we have pre-litigation things going on all the time, and
19 so I'll let you know if additional cases get filed. And
20 so I'm going to take a little break here before I go into
21 regulations, is that all right, George, so you can
22 introduce the members?

23 DIRECTOR ALEXEEFF: Certainly. So I'd like to
24 introduce the two members. We have on my right, after Dr.
25 Gold, is Dr. Laurence Baskin. He's the Chief of Pediatric

1 Urology and professor of urology and pediatrics and
2 surgeon scientist at University of California at San
3 Francisco. Welcome.

4 And to my far left is Dr. Tracey Woodruff. She
5 is professor at Department of Obstetricians, Gynecology,
6 and Reproductive Sciences at the University of California
7 at San Francisco. So welcome. And just to let you know,
8 we've been -- we started with staff reports, so we'll
9 continue with staff reports before we get to any
10 discussion or decision items. So we're doing -- Carol
11 Monahan-Cummings is giving us our legal update right now.

12 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Welcome.

13 So the other issues I wanted to mention to you
14 that may have -- may be of interest to you as individuals
15 or members of the Committee, and you're welcome to comment
16 on these during the public comment periods. We are -- we
17 have proposed a new regulation to be adopted into our
18 regulations regarding Prop 65. And it has to do with
19 listings under what we call the Labor Code mechanism,
20 which we'll talk about again, because the chemicals that
21 are in front of you today have to do with the Labor Code
22 listings.

23 But we haven't, in the past, had a regulation
24 that defined how we list chemicals under that particular
25 mechanism, though we have some limited regulations on the

1 other three listing mechanisms. And we're not required to
2 have them, but we decided that it -- for purposes of
3 transparency and understanding for the public, that we
4 would adopt a regulation.

5 We have the regulatory language, Statement of
6 Reasons, and related documents on our website. And there
7 is a formal regulatory hearing on that proposal this
8 Friday, which will be webcast. And people on the webcast
9 can make comments via email. That's in the morning from
10 10:00 to noon or so.

11 The second one I wanted to mention is we are in
12 the pre-regulatory process for changes -- significant
13 changes to the regulations that have to do with providing
14 warnings to individuals that are being exposed to
15 chemicals that you have listed, or that we have listed
16 under other mechanisms. Pre-regulatory means that we
17 haven't proposed it for formal adoption. This is -- this
18 will be our second pre-regulatory workshop, which will be
19 held on April 14th.

20 If you take a look at the proposed regulations,
21 they're pretty extensive for us, and they would make some
22 really significant changes. We think positive changes in
23 terms of giving people more information about the
24 exposures that they have, and also increasing the
25 information that we have available on our website for

1 individuals that want more information than we can
2 actually get included on the warnings. And as I said,
3 your input would be most welcome.

4 The last one I wanted to mention is completed,
5 and that was our regulation that defined the
6 qualifications for this Committee and for the CIC
7 Committee. And you'll be happy to know that you all
8 qualify to be on this Committee.

9 We made sure, before we adopted the regulation.
10 So -- and I think you've had an opportunity to see that.
11 If you haven't already, it's on our website as well.

12 Currently, that is over at the Office of
13 Administrative Law for their final approval, which we
14 anticipate will come within the next couple weeks.

15 So does anybody have any questions on that or
16 other stuff?

17 Okay. I guess next is Cindy.

18 MS. OSHITA: Good morning. I'm going to just
19 give you a quick update on the administrative listings
20 that have happened since you last met in November. We
21 have added two chemicals to the Prop 65 chemical list.
22 Both were added in January. It was the emissions for high
23 temperature unrefined rapeseed oil and trichloroethylene.
24 Both were added as known to cause cancer.

25 We've completed our review of the comments that

1 we received on methyl isobutyl ketone. And we expect to
2 proceed with its listing next week.

3 There are a couple of other chemicals that are
4 still under consideration for administrative listing that
5 we mentioned at the last meeting. That includes
6 beta-myrcene and pulegone. We received one comment on
7 pulegone that we are currently reviewing, an extension to
8 the comment period for beta-myrcene was granted, and it
9 will close on March 24th.

10 We've also since issued Notices of Intent to List
11 for atrazine, propazine, simazine, and their
12 chlorometabolites, DACT, DEA, and DIA. Those are being
13 considered for listing for reproductive toxicity.

14 And then we have also issued notices for nitrite
15 in combination with amines or amides, megestrol acetate.
16 Three drugs, pentosan polysulfate sodium, pioglitazone,
17 and triamterene. And then also n,n-dimethyl-p-toluidine.
18 These are all being considered for listing for cancer. We
19 received no comments on megestrol acetate, and so we will
20 proceed with its listing next week as well.

21 And we await the close of the various other
22 comment periods. And if we receive any comments, they
23 will be reviewed before we proceed with any listing
24 decisions.

25 Thank you.

1 CHAIRPERSON GOLD: Yes, Dr. Woodruff.

2 COMMITTEE MEMBER WOODRUFF: What authority were
3 they listed -- under what authority were they listed?

4 MS. OSHITA: Under the -- most of them under the
5 authoritative bodies mechanism. Do you mean which --

6 COMMITTEE MEMBER WOODRUFF: Which authoritative
7 bodies, I was just curious?

8 MS. OSHITA: Oh, okay. For the triazine
9 pesticides, they are being listed by -- under the U.S.
10 EPA. The nitrite by IARC. The megestrol acetate is a
11 formally required, so that would be the FDA. The three
12 drugs that I mentioned are via the Labor Code. And then
13 the n,n-dimethyl-p-toluidine is by NTP.

14 CHAIRPERSON GOLD: Okay. Barring any other
15 comments or questions, I think we can now resume our
16 normal agenda, which we had planned to start 45 minutes
17 ago, but Amtrak sort of interfered with that.

18 So the plan is to go through six chemicals, three
19 glycidyl ethers and three ketones. And we will do it very
20 much the same way we did it back in November. There will
21 be some introductory comments I believe about why we are
22 doing this and the process. And then we will have staff
23 presentations for each of the chemicals. We'll go
24 chemical by chemical with staff presentations, public
25 comments, and then Committee discussion and Committee

1 vote. So we'll complete that for each of the six before
2 we go on to the next one.

3 So I think I'll turn it back to Carol.

4 (Thereupon an overhead presentation was
5 presented as follows.)

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Hello again. I
7 just wanted to give you a brief background on the
8 chemicals that are before you. I know we just had a
9 meeting recently. But given that you do a few other
10 things besides be on this Committee, I just want to remind
11 you why we're here.

12 I think the slides are in front of you. These
13 chemicals that you're going to be considering today were
14 added to the Prop 65 list a number of years ago. And
15 it -- they were based on some provisions of Prop 65 that
16 incorporate the federal Hazard Communication Standard. So
17 I'm going to just give you a little background on that,
18 and then we'll talk about the next steps for some of the
19 chemicals that are being considered, and answer whatever
20 questions you might have.

21 Next slide.

22 --o0o--

23 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So for
24 these chemicals, we're -- the reason that we have to look
25 at them again is because we need to change the basis for

1 listing the chemicals or remove them from the list,
2 because they no longer meet the listing requirements for
3 administrative listings under the Labor Code. And so we
4 have referred some of those to you for review of the basis
5 for listing.

6 There was a basis for listing for six other
7 chemicals that we've considered for -- under a different
8 authoritative body or formally required listings. I don't
9 know if you remember our introduction to the Committee
10 some time ago, where we did talk about the four different
11 listing processes. We have administrative authority to
12 list chemicals under the authoritative bodies process,
13 where this Committee and the CIC have identified
14 certain -- we should probably go to the next slide.

15 --o0o--

16 CHIEF COUNSEL MONAHAN-CUMMINGS: -- certain
17 bodies, including United States agencies and international
18 agencies that identified chemicals that are known to cause
19 cancer or reproductive toxicity. We have another
20 procedure for identifying chemicals via what's called the
21 formally required listing mechanism. Formally required
22 means that there's already a warning that's required by a
23 State or federal agency.

24 And so we just tag along on that. Generally
25 speaking, we have, in the past, listed mostly drugs under

1 this mechanism, but we can list them based on any
2 requirement for warnings. And so we are -- have -- as you
3 can see here, we've got three chemicals that we changed
4 the basis for listing from the Labor Code to formally
5 required, because they're already required to have a very
6 specific warning for reproductive toxicity that's required
7 by federal OSHA.

8 And that's a different provision of the OSHA
9 regulations than the ones that we're going to talk about
10 today. The authoritative bodies process we've listed --
11 or changed the basis for listing of three chemicals, based
12 on some findings of the Environmental Protection Agency.

13 Okay. Next slide.

14 --o0o--

15 CHIEF COUNSEL MONAHAN-CUMMINGS: So the chemicals
16 you're going to consider today are on the left-hand side
17 of -- at least my left on this chart. I'm not going to
18 try and pronounce them, but you have six that are in front
19 of you today. And then we have three more that we're
20 going to propose to you at our future meeting, which I
21 think is currently scheduled for May.

22 Next slide.

23 --o0o--

24 CHIEF COUNSEL MONAHAN-CUMMINGS: Each of these
25 chemicals, the nine that we have remaining have stated on

1 the list, because we are waiting for your decision as to
2 whether or not they should remain on the list based on
3 your own criteria, which is whether or not the chemicals
4 have been clearly shown through scientifically valid
5 testing, according to generally accepted principles to
6 cause reproductive toxicity.

7 So that's a de novo review basically by this
8 committee. And so you don't have to rely on what the
9 other listing mechanisms -- or the other authorities have
10 said. You make your own decision regarding whether these
11 chemicals should remain on the list.

12 Next slide.

13 --o0o--

14 CHIEF COUNSEL MONAHAN-CUMMINGS: You can skip
15 that one.

16 --o0o--

17 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So just
18 some general background. As I mentioned, these chemicals
19 were added to the list of chemicals known to cause
20 reproductive toxicity based on, what we call, the Labor
21 Code listing mechanism, which is a provision of Prop 65
22 that incorporates a very small subset of the regulations
23 that are in the California Labor Code. And the
24 proposition requires these chemicals to be listed, if
25 they're identified through that mechanism.

1 One of the Labor Code provisions, the 6382(d),
2 incorporates by reference the federal Hazard Communication
3 Standard.

4 And so -- next slide.

5 --o0o--

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Until March of
7 2012, the Hazard Communication Standard referred to the
8 ACGIH, which is the American Conference of Governmental
9 Industrial Hygienists list of threshold limit values, and
10 subpart (z) of the regulations as mandatory listing -- or
11 mandatory ways to identify chemicals that cause
12 reproductive toxicity or other adverse effects on humans.

13 And -- next slide.

14 --o0o--

15 CHIEF COUNSEL MONAHAN-CUMMINGS: In March 2012,
16 OSHA changed their regulations pretty substantially. And
17 so before 2012, we had a legal decision that went up to
18 the court of appeal, the California Chamber of Commerce
19 versus Brown, which made it very clear that we have to
20 list chemicals under the Labor Code. And so we had been
21 listing these chemicals based on the ACGIH TLVs, or
22 subpart (z).

23 And given the changes to those regulations, we no
24 longer are able to do that, because the regulations are no
25 longer mandatory, and businesses are able to look at

1 more -- I guess they have more ability to classify the
2 chemicals themselves, rather than have a base list at the
3 federal level, so -- next slide.

4 --o0o--

5 CHIEF COUNSEL MONAHAN-CUMMINGS: I think I
6 already mentioned the points on this slide, that the
7 chemicals were already listed via the Labor Code. We've
8 looked at them and their background, and we're not able to
9 find another administrative listing process for them, so
10 we've referred them to you for consideration. You don't
11 need to look at the underlying TLVs or the basis for why
12 ACGIH identified them as reproductive toxins, although we
13 have included that material for you.

14 So what you're doing today is looking at these
15 chemicals basically de novo in the same way as you would
16 look at other chemicals that we bring to you.

17 Next slide.

18 --o0o--

19 CHIEF COUNSEL MONAHAN-CUMMINGS: So today in your
20 consideration of these six chemicals, the -- your
21 Committee will decide whether or not they meet your
22 criteria for listing or you can defer them --
23 consideration of the chemicals to another meeting, if you
24 feel like you don't have enough information or we don't
25 have enough time.

1 And then we've got the three additional chemicals
2 that we'll be presenting to you on May -- in May -- oh,
3 two additional chemicals, because we're not going to be
4 able to present chloroform apparently.

5 So we most likely will have another meeting of
6 this Committee later in the year. So, you know, we used
7 to in the past only have one meeting a year, and now we're
8 having a number of them. But at least under our
9 regulations, we are meeting our mandate, because we have
10 to meet at least once a year, but they don't count forward
11 unfortunately.

12 So any questions on that?

13 Okay. One -- I'm sorry. Go ahead.

14 COMMITTEE MEMBER PESSAH: I have a question. I
15 just wondering when you come across a situation where a
16 chemical doesn't -- or you feel it doesn't have enough
17 information, you said you'd move it to a future meeting,
18 but what if it's unlikely there will be additional
19 information, does that influence our...

20 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think
21 what we do is we just let you know what the existing
22 information is on it, and if you feel like there's not
23 enough, then you can advise us to take it off the list,
24 until -- you know, we keep tracking them anyway just to
25 make sure that something new doesn't come up.

1 DIRECTOR ALEXEEFF: This is George Alexeeff. I
2 think what Carol was saying is that staff didn't have
3 enough time to prepare the package of information for the
4 Committee.

5 CHIEF COUNSEL MONAHAN-CUMMINGS: Oh, sorry. I
6 just want to make a couple other quick comments that I
7 always make for the Committee hearings. And that is
8 that just to remind you, of course, that you have your own
9 scientific standard for listing chemicals. It's not a
10 legal standard. It's a scientific decision. You're
11 scientists or doctors or professionals in the
12 identification of these kinds of chemicals for these
13 endpoints. And so you don't have to worry about making a
14 legal decision.

15 Your decision, of course, has a legal effect, but
16 it's not -- the standard isn't beyond a reasonable doubt
17 or, you know, clear and convincing or whatever. It's
18 your -- what it says in the statute is you have to
19 determine whether it's been clearly shown through
20 scientifically valid testing, according to generally
21 accepted principles to cause cancer -- or not cancer,
22 reproductive toxicity.

23 So you don't have to consider. Although, lots of
24 time you get some testimony on it, whether or not the
25 current doses that humans are receiving are significant

1 enough to worry about. You don't have to worry about
2 whether or not the chemical actually causes human
3 reproductive effects. You can list it based on only
4 animal evidence, as long as you find that it would be
5 generally applicable to humans. And you do have your own
6 criteria that you have -- or your prior Committee members
7 adopted for you, so you can look at that in terms of what
8 scientific evidence you want to consider and how to apply
9 that. So I think that's all I have unless you have
10 questions.

11 Okay. And if questions come up as you go along,
12 I'm certainly happy to answer them.

13 Thank you.

14 CHAIRPERSON GOLD: Thank you. Very helpful. So
15 next on my agenda I have that Jim McDonald(sic) is going
16 to make some introductory comments.

17 (Thereupon an overhead presentation was
18 presented as follows.)

19 DR. DONALD: Good morning. Just before I being
20 on this as a minor clarification to avoid probably
21 confusion more in the audience than among the Committee,
22 we actually announced last Friday that the three chemicals
23 that will be considered by the Committee at your meeting
24 in May. So it's hexafluoroacetone, phenylphosphine and
25 chlorsulfuron.

1 --o0o--

2 DR. DONALD: Okay. I won't reiterate what Carol
3 has already so thoroughly covered. Of course, the
4 Committee is going to be making its usual decision about
5 whether the chemical has been clearly shown to cause
6 reproductive toxicity. So to that end, we have provided
7 relevant data to the Committee in the form of summary
8 tables, but also in the form of the original study reports
9 and published papers, when they were available. And in
10 this case, all of the papers that we have summarized were
11 provided to the Committee.

12 --o0o--

13 DR. DONALD: We identified those publications
14 through literature searches that covered the three major
15 endpoints of reproductive toxicity, which are, of course,
16 developmental toxicity, male reproductive toxicity, and
17 female reproductive toxicity. Those searches were
18 conducted by professional librarians through a contract
19 with the Public Health Library at the University of
20 California at Berkeley. And the search protocol that they
21 followed is described in the hazard identification
22 document that you have as Appendix A.

23 --o0o--

24 DR. DONALD: As usual, we will make
25 presentations -- brief presentations of the information on

1 each chemical. Since we still have six chemicals to get
2 through today, we will keep the presentations quite short,
3 but we will, of course, be happy to answer any questions
4 you may have.

5 And the chemicals will be presented in the same
6 order as they appear in the hazard identification
7 document, which is first the three glycidyl ethers,
8 followed by two ketones, and then finally alpha-methyl
9 styrene.

10 So I will turn this now over to the Dr. Francisco
11 Moran, who will make the presentations on each of the
12 chemicals.

13 --o0o--

14 DR. MORAN: Thank you. Good morning. I will
15 present the summary information on the reproductive
16 toxicology for three glycidyl ethers first. I will start
17 by presenting the summary of the finding for n-butyl
18 glycidyl ether.

19 --o0o--

20 DR. MORAN: A comprehensive literature search
21 resulted in three references with data on the potential
22 reproductive toxicity for BGE in rats and mice.

23 --o0o--

24 DR. MORAN: In a subchronic toxicity study in
25 rats by Anderson et al. in 1957, ten male rats per group

1 exposed to BGE by inhalation at 0, 0.2 to 1.6 grams per
2 cubic meter for seven hours a day for five days a week for
3 ten weeks. The endpoints were organ weight and pathology
4 at the end of the experiment.

5 Oh, I think I pressed too fast.

6 The results for systemic toxicity they found that
7 at the two higher doses there were -- there was an
8 increased mortality and reduced weight gain, and increased
9 lung and the liver -- and liver weight, statistically
10 significant at 1.6 grams per cubic meter and
11 bronchopneumonia in one rat at 0.4 and five rats at 0.8
12 grams per cubic meter.

13 For reproductive toxicity, there were atrophic
14 testes in four of five surviving animals and one animal
15 that died after 40 exposures at 1.6 grams per cubic meter;
16 very small testes in one of ten at 1.6 grams per cubic
17 meter; a slight patchy testes atrophy in one animal at 0.4
18 grams per cubic meter that also presented pneumonia; only
19 one case with testes atrophy was reported that had no
20 other organ pathology.

21 --o0o--

22 DR. MORAN: In a dominant lethal study by Pullin
23 and Legator in 1977 -- are we on the right -- yes -- ten
24 male mice were exposed dermally to 0 or 1.5 grams per
25 kilogram of BGE three times a week for eight weeks. Each

1 male was mated to three untreated females per week for two
2 weeks. The endpoints were evaluated at 13 or 14 days from
3 presumptive mating, since they were -- the vaginal plug
4 was not checked. The endpoints were pregnancy rate,
5 implantations, and fetal mortality. They found a lower
6 pregnancy rate at one and two weeks after exposure with a
7 P equal to 0.05, and greater fetal mortality and
8 post-implantation loss.

9 --o0o--

10 DR. MORAN: In another dominant lethal study by
11 Whorton et al. in 1983, 36 to 44 -- there is a small
12 correction here with what appeared in the HID from 42 to
13 44 animals -- male rats were exposed dermally to three
14 doses of BGE three times per week Monday, Wednesday, and
15 Friday, eight weeks -- for eight weeks and saline control.
16 Each male was mated to three virgin females per week for
17 three weeks.

18 The endpoints were a weekly body weight and
19 testicular pathology after the final mating period for
20 males, and in the females, pregnancy, implantation, and
21 fetal death were evaluated at 13 or 14 days from
22 presumptive mating. They found no significant
23 dose-related testicular changes, low number of altered
24 cells; greater fetal death rate at 1.6 grams per kilogram
25 per day after one week of mating only.

1 --o0o--

2 DR. MORAN: That concludes this chemical.

3 CHAIRPERSON GOLD: Okay. Thank you very much,
4 Dr. Moran.

5 So we're now open for public comments on
6 n-glycidyl ether -- n-butyl glycidyl ether, sorry.

7 DR. MORAN: N-butyl glycidyl ether.

8 CHAIRPERSON GOLD: Sorry.

9 Any public comments?

10 Okay. Hearing none -- sorry. So hearing no
11 public comment, we'll turn to the Committee discussion.
12 And I've asked Dr. Baskin to take the lead followed by Dr.
13 Nazmi, and then we'll open up to the general Committee.

14 COMMITTEE MEMBER BASKIN: Good morning. This is
15 a chemical that's used in epoxy resins, and evidently
16 stabilizes chlorinated solvents. Dr. Moran's nice summary
17 presentation points out that in the literature there's
18 three studies, and none of these studies are really
19 directed at reproductive toxicology. There were some
20 serious systemic effects, but the focus of our evaluation
21 relates to reproductive toxicology.

22 And I'd like to look at the Whorton study in 1983
23 first. This was a mice study. Dermal application. And
24 the reason I think this study should be highlighted is
25 that they actually, as a secondary analysis, clearly

1 looked at the testes. The testes were evaluated
2 histologically. They were done in proper fashion. They
3 were put in Bouin solution. There was fixation and
4 bedding and direct analysis of really the cellular
5 pathology. And there was really no positive findings.

6 So I think that it is of significance, because
7 it's the most recent study and it actually was done in a
8 scientifically valid way.

9 The 1977 study by Pullin was also a mice dermal
10 exposure, and they didn't real do any gonadal histology.
11 And although, as pointed out, there was clearly increased
12 fetal mortality, there was no findings related to
13 reproductive toxicology in the testes.

14 As an aside, I didn't see any evidence that the
15 ovary was evaluated in any of these studies. The 1957
16 study, before I was born, rats were given an inhalation
17 agent. And there are some positive gross findings as
18 pointed out, which have some concern, but they're not
19 really substantiated with any statistics or follow-up
20 histology. And the gross findings that are of concerning
21 is that there was an atrophic -- atrophic testes found or
22 what is called slightly patchy testes atrophy. And I'm
23 not 100 percent sure what that means.

24 So I personally don't think we have a huge amount
25 of evidence here by present standards to be able to make a

1 solid statement.

2 CHAIRPERSON GOLD: Dr. Nazmi, would you like to
3 follow up?

4 COMMITTEE MEMBER NAZMI: I have nothing to add.
5 Thank you.

6 CHAIRPERSON GOLD: Okay. I'll turn to the rest
7 of the Committee and ask if they have any questions or
8 further points of discussion on this chemical?

9 Awfully quiet group this morning.

10 Nothing?

11 Okay. Are we ready to vote?

12 Yes?

13 All right. So I have -- yeah, so I have my
14 voting protocol.

15 All right. So we have to vote on each of the
16 three endpoints, so we'll take them one at a time, right?
17 So has n-butyl glycidyl ether been clearly shown through
18 scientifically valid testing, according to generally
19 accepted principles to cause developmental toxicity?

20 All those voting yes, please raise your hand?

21 (No hands raised.)

22 CHAIRPERSON GOLD: I see zero.

23 Has n-butyl glycidyl ether been clearly shown
24 through scientifically valid testing, according to
25 generally accepted principles to cause female reproductive

1 toxicity?

2 (No hands raised.)

3 CHAIRPERSON GOLD: Again, I see zero.

4 DIRECTOR ALEXEEFF: Could I just ask -- George
5 Alexeeff. You may as well ask for no votes, just so we
6 see, maybe for each endpoint.

7 CHAIRPERSON GOLD: All right. So let's go back
8 to developmental. Sorry. Thank you.

9 How many are voting no that for developmental
10 toxicity that n-butyl glycidyl ether has not -- has been
11 clearly shown through scientifically valid testing to
12 generally accepted principles to cause developmental
13 toxicity? How many are voting no?

14 (Hands raised.)

15 CHAIRPERSON GOLD: I see three -- six.

16 And there's no abstentions, yes.

17 Okay. Now back to female reproductive toxicity.
18 Has n-butyl glycidyl ether been clearly shown through
19 scientifically valid testing, according to generally
20 accepted principles to cause female reproductive toxicity.
21 If you believe yes, please raise your hand?

22 (No hands raised.)

23 CHAIRPERSON GOLD: I see zero.

24 If you believe no, please raise your hand.

25 (Hands raised.)

1 CHAIRPERSON GOLD: I see six.

2 No abstentions.

3 And finally has n-butyl glycidyl ether been
4 clearly shown through scientifically testing, according to
5 generally accepted principles to cause male reproductive
6 toxicity. If you believe yes, please raise your hand?

7 (No hands raised.)

8 CHAIRPERSON GOLD: I see none.

9 Those believing no?

10 (Hands raised.)

11 CHAIRPERSON GOLD: Three -- six.

12 And no abstentions.

13 So the result is for all three endpoints that a
14 unanimous vote of no in terms of listing, in terms of
15 showing that it causes developmental, female reproductive
16 or male toxicity.

17 Okay. All right. Very good. Thank you.

18 So next we will go on. And, Dr. Moran, I see
19 you're on for all of these, is that correct?

20 DR. MORAN: Yes.

21 CHAIRPERSON GOLD: So you'll do the staff
22 presentation for diglycidyl ether.

23 DR. MORAN: Yes.

24 CHAIRPERSON GOLD: Thank you.

25 (Thereupon an overhead presentation was

1 presented as follows.)

2 DR. MORAN: Okay. Our next chemical as was
3 introduced is diglycidyl ether.

4 A comprehensive literature search produced one
5 reference regarding male reproductive toxicity of DGE in
6 laboratory animals. The single reference found for DGE by
7 Hine et al. in 1961 has several toxicological studies
8 rats, rabbits, and dogs.

9 These studies were designed to assess:

10 Peripheral blood, bone marrow, body weight, and
11 mortality; physical observation and histology for testes
12 among other organs at necropsy were performed;
13 specifically for males, weekly body weight, testicular
14 pathology, and for females pregnancy, implantations, and
15 fetal death.

16 --o0o--

17 DR. MORAN: The rat study number one on this
18 document, we have the results from treated rats to
19 cutaneous exposure of DGE where five males per rat per
20 dose group were treated at 0, 125, 250, or 500 milligrams
21 per kilogram daily for five days a week for four weeks.

22 For systemic toxicity, the observed effects were:

23 In the 125 milligrams per kilogram group, there
24 were two deaths by the second week and a third death by
25 the third week of treatment; two deaths each at 250 and

1 500 milligrams per group -- per groups were, at this time
2 point, the treatment stopped in this group.

3 And at all doses, they found: Weight loss,
4 reduced leukocyte, necrosis of the skin, lymphoid tissue
5 and kidney and hemorrhage of the adrenal medulla.

6 --o0o--

7 DR. MORAN: For reproductive toxicity, they found
8 focal necrosis of the testes at all doses. No specific
9 findings for the different dose groups were provided, and
10 the P values were not provided either.

11 --o0o--

12 DR. MORAN: The study number two of cutaneous
13 exposure, five males per rat per group were treated with
14 doses of DGE and at 0, 15, 30, or 60 milligrams per
15 kilogram daily for five days a week for four weeks.
16 Changes in the method will be indicated by the red color
17 font in the slide that is kind of faded, but it will
18 continue through the presentation.

19 Systemic toxicity. They found that weight gain
20 reported to be significantly retarded at 30 and 60
21 milligrams per kilogram, and where the data was not
22 provided; no deaths; no visceral abnormalities. For
23 reproductive toxicity, it was reported that there were no
24 adverse effects on testes to body weight ratio

25 --o0o--

1 DR. MORAN: In the third study, we have results
2 from an inhalation study, where 30 male rats were exposed
3 to diglycidyl ether at 3 ppm for four hours a day, five
4 days a week for 29 days. Ten animals served as control,
5 where only 15 treated and all control animals were
6 evaluated after the final exposure. The basis for this
7 selection was not stated.

8 In the systemic toxicity, they found five animals
9 died during exposure, where pneumonia, bronchopneumonia,
10 necrosis of the pancreas and the spleen were reported for
11 some of them; reduced percentage body weight gain; reduced
12 total leukocyte count, percentage of polymorphonuclear
13 cells and number of nucleated cells femoral marrow.

14 The rest of the animals, ten, were held for a
15 year with apparent normal range on the endpoints analyzed
16 at that time.

17 --o0o--

18 DR. MORAN: For reproductive toxicity, we have
19 that one case of necrosis of the tubules of the testes was
20 reported. The authors reported an apparent nonsignificant
21 increase, about 10 percent in relative testes weight.

22 --o0o--

23 DR. MORAN: The fourth study in this continues --
24 report is where they used 30 rats were exposed by
25 inhalation to diglycidyl ether at 0 or 0.3 ppm for four

1 hours a day for five days a week for 90 days. Ten treated
2 animals and five controls were killed after 20 exposures,
3 30 days, with only one case of pneumonia in the
4 experimental group. No other differences were reported.

5 After 60 exposures in 90 days, ten more treated
6 animals with no control were killed and the results are
7 shown here.

8 For the systemic toxicity, we have one animal had
9 acute peribronchiolitis. Not reported if it was one of
10 the five showing reproductive toxicity that we'll present
11 soon. No other systemic toxicity reported. For
12 reproductive toxicity, five rats had poorly defined focal
13 degeneration of the germinal epithelium.

14 The last ten treated animals and ten control
15 animals of the experimental group were kept for a year,
16 where it was reported three cases of bronchopneumonia, two
17 of these in the control group with no differences in
18 testes to body weight ratios.

19 --o0o--

20 DR. MORAN: In the fifth study is a result from
21 an inhalation exposure, where three male rabbits were
22 treated with DGE at 0, 3, 6, 12, or 24 ppm for 24 hours.

23 For systemic toxicity we have the two rabbits in
24 the 24 ppm, the high dose group, died with 30 and 35
25 percent of weight loss. One had confluent

1 bronchopneumonia and serous hepatitis and the other had
2 focal atelectasis, peribronchiolitis, and focal hemorrhage
3 in the kidneys and lungs. The third rabbit died two days
4 later with 35 percent weight loss and was not necropsied.
5 Rabbits exposed to lower levels showed no gross changes at
6 necropsy and were not studied histologically.

7 --o0o--

8 DR. MORAN: And for the reproductive toxicity, we
9 have the first two animals that died at 24 ppm had greatly
10 atrophied testes. No additional testicular effects were
11 reported.

12 --o0o--

13 DR. MORAN: The sixth study, where they have
14 three males dogs were treated intravenously to DGE at 25
15 milligrams per kilo per week for three weeks and no
16 controls were reported.

17 For systemic toxicity, we have low leukocyte
18 count; two dogs died, one died seven days after the second
19 injection, apparently of pneumonia. The other at six days
20 after the third weekly injection.

21 For reproductive toxicity, we have that the
22 animal that died at seven days after the second injection,
23 presented hyaline degeneration of the testicular tubules.

24 No control group was described for this study,
25 but three additional animals treated at 12.5 milligrams

1 weekly apparently following the same protocol did not show
2 signs of toxicity.

3 --o0o--

4 DR. MORAN: That concludes this presentation.
5 Thank you.

6 CHAIRPERSON GOLD: Thank you. We would now
7 invite public comments on diglycidyl ether?

8 We have not been notified of any.

9 Hearing none.

10 Okay. We will now ask the Committee for a
11 discussion. And we've asked Dr. Woodruff to do the
12 primary on this one.

13 COMMITTEE MEMBER WOODRUFF: Thank you. Thank you
14 for the presentation. It was very thorough.

15 As you said, there's only one study, even though
16 they did several different types of exposures in animals.
17 In the experiment though, of course, I think you noted
18 that this study is also older as the one that we just --
19 some of the ones that we just discussed. And a lot of the
20 focus of these studies were on systemic toxicity, even
21 though there was some focus on pregnancy outcomes --
22 didn't really hear that reported -- and also the primary
23 focus was on male reproductive effects, of which there was
24 mixed findings among the different animal groups that were
25 evaluated.

1 So there was a cutaneous exposure, an inhalation
2 exposure, and then inhalation and intravenous exposure.
3 We had rats, male rats -- all male rats, a few rabbits,
4 and a study of a few dogs. I would say these studies are
5 generally very small, so it's very difficult to really
6 draw any conclusions.

7 My conclusion is that, as you have said, that
8 really there weren't very many -- there was a lot of
9 findings on systemic toxicity and it's -- and there was,
10 it seemed to me, findings focused on effects on pulmonary
11 function. But as far as reproductive findings, those were
12 either very not evaluated, or when they were evaluated did
13 not appear -- primarily male reproductive effects did not
14 appear to be significant.

15 CHAIRPERSON GOLD: Thank you.

16 Dr. Baskin, do you have any further comments?

17 COMMITTEE MEMBER BASKIN: I agree with Dr.
18 Woodruff's summary, and would just reiterate that the
19 primary design of the study was to look at the outcome in
20 the blood. And there were -- this is clearly a chemical
21 that you probably don't want to take. It killed a lot of
22 the animals.

23 But for reproductive toxicology, there was some,
24 what I would say, concerning descriptors, degeneration of
25 testes tubules, hyaline degeneration. I mean, that's

1 common terms that are used. But again, as a secondary
2 data analysis, there was no statistics, and there were no
3 imaging to really be able to definitively say that this is
4 a primary problem.

5 CHAIRPERSON GOLD: Okay. Thank you.

6 So I'll now open up the discussion to the rest of
7 the Committee. Is there any further discussion on
8 diglycidyl ether?

9 Seeing none.

10 Are we ready to vote?

11 Yes.

12 Okay. Has diglycidyl ether been clearly shown
13 through scientifically valid testing, according to
14 generally accepted principles to cause developmental
15 toxicity? If you believe yes, please raise your hand.

16 (No hands raised.)

17 CHAIRPERSON GOLD: I see none.

18 If you believe no, please raise your hand?

19 (Hands raised.)

20 CHAIRPERSON GOLD: One, two, three, four, five
21 six.

22 No abstentions.

23 Has diglycidyl ether been clearly shown through
24 scientifically valid testing, according to generally
25 accepted principles to cause female reproductive toxicity?

1 If you believe yes, please raise your hand?

2 (No hands raised.)

3 CHAIRPERSON GOLD: I see none.

4 If you believe no, please raise your hand?

5 (Hands raised.)

6 CHAIRPERSON GOLD: I see six. And no
7 abstentions.

8 Finally, has diglycidyl ether been clearly shown
9 through scientifically valid testing, according to
10 generally accepted principles to cause male reproductive
11 toxicity? If you believe yes, please raise your hand?

12 (No hands raised.)

13 CHAIRPERSON GOLD: I see none.

14 If you believe no, please raised your hand?

15 (Hands raised.)

16 CHAIRPERSON GOLD: I see six, and no abstentions.

17 Therefore, we are unanimous in stating that we do
18 not believe that through scientifically valid testing,
19 diglycidyl ether has been shown to cause developmental
20 toxicity or male or female reproductive toxicity.

21 Okay. Thank you.

22 All right. Our next chemical for Dr. Moran is
23 phenyl glycidyl ether.

24 DR. MORAN: Yes. Thank you. A comprehensive
25 literature search resulted in two references with data on

1 the potential reproductive toxicity of PGE in rats and
2 dogs.

3 --o0o--

4 DR. MORAN: The first study by Terrill et al. in
5 1977 is a toxicological study, where six male rats per
6 group were exposed by inhalation to phenyl glycidyl ether
7 at 0 or 29 ppm for four hours a day, five days a week for
8 two weeks.

9 The endpoints assessed were: Daily weight and
10 physically examination; at the end of testing, half of the
11 rats were sacrificed for histopathology; the rest of the
12 animals were sacrificed and examined histologically after
13 two weeks.

14 --o0o--

15 DR. MORAN: In the second study by Terrill et --
16 oh, sorry. In the systemic -- the results. Twenty-five.
17 Sorry.

18 For systemic toxicity we have that depressed
19 weight gain where the P value was not provided. And
20 reproductive toxicity results, we have the atrophic
21 changes in various organs, including testes, was
22 described, where the P values are not provided either.

23 --o0o--

24 DR. MORAN: In the second study, by Terrill et
25 al. in '77, 32 male and female rats per group were exposed

1 by inhalation to phenyl glycidyl ether at 1, 5, and 12 ppm
2 for six hours a day for five days a week for 90 days.

3 The endpoints were daily physical inspection,
4 weighed twice a week; sections of testes, prostate, ovary,
5 uterus, mammary gland, among other tissues were fixed and
6 examined by histology.

7 And they found no adverse effects on systemic
8 toxicity, and no significant changes in histological
9 examination of relevant reproductive tissues.

10 --o0o--

11 DR. MORAN: In the first study by Terrill in '77,
12 the same protocol as previous study in rats, but in this
13 study six male dogs were exposed by inhalation to phenyl
14 glycidyl ether at 1, 5, 12 ppm for six hours a day for
15 five days a week for 90 days. In this study also were no
16 adverse effects on systemic toxicity and no significant
17 changes in histological examinations of relevant
18 reproductive tissues.

19 --o0o--

20 DR. MORAN: In this report -- in this report,
21 there are two studies: A two-generation of rat
22 reproduction and dominant lethal, teratogenic study by
23 Terrill et al. in 1982. The dominant lethal study was
24 flagged in HID as considered invalid by the U.S. EPA. In
25 the first study, eight males per group were exposed to PGE

1 by inhalation at 0, 2, 6, and 11 ppm for six hours a day
2 for 19 consecutive days. Three untreated females were
3 used for mating for six weeks.

4 Depending on the number of pregnant females --
5 females per male, one-third to a half of the females had
6 autopsy GD 18, gestational day 18; two-thirds allowed to
7 deliver and F1 raised to weaning. Then, 20 males and 40
8 females per group per week, plus any abnormal pups were
9 raised to 12 weeks. From these, eight males were mated to
10 24 females per group per week, mate normal and abnormal
11 also.

12 Finally, the F2 raise to five weeks and killed
13 for examination, discard F1 parents, and preserve abnormal
14 F1 and F2 for examination.

15 The endpoints were: Fertility parameters; on
16 gestational day 18 gross examination of uterine content
17 and fetuses in some, one-third to one-half of the pregnant
18 rats as explained, corpora lutea, implantation and
19 resorptions; gross pathology on rest of the females at
20 gestational day 23, if they did not conceive, and F1 males
21 and females of 12 weeks post weaning; histopathology on
22 testes of the F0 males.

23 --o0o--

24 DR. MORAN: The results are for systemic
25 toxicity, there were no increase in mortality on the F0.

1 --o0o--

2 DR. MORAN: In the dominant -- yeah, 30. For the
3 dominant lethal study by Terrill in '82 for the
4 reproductive toxicity, there were no increase in
5 resorptions; no differences in number and survival of
6 pups; lower number of pregnant females in week 1 and 11
7 with P of 0.05; low fertility indices in F1 and F2a in all
8 groups including controls; no evidence of dominant lethal
9 response.

10 --o0o--

11 DR. MORAN: This second study by Terrill et al.
12 '82, 25 females rat per group -- are we on this slide?

13 Yes.

14 Twenty-five females per group were exposed by
15 inhalation to PGE at 0, 1, 5, 12 ppm for six hours a day
16 from gestational day four to gestational day 15.

17 The endpoints assessed at autopsy on gestational
18 day 20: Fetal body weight and length; number of
19 implantations; live fetuses and resorptions; fetuses were
20 fixed for examination of skeletal and soft tissue
21 examination.

22 The results are summarized as no changes in
23 clinical science or body weight of dams compared to
24 controls.

25 And for the offspring we have: No changes in

1 number of implantations, fetuses and resorptions; and
2 fetuses had similar length and weight, and all appeared
3 normal upon gross examination.

4 --o0o--

5 DR. MORAN: That concludes the phenyl glycidyl
6 ether presentation.

7 CHAIRPERSON GOLD: Thank you very much. So we
8 now are open for public comments on phenyl glycidyl ether.

9 Any comments from the public?

10 Hearing none.

11 We'll turn to Committee discussion, and Dr. Nazmi
12 is going to start us off.

13 COMMITTEE MEMBER NAZMI: Thank you. Thanks, Dr.
14 Moran for that very thorough overview.

15 I'd like to begin with the Terrill 1982 study.
16 And, of course, there's one serious and I'd say
17 intractable problem with this study and that was the fact
18 that it was invalidated -- at least a part of it was
19 invalidated by the U.S. EPA. And, in my opinion, that
20 brings into question the entire study. But even the other
21 proportion that was not considered and invalidated, due to
22 the falsification of the data by the laboratory, did not
23 indicate any developmental or toxic -- reproductive
24 toxicological effects.

25 The other study from 1977, there was one finding.

1 They indicated referring to atrophic changes in the
2 testes. Although, no further details were provided, as
3 you mentioned, so it's very difficult to interpret.
4 Besides that, no other systemic -- no other reproductive
5 toxic findings were reported, and essentially no systemic
6 toxicity findings either.

7 So in light of that, I'd say we can conclude that
8 there are relatively weak indication of any default mental
9 or reproductive toxicant effects.

10 CHAIRPERSON GOLD: Thank you.

11 Dr. Rocca, anything further to add?

12 COMMITTEE MEMBER ROCCA: I must say that I agree,
13 since all the reproductive endpoints were invalidated for
14 the second study, even though there was no reproductive
15 toxicity. We really can't judge that accurately.

16 And the first set of studies, which were the
17 subchronic studies, I also think show no signs of
18 reproductive toxicity.

19 CHAIRPERSON GOLD: Thank you.

20 Any further comments by the rest of the Committee
21 regarding phenyl glycidyl ether?

22 Are we ready to vote?

23 CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Gold, did
24 you ask for public comments?

25 CHAIRPERSON GOLD: I did.

1 CHIEF COUNSEL MONAHAN-CUMMINGS: She did?

2 CHAIRPERSON GOLD: I did.

3 CHIEF COUNSEL MONAHAN-CUMMINGS: Oh, I'm so
4 sorry. I missed it.

5 DIRECTOR ALEXEEFF: No public comments.

6 CHAIRPERSON GOLD: Right, I asked?

7 DIRECTOR ALEXEEFF: Yes.

8 CHAIRPERSON GOLD: Okay. But it's always good to
9 check me. Thank you.

10 Okay. So for the vote. Has phenyl glycidyl
11 ether been clearly shown through scientifically valid
12 testing, according to generally accepted principles to
13 cause developmental toxicity? If you believe yes, please
14 raise your hand.

15 (No hands raised.)

16 CHAIRPERSON GOLD: I see zero.

17 If you believe no, please raise your hand.

18 (Hands raised.)

19 CHAIRPERSON GOLD: I see six.

20 And no abstentions.

21 Has phenyl glycidyl ether been clearly shown
22 through scientifically valid testing, according to
23 generally accepted principles to cause female reproductive
24 toxicity?

25 If you believe yes, please raise your hand.

1 (No hands raised.)

2 CHAIRPERSON GOLD: I see zero.

3 If you believe no, please raise your hand?

4 (Hands raised.)

5 CHAIRPERSON GOLD: Six, and no abstentions.

6 And finally, has phenyl glycidyl ether been
7 clearly shown through scientifically valid testing, accord
8 to generally accepted principles to cause male
9 reproductive toxicity? If you believe yes, please raise
10 your hand?

11 (No hands raised.)

12 CHAIRPERSON GOLD: I see zero.

13 If you believe no, please raise you hand?

14 (Hands raised.)

15 CHAIRPERSON GOLD: Thank you. Six, and no
16 abstentions.

17 And so we're unanimous again that phenyl glycidyl
18 ether has not been shown to produce developmental, female
19 reproductive or male reproductive toxicity.

20 Very good.

21 So, Dr. Moran, we will call on you again to do
22 the summary of the first ketone, methyl n-butyl ketone.

23 --o0o--

24 DR. MORAN: Thank you. So Mike.

25 So we'll start with methyl n-butyl ketone, MnBK,

1 where a comprehensive literature search resulted in three
2 references with data on the potential reproductive
3 toxicity of methyl n-butyl ketone in rats.

4 In a developmental neurotoxicity study by Peters
5 et al. in 1981, 25 female rats per group were exposed by
6 inhalation to MBK at 0, 500, 1,000 or 2,000 ppm for six
7 hours a day from gestational day zero to gestational day
8 20.

9 The endpoints were: Daily maternal weight;
10 pregnancy outcome at birth, post-natal day two behavior
11 observation, post-natal developmental indices at weeks
12 four, eight, 12 and month 18 to 20 gross and
13 histopathology and behavioral test battery.

14 Ages tested were newborn, weanling, puberty,
15 adult, and geriatric.

16 --o0o--

17 DR. MORAN: For developmental -- in the study we
18 have for parental results decreased maternal weight gain
19 at 1,000 ppm, about 10 percent, and 2,000 ppm at about 14
20 percent of decreased maternal weight gain. Clinical signs
21 at 2,000 ppm, hair loss, incoordination statistics were
22 not given.

23 --o0o--

24 DR. MORAN: For the offspring they found that
25 decreased litter size -- Sorry. For the offsprings they

1 found decreased litter size and birth weight at 2,000 ppm;
2 decreased postnatal and adult weight in males at 1,000 and
3 2,000 ppm; grip strength, maze latency, activity at 1,000
4 and 2,000 ppm, male and/or female at least at one age of
5 the -- age considered; pentobarbital increased sleeping
6 time at 2,000 males at puberty; decrease testes weight in
7 weanlings; and ovarian cysts at 18 months.

8 --o0o--

9 DR. MORAN: In this adult neurotoxicity study by
10 Katz et al. 1980, five male rats were exposed by
11 inhalation at 0 and 700 ppm for 72 hours a week for 81
12 days, two times 20 hours and two times 16 hours exposure
13 periods per week.

14 The endpoints were body weight, clinical
15 chemistry, gross and histopathology of various organs
16 including the testes and neurotoxicity.

17 --o0o--

18 DR. MORAN: All treated rats were killed at the
19 time they developed hindlimb weakness: 34 exposure for
20 the three rats and 42 exposures for two rats.

21 Systemic toxicity they have found that markedly
22 reduced weight gain, decreased white cell counts at 31
23 exposures.

24 For reproductive toxicity we have decreased
25 absolute and relative testes weights, atrophy of testes

1 germinal epithelium described where the data was not
2 presented.

3 --o0o--

4 DR. MORAN: Forty.

5 In this neurotoxicity study in male rats by
6 Krasavage et al. in 1980, five animals per group were
7 exposed by gavage at 0 and 660 milligrams per kilogram for
8 five days a week for 90 days. The endpoints were body
9 weight; for histopathology the testes and epididymides
10 were fixed in 10 percent buffered formalin, embedded in
11 paraffin and sectioned, stained with hematoxylin-eosin.

12 The neurotoxicity endpoint used to assess
13 neuropathy was severe hindlimb weakness or paralysis
14 exhibited by dragging a least one hind foot.

15 --o0o--

16 DR. MORAN: The results are summarized here. We
17 have reduced body weight gain, and for reproductive
18 toxicity they described atrophy of the testicular germinal
19 epithelium over 55-day period.

20 That concludes this chemical presentation.

21 Thank you.

22 CHAIRPERSON GOLD: Thank you very much.

23 So are there any public comments regarding methyl
24 n-butyl ketone?

25 Hearing none.

1 I believe we're ready to move to the discussion
2 by the Committee. And I've again ask Dr. Baskin to take
3 the lead on this one.

4 COMMITTEE MEMBER BASKIN: Thank you. Outstanding
5 summary. There's three papers that were in the
6 literature. I'd like to turn your attention to the 1980
7 paper by Krasavage. And as presented elegantly by Dr.
8 Moran, there is some concerning findings that were
9 quantitated by histology in the paper showing testicular
10 germinal epithelium. And there's two figures. One is a
11 control and one is an experimental figure. And they look
12 bad, at least the experimental one does.

13 The problem is is that there's no statistics. I
14 don't really get a handle on how many animals. In fact,
15 there's no way to know, at least in my reading. And we
16 know that there were five animals per group, so it's hard
17 to be able to hang your hat on that. Although, it is
18 concerning when you see a picture like that. But without
19 really any substantiating statistics, I'm having a hard
20 time trying to, you know, move forward with any type of,
21 you know, reliable science that I think we need to have.
22 That's the 1980 paper.

23 There was some clear neurotoxicity that was
24 shown, again not with fantastic statistics but with a
25 picture of an animal whose not walking very well.

1 The 1991 -- or, I'm sorry, 1981 paper by Peters,
2 there's -- the data really is -- it's an inhalation
3 experiment. The data is not reported accurately to make
4 any determination, and as pointed out, except that
5 possibly the weight of the testes decreased.

6 And the 1980 paper by Katz, again looking at
7 neurotoxicity, there's no histology shown and no
8 statistics for the testes. Although, they report also
9 decreased testicular weight and atrophy of testicular
10 germinal epithelium. But I think without the statistics,
11 it's again hard pressed to really make any definitive
12 statement.

13 Thank you.

14 CHAIRPERSON GOLD: Thank you. Dr. Pessah,
15 additional comments.

16 COMMITTEE MEMBER PESSAH: Yes. So I'm going to
17 focus on the evidence for neurotoxicity. I don't have any
18 additional comments about the reproductive toxicity. Dr.
19 Baskin did a thorough job as did the presenter.

20 One of the concerns that I have is that this
21 particular compound is metabolized through hexanedione,
22 the 2,5. And that has been shown to be a neurotoxic
23 agent at relatively reasonable exposure levels, both in
24 terms of producing a peripheral neuropathy, as well as a
25 few studies that have indicated that it's a central

1 neurotoxicant.

2 The peripheral neuropathy, depending on dose and
3 time of exposure can be severe, but is reversible. The
4 central effects are probably less reversible. And so
5 based on several papers in the literature, and the
6 implication of 2,5-hexanedione in the metabolism of MBK, I
7 would say that there's sufficient evidence to suggest that
8 it's a problem.

9 CHAIRPERSON GOLD: Just to clarify, a problem
10 from a neurotoxicological --

11 COMMITTEE MEMBER PESSAH: Yes.

12 CHAIRPERSON GOLD: So -- but if we have to vote
13 on reproductive toxicity and developmental toxicity, do
14 you have any comments relevant to that?

15 COMMITTEE MEMBER PESSAH: That's a little
16 tougher. There is some indication that neonatal behavior
17 is affected, but I think the data is a little less strong
18 on that. There's not a lot of data on that, that I've
19 seen anyways.

20 COMMITTEE MEMBER WOODRUFF: Can I ask a question.

21 CHAIRPERSON GOLD: Dr. Woodruff.

22 COMMITTEE MEMBER WOODRUFF: Did you -- this first
23 study by Peters this is a developmental neurotox study.
24 Does that -- is that part of the things that you were
25 talking about in terms of your -- I mean, even though it's

1 a -- it could be a neurotoxicant, could that implicate it
2 for developmental neurotoxicity, because I was looking at
3 the food maze behavior results, did you -- I just wondered
4 if you had a comment on those?

5 COMMITTEE MEMBER BASKIN: I think we need some
6 clarification on what we mean by neurotoxicity versus
7 developmental toxicity, because I kind of equate them. I
8 mean, if you can't walk on your hind legs, you have
9 developmental problems, and I don't know if --

10 COMMITTEE MEMBER WOODRUFF: Well, I think that --

11 COMMITTEE MEMBER BASKIN: You know, how -- I
12 mean, I would like some clarification on that or how we're
13 supposed to deal with that?

14 COMMITTEE MEMBER WOODRUFF: Well, I mean one
15 option is that I would be concerned if something was a
16 neurotoxicant that it would also be a developmental
17 neurotoxicant. So meaning that if you had the exposures
18 during development, it would impair neurological
19 development.

20 CHAIRPERSON GOLD: I think the question before us
21 is do we have evidence that when it's given during
22 pregnancy, is it a developmental neurotoxicant? So I'd
23 invite the Committee to comment on that.

24 Dr. Rocca.

25 COMMITTEE MEMBER ROCCA: Yes, it was indeed given

1 to the females during the entire pregnancy period. There
2 was severe maternal weight loss at the 1,000 and 2,000
3 parts per million. And unfortunately, all the 500 part
4 per million group had to be terminated because of
5 technical issues.

6 One of the things that's missing from this paper,
7 which surprises me from the NIEHS, but this is 1981, is
8 that they did not use body weight as a covariate for any
9 of their statistics. That we know that the mothers had
10 severe weight loss. And in the high dose, they lost 14
11 percent, and that's despite pair feeding of one of the
12 control groups. So they had -- there were very sick
13 animals. And we know from lots of other data that many of
14 these other things that you would see, in terms of
15 activity and grip strength and all those sorts of things
16 are highly correlated with body weight.

17 And since we don't have any body weight as a
18 covariate, I don't find that there's anything here that we
19 can say is a toxin in that paper.

20 CHAIRPERSON GOLD: Dr. Woodruff.

21 COMMITTEE MEMBER WOODRUFF: Yeah, I -- it
22 looks -- what is the definition of severe weight loss for
23 you? Because I'm looking at the numbers, and -- I mean,
24 they have some weight loss in 1,000 ppm, but at day --
25 gestational day 20, it looks like 10 percent in the 1,000

1 ppm, and for the 2,000 ppm it's down to 13. Is that
2 severe to you?

3 COMMITTEE MEMBER ROCCA: Yes, for pregnant
4 animals it is.

5 COMMITTEE MEMBER WOODRUFF: But that would be
6 considered a reproductive effect then, right, if we have
7 weight loss during pregnancy? I think it's a listed as
8 one of the --

9 COMMITTEE MEMBER ROCCA: No. In this case, this
10 is systemic toxicity of the mother, and I would not
11 consider that to be reproductive toxicant.

12 COMMITTEE MEMBER WOODRUFF: Um-hmm. But in our
13 list of sufficient evidence in experimental animals,
14 consideration of maternal and systemic toxicity is in
15 here.

16 I mean, I guess I think that if you have weight
17 loss during pregnancy -- I know this has come up before --
18 that if a chemical is causing weight loss during
19 pregnancy, I as a -- you know, looking at humans, that
20 would be concerning to me. So I wouldn't -- I think if
21 that's a concern for this chemical, then we should
22 consider that as an endpoint.

23 DR. DONALD: Just to clarify, in case there any
24 confusion, the reported result was not weight loss. It
25 was a reduction in weight gain during pregnancy. And even

1 weight loss during pregnancy is recognized by regulatory
2 guidelines is not necessarily a basis for discounting
3 developmental effects. The degree of reduction in
4 maternal weight gain, of course, is a factor that you have
5 to, you know, individually take into account. Whether or
6 not it's considered severe is probably open to debate.

7 CHAIRPERSON GOLD: Dr. Pessah.

8 COMMITTEE MEMBER PESSAH: Two things here. I
9 think we've lost sight of the fact that there is known
10 mechanisms that cause neuronal damage by the parent, and
11 most likely by the metabolite, the major metabolite, of
12 this compound.

13 Second, the behavioral studies they did were very
14 blunt instruments. I bet if -- I would predict that if
15 they had done finer behavioral studies, they would have
16 seen what would be clearly outcomes that were
17 developmental outcomes.

18 CHAIRPERSON GOLD: Referring to the offspring.

19 COMMITTEE MEMBER PESSAH: In the offspring, yes.

20 CHAIRPERSON GOLD: Right.

21 Other comments?

22 Dr. Baskin.

23 COMMITTEE MEMBER BASKIN: I mean, so one of the
24 issues, they didn't do the studies, I mean, like we would
25 have done them now. So we just have to take the available

1 data. But I'm going to then re-ask the question, because
2 I am suspicious from the data present. And I'm concerned
3 to vote positive for a neurotoxicity issue with this -- I
4 don't see any reproductive toxicities, but can I equate
5 that with a developmental problem? Because that's what
6 we're really supposed to vote on, not specifically
7 neurotoxicity.

8 COMMITTEE MEMBER PESSAH: Well, what you have to
9 go on is this one study and some human assessments that
10 were in the fact sheet that was provided here.

11 COMMITTEE MEMBER BASKIN: Yeah.

12 COMMITTEE MEMBER PESSAH: And they did see
13 essentially that in the young offspring after
14 developmental exposure that there was hyperexcitability,
15 again scored in a very rough manner. That there was no
16 numbers on it as we would do it today. And that there
17 were other types of behavioral anomalies, again without
18 really systematic analysis of behavior.

19 COMMITTEE MEMBER BASKIN: And along those lines,
20 there's very impressive histology of neuronal degeneration
21 on the axons. But again, like the testicular histology,
22 if I'm reading this right, there's no statistics. In
23 other words, they're not -- they didn't show the numbers
24 that had -- compared to controls.

25 COMMITTEE MEMBER PESSAH: They didn't.

1 CHAIRPERSON GOLD: So I would just remind the
2 Committee that what we're going to vote on is if they've
3 used scientifically valid methods, and through those
4 clearly shown developmental toxicity or reproductive
5 toxicity. So could I invite you to comment sort of on the
6 scientific soundness on whether you're clearly convinced?

7 Yes.

8 DR. ZEISE: I don't know if this would be
9 helpful, but one of the options -- Hi. I'm Lauren Zeise.
10 I am with OEHHA, Deputy Director for Scientific Affairs.

11 This is an NIEHS study. There is the possibility
12 that we could provide you with more information on it.
13 One of the options you have is to defer, if you'd like to
14 see more information on a study. So I just put that out
15 there as an option for you.

16 COMMITTEE MEMBER WOODRUFF: Can I ask a question?

17 CHAIRPERSON GOLD: Yes, Dr. Woodruff.

18 COMMITTEE MEMBER WOODRUFF: You mean the Peters
19 study is an NIEHS study?

20 DR. ZEISE: (Nods head.)

21 COMMITTEE MEMBER WOODRUFF: So there's an
22 underlying -- whatever that document that they put
23 together for that might have more information, because
24 there is some information here that's not -- like in the
25 table on the food maze behavior, they don't have the

1 results for the -- all the doses, so...

2 COMMITTEE MEMBER ROCCA: They didn't do the test
3 at all times?

4 COMMITTEE MEMBER WOODRUFF: Yeah, but would we be
5 able to see more of that in the underlying documentation,
6 you think? Have you guys looked at it?

7 DR. ZEISE: Well, we didn't have it in front of
8 us, and that's why it's not discussed in the report. But
9 if it would be helpful, we could go back to NIEHS, see if
10 they have the individual data, see if we could run the
11 statistics, and give you more information to make a
12 decision on what is available, if we dig a little bit
13 more.

14 CHAIRPERSON GOLD: Dr. Pessah.

15 COMMITTEE MEMBER PESSAH: Again, I really would
16 like to see that data based on what we know about how this
17 chemical acts as a neurodegenerative agent.

18 CHAIRPERSON GOLD: Okay. So are we maybe
19 suggesting then we'd like to defer and request from NIEHS
20 more information on sort of a complete set of outcomes,
21 the timing of those, the dosages for those, and the
22 statistics that go along with them?

23 Anything else?

24 COMMITTEE MEMBER WOODRUFF: That's good.

25 COMMITTEE MEMBER BASKIN: This is from 1981.

1 CHAIRPERSON GOLD: Yeah, so there's a risk they
2 won't have it.

3 DR. ZEISE: Yes, there is a risk.

4 CHAIRPERSON GOLD: In which case, it will come
5 back to us with the same information we have right now.

6 (Laughter.)

7 CHAIRPERSON GOLD: But there's a chance, you
8 know, that they keep really good records for long periods
9 of time and they can get back to us and respond. So is
10 that what we would prefer to do is to defer for that
11 information?

12 I'm getting a general sense of yes?

13 Yes. Yes. Couldn't hurt.

14 COMMITTEE MEMBER WOODRUFF: Yes.

15 CHAIRPERSON GOLD: Okay. So that's what we'll
16 do. We will not vote on this one right now.

17 COMMITTEE MEMBER BASKIN: For clarification, are
18 we asking for more information related to everything or to
19 reproductive or to neurotoxicity?

20 CHAIRPERSON GOLD: Well, it's the Committee's
21 pleasure, but I think we should ask for things that are
22 directly related to what we have to vote on. And so that
23 would be developmental toxicity that could be in the form
24 of neurotoxicity, but also anything additional on male or
25 female reproductive toxicity if they have it. Is that

1 okay?

2 DIRECTOR ALEXEEFF: So I was going to ask if
3 staff wanted to provide a clarification regarding the
4 question that Dr. Baskin has trying to sort out the issue
5 of neurotoxicity and how that plays out into the
6 evaluation of reproductive toxicity overall? Maybe you
7 could just clarify that for him.

8 COMMITTEE MEMBER BASKIN: Or developmental, I
9 mean.

10 DR. DONALD: In someways that's two different
11 questions. This, of course, was specifically a
12 neurobehavioral developmental study. The exposure was
13 during the prenatal development period. One of the
14 criteria for conducting such a study is that there's some
15 evidence that the chemical causes neurotoxicity in adults,
16 but the intent of the study is, of course, to look
17 specifically at the sensitivity of the developing organism
18 to the neurotoxic agent. As was pointed out, in most
19 instances, we would -- well, the reason for doing the
20 study is that there's a high likelihood that there will be
21 sensitivity during the developmental period.

22 With regard to neurotoxicity itself, it may well
23 be a contributing factor in reproductive function. We
24 know, of course, that the pituitary hypothalamic gonadal
25 access is very important in reproduction. There may well

1 be aspects of neurotoxicity that have direct or indirect
2 effects on reproductive toxicity.

3 But we would generally only consider evidence
4 that those effects are occurring as relevant to
5 reproductive toxicity as opposed to general evidence of
6 neurotoxicity that was not directly or indirectly related
7 to a reproductive outcome.

8 COMMITTEE MEMBER ROCCA: So that I have this
9 correct, my understanding from what you said, is that if
10 we have an effect if they were exposed during development,
11 that then when they're tested later on as adolescent and
12 adults, there is still an effect, then that would be
13 considered a developmental effect?

14 DR. DONALD: That's absolutely correct.

15 COMMITTEE MEMBER ROCCA: So this doesn't have to
16 do with whether if you give juveniles a neurotoxin you see
17 effects, correct?

18 DR. DONALD: Well, for purposes of Proposition
19 65, that's correct. Normally, in neurobehavioral
20 developmental studies, the exposure can continue
21 postnatally into the postnatal period, but it happens in
22 this case that the exposure was limited just to the
23 prenatal period, which actually makes a simpler issue for
24 the Committee.

25 CHAIRPERSON GOLD: Dr. Zeise.

1 DR. ZEISE: If it would help the Committee, we
2 could layout this issue of the relationship between
3 developmental toxicity and maternal toxicity in a little
4 bit more detail at the next meeting.

5 CHAIRPERSON GOLD: I think that would be helpful,
6 but I also have a question of whether you're clear on what
7 our request is for NIEHS or do you need any further
8 clarification?

9 DR. DONALD: It -- I guess I would paraphrase it
10 and say that you would like us to find any additional
11 relevant data that can be gleaned from the study that
12 NIEHS did, is that about correct?

13 CHAIRPERSON GOLD: Well, that's certainly true,
14 but if they need specifics, like if they can only dig up
15 certain things, I think we're interested in dosage effect
16 levels, and timing of those, and whether then they're
17 developmentally related or not, and any statistical tests
18 that they could run that maybe they have somewhere or they
19 could run, if they don't have them already.

20 Dr. Baskin, did you want to say something?

21 COMMITTEE MEMBER BASKIN: Yeah, I have two
22 points. So when you walk around a hospital or a
23 children's hospital, there's typically a neurodevelopment
24 department or clinic, and that's where the confusion lies
25 with me. I kind of equate them as similar. If you have a

1 neuro issue that's going to affect your development? And
2 I see that in patients all the time. So that's where, if
3 indeed we found that from a neurotoxicity point of view
4 there was concerns here based on the science, can I vote
5 yes in the development column? Because that's where I'm
6 asked to vote. And I kind of think yes is the answer, but
7 I need guidance there.

8 The second point I want to make is I don't want
9 to create a slippery slope on every paper that we're not
10 happy with we ask for more data. I think that's the wrong
11 thing to do. I thought we were supposed to evaluate this
12 on the data that's available presently. So I don't want
13 to create massive amounts of work, and we could
14 essentially table every chemical. So I think we have to
15 be a little careful here.

16 CHAIRPERSON GOLD: Dr. Woodruff.

17 COMMITTEE MEMBER WOODRUFF: Yeah, I wouldn't say
18 we're tabling every chemical, because we just voted on --
19 well, how many did we vote on? Four, three. Thank you.

20 So, I mean, I think this one is -- I mean, I
21 think what would be useful actually in these is when you
22 have an NIEHS study, just generally going forward, is
23 that -- I don't know. Do you normally go to NIEHS and say
24 can you give us the underlying data? I don't know what
25 your standard practice is?

1 DR. ZEISE: We typically don't do that. In this
2 particular case -- for -- well, let me step back. On the
3 cancer side, NIEHS maintains individual animal data. And
4 if there is a question, we'll get that individual animal
5 data and look. That's been our practice on the cancer
6 side.

7 On the developmental and reproductive toxicity
8 side, we're not -- there aren't as many studies, so we
9 really haven't developed a practice around going to NIEHS,
10 but -- so I think in this case, why don't we try, see what
11 we find. If there are data -- individual animal data, we
12 actually can do the statistics ourselves as well. So I
13 don't see this as a large amount of work.

14 COMMITTEE MEMBER WOODRUFF: Well, I would just
15 say generally that -- because I think there's often issues
16 with limitations in terms of what you can publish in a
17 paper online that there won't be all the underlying data
18 in order to do all the statistics we might want to
19 evaluate, that I would say going forward if there are
20 papers that are published that NIEHS studies, that the --
21 just like you're doing for cancer, that the underlying
22 data are collected from NIEHS and then evaluated, because
23 I -- I know with the one we're going to be discussing
24 next, having the individual animal data for me was very
25 helpful, because I could like go back and basically grab

1 things and look at them. And you can't really get that
2 necessarily from these published papers, because they
3 aren't allowed to include all that information all the
4 time in the papers.

5 DR. ZEISE: And you'll see at the next meeting,
6 you have a pesticide in front of you, and the registrant
7 has given us -- or given you the studies. So you have all
8 the individual animals for those submitted studies.

9 CHAIRPERSON GOLD: I would say in the context of,
10 you know, being concerned about overburdening the staff
11 and these -- in these requests, I mean we can be judicious
12 about them, but I think as the Committee is reading
13 things, if they see things that maybe actually might exist
14 that would be helpful, maybe we can transfer those
15 requests to even ahead of time, if that would be helpful.

16 DR. ZEISE: Yes, you can certainly do that.

17 CHAIRPERSON GOLD: I mean, this is really at
18 least the first one in recent memory that I can think of
19 where we're asking for additional information. So it's
20 not like we've been sort of going overboard on that,
21 but -- okay. So the plan is to defer this for additional
22 information from NIEHS, if they can provide it. And if
23 not, you'll come back to us and we'll try and do our best
24 to vote intelligently at that point.

25 Dr. McDonald(sic) you look like you had something

1 you wanted to say -- is that, no?

2 DR. DONALD: For what it's worth, I was just
3 going to tell the Committee that it's not unprecedented.
4 We have had other chemicals in the past which have been
5 deferred for similar reasons. And we have gone back to
6 authors of reports to ask for additional information.

7 CHAIRPERSON GOLD: Right. I do recall that, but
8 I think this Committee has not done a lot of that. And so
9 in terms of a burden, I think at least so far we haven't
10 caused a major burden.

11 Okay. So we will defer that one and we will move
12 on to methyl isopropyl ketone. And Dr. Moran is going to
13 start us off with that.

14 --o0o--

15 DR. MORAN: I hope you will like my accent by the
16 end of the day.

17 (Laughter.)

18 DR. MORAN: Okay. We're ready. Number 42.

19 So a comprehensive literature search resulted in
20 one reference with data on the potential reproductive
21 toxicity of methyl isopropyl ketone in rats. In addition
22 to this, we are presenting a summary of data from a
23 guideline study submitted during the comment period. This
24 report was made available in full to the Committee members
25 and posted on the OEHHA webpage.

1 --o0o--

2 DR. MORAN: This is a reproductive and
3 developmental toxicity screening study by Bernard in 2001,
4 where 12 males and 12 female rats were exposed by
5 inhalation at 0, 1, 2.5, and 5 milligrams per liter --
6 there's a small mistake in the handout. It says per ml.
7 It's milligrams per liter, the concentration -- for six
8 hours a day, seven days a week, from two weeks pre-mating
9 to gestational day 19. Necropsy on day 51 for females and
10 gestational day 23 for not delivering pregnant females or
11 days four to six post-partum gestational day.

12 The endpoints analyzed were systemic toxicity,
13 including body weight, food consumption; fertility; sperm
14 parameters, epididymal number, morphology and motility;
15 pregnancy outcome, postnatal growth and mortality on
16 postnatal day zero to four.

17 --o0o--

18 DR. MORAN: The systemic toxicity is summarized
19 here. There was a decreased paternal food intake and body
20 weight at 1 milligram per liter; decreased maternal food
21 intake pre-mating and first week of gestation at all doses;
22 decreased maternal body weight second pre-mating week and
23 last week of pregnancy; maternal clinical signs during
24 exposure.

25 --o0o--

1 DR. MORAN: There was no reported reproductive
2 toxicity. Body weights, reproductive organs -- yeah. For
3 the offsprings result we have the body weights,
4 reproductive organ weights, sperm motility, epididymal
5 spermatozoan counts, and testicular sperm counts were
6 comparable among the groups.

7 For offsprings we have that it was also reported
8 we have decreased number of live pups on postnatal day
9 zero and four at 5 milligrams per liter; increased number
10 of dead pups on postnatal day zero at 2.5 milligrams per
11 liter; increased pups dying on postnatal day zero to four
12 at 5 milligrams per liter.

13 It was also reported that there was a significant
14 decrease in litter weight at 5 milligrams per liter. This
15 difference disappear when a single litter with four pups
16 in the high dose group was not considered for the
17 statistic analysis -- statistical analysis.

18 --o0o--

19 DR. MORAN: This is a report that was made
20 available to OEHHA during the comment period. It is
21 developmental toxicity study in rats by Edwards in 2012.
22 In this study, 25 pregnant rats were exposed by inhalation
23 at 0, 300, 750, and 1,500 ppm for six hours a day, seven
24 days a week from gestational day zero to gestational day
25 19, necropsy on gestational day 20. It's good to note

1 that this concentration range is comparable to the one
2 used in the screening study by Bernard in 2001.

3 The endpoints were record clinical observations,
4 body weight, and food consumption; laparohysterectomy on
5 gestational day 20; uteri, placentae, and ovaries were
6 examined, number of fetuses, early and late resorptions,
7 total implantations and corpora lutea were recorded.

8 --o0o--

9 DR. MORAN: There was a decrease in food intake
10 and body weight gain at 750 and 1,500 ppm. And for
11 reproductive toxicity, it was reported as significant
12 reduction in fetal body weight at 750 ppm with a similar
13 but not significant decrease at 1,500 ppm. There was also
14 non-significant effect on fetal survival.

15 --o0o--

16 DR. MORAN: That concludes this presentation.

17 CHAIRPERSON GOLD: Thank you very much.

18 We now have time for public comments.

19 Thank you. Dennis Naas. I believe the podium is
20 over here and you have five minutes.

21 MR. NAAS: Thank you. My name is Dennis Naas.
22 I'm an independent toxicology consultant with 35 years of
23 experience. I am here representing Eastman Chemical
24 Company in their petition to delist methyl isopropyl
25 ketone as a developmental toxicant from Prop 65.

1 A recent ECGIH assessment in 2011, and the
2 subsequent Prop 65 listing in February of 2012 didn't
3 consider this new study, the data that was just presented.
4 It's important to point out, I think, that this study is
5 very recent. It was completed in 2012 just about two
6 years ago. It was a very powerful study. It was done in
7 compliance with OECD and EPA test guidances, as well as
8 the good laboratory practices for both here and Europe.
9 And it was also, I'll note, done at a highly reputable
10 laboratory with a great deal of expertise in both
11 developmental toxicity and inhalation toxicity.

12 This study had -- oh, and it did not -- this
13 particular study did not address reproductive toxicity.
14 It's a developmental toxicity study. The definitive
15 developmental toxicity study that we're talking about now,
16 the new one, was very powerful because of its size.
17 There's an N of 25 in each group. This allows very robust
18 assessments of the littering data, and it also included
19 detailed assessments of the offspring. This would be
20 external examinations, fetal -- excuse me, internal exams,
21 viscerals and also skeletal examinations. So this is
22 all -- it's a very robust guideline compliance study.

23 And in our opinion, the study did not cause any
24 developmental toxicity. There was that small difference
25 in fetal body weight, which was only seen a the mid

1 exposure level and not at the high level, but there were
2 no -- there was no evidence of developmental toxicity in
3 this study. And on the basis of this study, we feel that
4 MIPK should be delisted.

5 Thanks for your time.

6 CHAIRPERSON GOLD: Thank you.

7 Any questions?

8 COMMITTEE MEMBER WOODRUFF: Yeah, I have a
9 question.

10 CHAIRPERSON GOLD: Dr. Woodruff.

11 COMMITTEE MEMBER WOODRUFF: Why wasn't the study
12 available when you guys were doing your review?

13 MR. NAAS: It's not published.

14 COMMITTEE MEMBER WOODRUFF: Oh.

15 CHAIRPERSON GOLD: Other questions?

16 COMMITTEE MEMBER WOODRUFF: Is it publicly
17 available otherwise before this?

18 MR. NAAS: I don't believe so, no. It was a
19 privately contracted study by Eastman Chemical.

20 COMMITTEE MEMBER WOODRUFF: I see. So just
21 generally, could there be other studies that companies
22 have on these chemicals that we don't know about?

23 DR. DONALD: Basically, we know about what we
24 know about. There certainly may be studies of which we're
25 unaware. That's one of the reasons why we invite public

1 comment on the process, so that parties who are aware of
2 additional data can make them available to the Committee.
3 But this study did not show up in our searches, which we
4 made as comprehensive as we were able.

5 CHAIRPERSON GOLD: I mean, I guess I'd point out
6 the plus of such efforts is that we see papers that
7 haven't been published. That's also the downside. They
8 haven't been subjected to peer review, in terms of the
9 publication process. So we get more information, but it
10 hasn't undergone review.

11 MR. NAAS: It is however a GLP compliant study.

12 CHAIRPERSON GOLD: Yeah. Okay. Thank you.

13 All right. So, Dr. Pessah, is going to lead the
14 Committee off with some discussion of this.

15 COMMITTEE MEMBER PESSAH: Sure. Thank you for
16 the presenters for a very nice job presenting the
17 information. So based on what we do know, it seems that
18 the female exposure developmental study between GD zero
19 and 19 was adequately powered. And as far as the
20 information that I had access to, there seems to be really
21 very little to no evidence that there's developmental
22 effects with relatively high exposure levels of methyl
23 isopropyl ketone.

24 With respect to the male exposure study, which is
25 a little less powered, it seems that the major effects, if

1 I'm reading -- if I went into the report correctly, were
2 associated with lack of weight gain, and so systemic
3 stressors that probably were not related to developmental
4 outcomes.

5 So based on these two studies, I would say there
6 isn't compelling evidence.

7 CHAIRPERSON GOLD: Okay. Dr. Woodruff next.

8 COMMITTEE MEMBER WOODRUFF: Yeah. I agree that
9 the way the summaries are presented may -- I think they
10 don't give a complete picture of all the information
11 that's in the actual document. So I went through --
12 mostly because when we first got the studies -- well,
13 actually let me just back up and say, when we first got
14 the information about the summary, we had one study to
15 evaluate.

16 And so I started with this study. And I'll just
17 remind everyone, the things that I like about these
18 studies is they both have the same dose groups, so that's
19 very useful. The GLP generally, they're a little bit --
20 they're done later in time, so we have a little more
21 confidence in the methodological, and there's good
22 information presented about the methods.

23 The 2001 study actually reports individual
24 information on each of the dams, and there -- from what
25 they have for their litters. I only had summary

1 information from the one that was given out -- that was
2 given to us during the public comment period.

3 I will note that the first study, the 2001 study,
4 actually follows the animals pre-conception, during
5 conception, during pregnancy, and follows the animals
6 after they're born. The study that was done -- the second
7 study that we were given only followed the animals after
8 gestation, from gestation days zero to 19, and then did
9 not follow the animals -- actually, they did not
10 actually -- the animals weren't born. They killed the
11 animals and then looked at the fetuses.

12 So those are important distinctions I think
13 between the two studies. The reason I decided to look
14 further into these studies is that if you'll note in the
15 2001 study, and as was presented, there is a decrease in
16 the number of live births and an increase in the number in
17 dead pups, which I know -- and those were actually
18 postnatal days. So that's actually an independent finding
19 from the second study, because they didn't follow the
20 animals postnatal. We only have what the fetuses were
21 when they were sacrificed.

22 So then my -- I went back and looked at some of
23 the underlying data, because what we don't have in here is
24 reported is some of the information about
25 post-implantation loss, which is actually they're reported

1 both in the 2001 and the 2012 study. Also, the number of
2 implants, which is indicative reproductive compromise or
3 fetal viability, also reported in the -- both -- reported
4 in both the 2001 and the 2012 study.

5 So the nice thing about that is that it gives us
6 some information about -- both -- two different studies
7 with different numbers of animals over the same dose
8 range. And just to -- so then if you look at the actual
9 data in the back that's in the charts and you compare
10 them, so in the 2001 study, there is actually a decline --
11 or an increase in post-implantation loss starting with the
12 control as it starts at a mean across the groups of two
13 and goes up to 2.8, 2.5, and 8.2. So even though the
14 highest group is significantly -- is higher, you see a
15 trend. And if you run a regression line, it's
16 significant.

17 And the thing that was pretty interesting was
18 also in the Eastman study, you see increases in
19 post-implantation loss. The control group is 4.5 and it
20 goes up to 6.5. So you actually see a pretty similar
21 increase across both the studies for post-implantation
22 loss, which gives -- raises concern for me that this
23 chemical is -- you're getting a dose response for exposure
24 for post-implantation loss.

25 Also, you see a decline in -- I mean, the live

1 births and the percent of viable fetuses is slightly
2 different, but in the Bernard -- in the 2001 study, as was
3 said, the percent of live births actually in the control
4 group is 98 percent and declines to 92, and then 92
5 percent in the highest dose group, so it's 98, 96, 93, and
6 92.

7 And in the Eastman, starts off the control group
8 is 95, so a similar -- that's viable fetuses, very similar
9 to what we're seeing in the Bernard study, and also it
10 goes down 95.3, 94.3, and 93.5. So again, we're seeing a
11 decline in percent either viable fetuses or percent live
12 birth across the dose groups in both the studies.

13 Now, I know there is -- we did see in the 2001
14 study some decline in maternal body weight at the highest
15 dose group. I think that that leads to some concern about
16 potential effects on the female -- as the pregnant female,
17 which I think is -- actually should be a concern, in terms
18 of viability of the pregnancy, if there's effects on the
19 pregnant dam.

20 So for these reasons, there's actually even -- if
21 you start to read this even a little bit more, there's
22 actually some -- also data in the Eastman on resorption as
23 well as number of implants. And the number of implants
24 also declines across the dose groups for both of the
25 studies. So for these reasons, I think there is a concern

1 about this chemical.

2 CHAIRPERSON GOLD: Dr. Pessah.

3 COMMITTEE MEMBER PESSAH: I have a question,
4 because I didn't actually analyze. So the question is are
5 the trends significant as you look over time and is there
6 a dose effect?

7 COMMITTEE MEMBER WOODRUFF: Oh, there's
8 definitely a dose effect. You definitely see a change
9 over the dose range. If you combine them -- when I ran a
10 regression line -- you know, it's a percent. So I ran a
11 regression, yes, you did see a significant in the
12 coefficient, if you adjust by the variance, because it's
13 not completely fair to do that without adjusting by the
14 variance, you still get a somewhat significant effect. I
15 think the P value was -- it was less than -- I'd have to
16 go back, but it was definitely -- depending it was
17 somewhere -- sometimes the P value was not -- well, that
18 was just for one of the studies. That was 0.07 or 0.0 --
19 less than 0.05.

20 So, I mean, I think the thing that was -- I
21 didn't do, which I think would be very advantageous is
22 because we have the same endpoint across both studies, is
23 to actually combine the data and do an analysis of them
24 statistically, which I'm sure because they were less than
25 0.1, the regression lines, that you would -- together they

1 would be significant.

2 COMMITTEE MEMBER PESSAH: Can you do that if one
3 was a male exposure and the other was a female exposure?

4 COMMITTEE MEMBER WOODRUFF: Well, just looked at
5 the -- I looked at the -- oh, I see what you're saying.
6 This was all -- these were all pregnancy exposures though.

7 MR. NAAS: Does the public have an opportunity to
8 respond?

9 COMMITTEE MEMBER WOODRUFF: The public is closed.

10 COMMITTEE MEMBER ROCCA: Question about how you
11 handled your statistics. Was this done on the means or by
12 the litter with the standard deviations?

13 COMMITTEE MEMBER WOODRUFF: Right. So the
14 challenge is, is that for the Eastman study, the data is
15 reported only on the means, and so -- but, we don't -- so
16 that's one of the -- so I would actually -- in some ways,
17 that makes the study less useful than the 2001 study,
18 which we have all complete data, so -- and I would also
19 caveat that there were significant findings, as you report
20 here, for the live pups from the analysis.

21 And not all the endpoints were analyzed in this
22 way. Sometimes they're analyzed just by looking at
23 individual comparisons to the control group. And I really
24 think that we should be looking at comparisons of trends,
25 because that's not as powerful a statistical test if we're

1 just looking at each of the dose groups compared to the
2 control, rather than looking at the dose response across
3 all the doses.

4 COMMITTEE MEMBER ROCCA: All the individual data
5 is in Appendix F, I believe it is. So I was able to look
6 at some of that.

7 COMMITTEE MEMBER WOODRUFF: And for -- yeah, for
8 the 2001 study.

9 COMMITTEE MEMBER ROCCA: No, for the Eastman.

10 COMMITTEE MEMBER WOODRUFF: Oh, for the Eastman
11 study.

12 COMMITTEE MEMBER ROCCA: Yeah, it's there. Yeah,
13 the complete GLP study report is there. It's just not
14 easy to find it sometimes in these very large studies.

15 COMMITTEE MEMBER WOODRUFF: Oh.

16 COMMITTEE MEMBER ROCCA: So I'm on page 222 to
17 get to some of that data. And that may be what it is, is
18 that it's reported differently.

19 Can I make one other comment?

20 CHAIRPERSON GOLD: Yeah, Dr. Rocca.

21 COMMITTEE MEMBER ROCCA: One of the things that's
22 nice about seeing these two is that they are indeed at the
23 same doses, and they did treat all during pregnancy. One
24 of the big differences is that they were allowed to
25 deliver in the first study and not in the second. But

1 there is a reason that you do developmental toxicology
2 studies the way you do, in that you intentionally do not
3 allow them to deliver, because what you're finding out is
4 the totality of the uterine contents.

5 When you allow the females to deliver, and they
6 are only counting pups when they first find the litter,
7 what you'll frequently find is that if there have been any
8 deaths, that they will have cannibalized the pups. And so
9 it's possible that you saw something that was postnatal
10 that --

11 COMMITTEE MEMBER WOODRUFF: I agree. And I
12 actually checked on the viable fetus data from Eastman,
13 which shows the percent of viable fetuses, like you're
14 saying, which -- well, first of all, actually, they didn't
15 say there was any cannibalization in the 2001 study, so --

16 COMMITTEE MEMBER ROCCA: Well, they wouldn't
17 know, is the issue with that design.

18 COMMITTEE MEMBER WOODRUFF: Well -- anyway, the
19 viable fetus percent starts at 95.5, goes 95.3, 94.3,
20 93.5. So we're seeing a decline across the dose groups in
21 viable fetuses. And I would just point out that it's
22 interesting because the viable -- I did look like at --
23 that's like, hmm, that's pretty interesting. And to look
24 at the viable fetuses and you compare it to the percent of
25 live births, which is in the 2001 study, and actually the

1 viable fetuses you have a lower percentage. So, for
2 example, in the control group in the Eastman study it's 95
3 percent are viable fetuses. You have 98 percent live
4 births in the control group. In the 2001 study, they're
5 uniformly a little bit -- they're about the same as in the
6 Eastman study, so it gives me more confidence that the
7 cannibalization is not actually occurring, because
8 otherwise you'd expect a lot lower in this 2001 study
9 under that theory, I would think.

10 CHAIRPERSON GOLD: Any further Committee
11 comments?

12 Did you want to respond?

13 MR. NAAS: I did, if I could, please.

14 CHAIRPERSON GOLD: Take two minutes. Can you
15 come up here.

16 MR. NAAS: Thank you very much.

17 I'm thank you for finding the individual data. I
18 knew it was there. These reports are required all to have
19 individual data.

20 Maternal toxicity, I just want to address that
21 very quickly. I think most of the Committee is aware that
22 that is required to occur on a valid developmental
23 toxicity study. And the presence -- there's numerous --
24 enumerable papers out there that we can't use the presence
25 of maternal toxicity to dismiss a developmental effect.

1 We're not really allowed to do that, but we're required to
2 show the maternal toxicity. Otherwise, the studies aren't
3 considered valid, unless you go to some very high limit
4 test type exposures.

5 It is important that these studies are different.
6 The first study is a 421 -- OECD 421 screening study. The
7 group size is only an N of 8. It does incorporate the
8 two-week pre-mating period, the entire gestational period,
9 at which point it ends. That is very different from the
10 other study, which was just the exposures only occurred
11 during gestation. So I think any attempt to combine those
12 data would be invalid because of the differences in the
13 design.

14 And the other thing that's a very, very important
15 point, and perhaps someone -- I was trying to check this.
16 These laboratories keep exquisite historical control of
17 databases. They're very specific for the strain of the
18 animal, the age, and the laboratory. And they
19 periodically -- I mean, they get changed.

20 So trying kind of to compare a 2000 study to a
21 2012 study, you might be talking apples and pears, but I
22 would suggest -- I believe that in the recent study you
23 will find the historical data have been appended to that
24 report. And these minor differences in implantation rates
25 are -- they're not statistically significant in a study

1 that's powered to detect those statistical differences.

2 And without seeing the data, I'm willing to state
3 that those are within the historical ranges of the control
4 animals. So I just kind of wanted to throw those out
5 there. Thank you.

6 CHAIRPERSON GOLD: Thank you. So, Dr. Pessah,
7 did you want to respond to anything to Dr. Woodruff said
8 before we vote?

9 COMMITTEE MEMBER PESSAH: No.

10 CHAIRPERSON GOLD: Okay. Are we ready to vote?

11 COMMITTEE MEMBER WOODRUFF: I would say --

12 CHAIRPERSON GOLD: Dr. Woodruff.

13 COMMITTEE MEMBER WOODRUFF: -- I do agree that
14 they have different design features. So, you know,
15 that -- and in some ways, we have more exposure -- we have
16 more exposure data in the 2001 study. I just was struck
17 though by how we see a very similar change in the
18 parameters related to reproduction in both the studies --
19 across, what's really great is you have, the same dose
20 range.

21 So I think that gives us -- well, it gives me
22 more confidence in what we're seeing in terms of these --
23 some of these effects that were not really highlighted in
24 the summary. So I think that's the other thing about the
25 study that I just wanted to point out is I think it would

1 be very useful in the future to -- I mean, obviously, what
2 the authors are saying about their summary is important,
3 but I think it would be also good to dig into some of
4 these other endpoints, that I would not have actually
5 really dug into, unless I had seen the fetal deaths. That
6 made me go back and look at the implantation and
7 resorption data. And I think that would have been --
8 having more of a summary on that for this Committee would
9 have been very useful for me.

10 CHAIRPERSON GOLD: Any further comments from the
11 Committee?

12 Dr. Pessah.

13 COMMITTEE MEMBER PESSAH: So you kind of brought
14 up -- thank you.

15 So if this decline, this trend is within the --
16 within the limits of the strain age that --

17 COMMITTEE MEMBER WOODRUFF: Yeah, I --

18 COMMITTEE MEMBER PESSAH: -- and you're seeing
19 this go across studies, would it suggest that we're
20 missing information on the older study that says those
21 declines are within what's expected for the strain?

22 COMMITTEE MEMBER WOODRUFF: Right. I agree that
23 if they -- we didn't -- I think that's an issue for if
24 that was -- we did not see a dose response. What makes
25 me -- right, because you have in your historical -- if

1 these rats have a certain amount of post-implantation loss
2 or fetal viability issues, those are always going to
3 be -- that's going to be your baseline within your
4 control.

5 But if you're seeing a change in that across the
6 dose range from the control, then even though they're
7 still historical -- or that's something that is a
8 percentage of you see in the animals, even a change from
9 that would be considered an effect. Does that make sense?

10 COMMITTEE MEMBER PESSAH: Right, but what's the
11 range of the trend from high to low?

12 COMMITTEE MEMBER WOODRUFF: Well, the range is it
13 depends on -- it goes from --

14 COMMITTEE MEMBER PESSAH: I think you --

15 COMMITTEE MEMBER WOODRUFF: What?

16 COMMITTEE MEMBER PESSAH: I think you stated it,
17 but I forget.

18 COMMITTEE MEMBER WOODRUFF: It depends on -- the
19 percent loss is anywhere from five to ten percent -- I
20 think it's nine -- it's around eight is the high. The
21 live births start at like anywhere from 90 -- it was 96 to
22 98 and go down to somewhere around 90 to 92. So you're
23 seeing like a 10 percent change.

24 I would say I agree that there's -- you know,
25 there's going to be noise in this, and that there's some

1 issues related to potential for changes among the
2 historical controls. I think what we also have to think
3 about is are we seeing a consistent finding among
4 different endpoints? So whether there's viability in the
5 fetuses, mortality among the infant -- of the pups when
6 they're born, then was there an issue with
7 post-implantation loss? So that's kind of in the
8 spectrum. And then was there an issue with implantation?

9 So I agree if it was just one endpoint, that
10 would be -- I'd be like, "Oh, okay. Well, that's just one
11 thing". But we're seeing kind of along the spectrum of
12 issues related to viability of the fetus a number of
13 different outcomes that are trending in the same
14 direction.

15 So I think that, you're right, it's -- we can't
16 just let one study or one dose. Okay, but when I look at
17 these different endpoints and look across them and they're
18 related, it adds strength to the evidence.

19 CHAIRPERSON GOLD: Any other comments from the
20 Committee?

21 Are we ready to vote?

22 Okay. So the question is has methyl isopropyl
23 ketone been clearly shown through scientifically valid
24 testing, according to generally accepted principles to
25 cause developmental toxicity? All those of who believe

1 yes, please raise your hand?

2 (No hands raised.)

3 COMMITTEE MEMBER ROCCA: Developmental, right?

4 CHAIRPERSON GOLD: I said development, yes.

5 CHAIRPERSON GOLD: I see no yeses.

6 Those who believe no?

7 (Hands raised.)

8 CHAIRPERSON GOLD: Five.

9 Abstain?

10 (Hand raised.)

11 CHAIRPERSON GOLD: One.

12 Okay. Has methyl isopropyl ketone been clearly
13 shown through scientifically valid testing, according to
14 generally accepted principles to cause female reproductive
15 toxicity? All those who believe yes, please raise your
16 hand.

17 (Hand raised.)

18 CHAIRPERSON GOLD: One.

19 Those who believe no?

20 (Hands raised.)

21 CHAIRPERSON GOLD: One, two, three.

22 Those who abstain?

23 (Hands raised.)

24 CHAIRPERSON GOLD: Two of us.

25 Okay. Has methyl isopropyl ketone been clearly

1 shown through scientifically valid testing, according to
2 generally accepted principles to cause male reproductive
3 toxicity? If you believe yes, please raise your hand.

4 (No hands raised.)

5 CHAIRPERSON GOLD: Zero.

6 If you believe no, please raise your hand.

7 (Hands raised.)

8 CHAIRPERSON GOLD: Six.

9 No abstentions.

10 Okay. So for developmental toxicity, we have
11 five out of the six voting no. And for female
12 reproductive toxicity we have one yes, three noes, and two
13 abstentions. And for male toxicity, we are in agreement
14 unanimously of all voting no.

15 Okay. Given the relative lateness of the hour,
16 the need for taking a break, et cetera. I'm going to
17 recommend that we take a lunch break at this time.
18 Perhaps reconvene about 1:15/1:20, if that seems
19 reasonable for people, and take up the remainder of the
20 agenda then.

21 Thank you.

22 (off record: 12:35 PM)

23 (Thereupon a lunch break was taken.)

24

25

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

2 (On record: 1:21 PM)

3 DIRECTOR ALEXEEFF: Okay. We're going to bring
4 the meeting back to order here. Here's Dr. Gold.

5 CHAIRPERSON GOLD: Okay. I think we're all
6 reconvened. And so we're going to ask Dr. Moran one last
7 time to make the staff presentation for alpha-methyl
8 styrene.

9 --o0o--

10 DR. MORAN: Thank you. Good afternoon.

11 A comprehensive literature search resulted in two
12 references with data on the potential reproductive
13 toxicity of alpha-methyl styrene in rats and mice.

14 --o0o--

15 DR. MORAN: This is a developmental toxicity
16 study by Hardin et al. in 1981, where 15 -- 10 to 15
17 inseminated female rats per group were exposed to AMS by
18 intraperitoneal injection at 0 or 250 milligrams per kilo
19 from gestational day one to gestational day 15. Animals
20 were sacrificed on gestational day 21.

21 And the endpoints were: Gross examination of
22 internal organs, brain, heart, lungs, liver, spleen,
23 kidneys, adrenals, and ovaries weighed and preserved for
24 histopathological examination.

25 --o0o--

1 DR. MORAN: Okay. For the offsprings endpoint,
2 they considered weight, measured for crown-rump length,
3 sexed, and examined for externally visible malformations.
4 One half to two-thirds of each litter used for internal
5 examination. The rest of each litter preserved in ethanol
6 for skeletal staining.

7 --o0o--

8 DR. MORAN: For the parents results, we have the
9 no treatment-related weight changes, no histopathological
10 changes. And for the offspring results, it was a
11 significantly increased incidence of fetal resorptions, P
12 was 0.05, altered fetal sex ratio with a deficit of female
13 fetuses.

14 --o0o--

15 DR. MORAN: In a three-months inhalation exposure
16 study in mice and rats by NTP in 2007, ten animals per sex
17 per group were exposed at 0, 75, 150, 300, 600, and 1,000
18 ppm for six hours a day, five days a week, for 14 weeks.

19 The endpoints were body weight, initially,
20 weekly, and at the end of the studies. At the end of the
21 three months and on the three higher doses epididymal sperm
22 concentrations and motility, cauda epididymis and testis
23 weights, and vaginal cytology for the last 12 days were
24 considered.

25 --o0o--

1 DR. MORAN: And the results for mice were that
2 five to 15 percent decrease in body weight significant in
3 both genders at 300, 600, and 1,000 ppm. For the
4 reproductive toxicity they found a decreased cauda
5 epididymal weight at 600 and 1,000 ppm with a P of less
6 than 0.05. No effect on other reproductive endpoints.
7 Longer estrous cycles at 600 and 1,000 ppm from 3.9 days
8 in the control group versus 4.8 and 5.2 respectively, both
9 of them significant.

10 --o0o--

11 DR. MORAN: There were no effects on body weight.
12 Kidney toxicity were observed in 300 ppm or greater for
13 males and from 600 ppm for females. For reproductive
14 toxicity results there were no observable adverse
15 reproductive effects reported in treated rats of either
16 sex.

17 --o0o--

18 DR. MORAN: That concludes the presentation.
19 Thank you.

20 CHAIRPERSON GOLD: Thank you. Dr. Rocca, will
21 you take the lead on this please.

22 COMMITTEE MEMBER ROCCA: Yes, thank you.

23 CHAIRPERSON GOLD: Oh, sorry. No.

24 Public comments? Are there public comments?

25 Okay. Now Dr. Rocca.

1 COMMITTEE MEMBER ROCCA: Thank you for that
2 review as well. The first study that was noted was the
3 one in 2007 where the route of administration was
4 intraperitoneal. So this one really is not relevant to
5 human exposure. However, they still found that there was
6 almost no toxicity. The only reproductive toxicity that
7 they showed is one plus mark in one table for increased
8 fetal resorptions, but there are no data to go along with
9 this, and this is an I.P. study.

10 For the second where we have the chronic
11 inhalation study for three months, they looked at the
12 effects on organ weight, sperm parameters, and histology
13 of reproductive organs. There they did have systemic tox
14 of body weight loss at the top three doses. However,
15 there were no effects on any of them on sperm parameters
16 or histology of testis or ovaries.

17 The only result that they did have for that one
18 was that they found a decrease in the weight of the left
19 testis. However, if you look in the organ weight data,
20 and look up the right testis, there was no difference. So
21 I think it's one of those very small changes that probably
22 does not make biological sense here.

23 So I think based on the data that we have here, I
24 would not call this a reproductive toxicant.

25 CHAIRPERSON GOLD: Thank you. The only thing I

1 would add to that was the increased estrous cycling length
2 that they showed which was a significant difference. It's
3 a relatively small study. It's one study in one animal,
4 and so I think I would not feel that I could conclusively
5 state that there was a reproductive effect, but as they
6 say, it's suggestive.

7 COMMITTEE MEMBER ROCCA: Yes. Thank you for
8 bringing that up. I did miss that.

9 COMMITTEE MEMBER ROCCA: They did this for 12
10 consecutive days, and in the footnotes, it says several of
11 the animals had unclear cycles. So I think that they
12 didn't even do three complete cycles in these animals.
13 And if they were unclear and they included those, then in
14 the analyses it makes it really difficult to interpret.
15 So I agree.

16 CHAIRPERSON GOLD: Thank you for that point.

17 Is there any further discussion among the
18 Committee on alpha-methyl styrene?

19 Questions, comments?

20 Are we ready to vote?

21 Okay. So has alpha-methyl styrene been shown
22 clearly through scientifically valid testing, according to
23 generally accepted principles to cause developmental
24 toxicity? If you believe yes, please raise your hand.

25 (No hands raised.)

1 CHAIRPERSON GOLD: I see none.

2 If you believe no, raise your hand.

3 (Hands raised.)

4 CHAIRPERSON GOLD: I see six.

5 No abstentions.

6 Has alpha-methyl styrene been clearly shown
7 through scientifically valid testing, according to
8 generally accepted principles to cause female reproductive
9 toxicity? If you believe yes, please raise your hand.

10 (No hands raised.)

11 CHAIRPERSON GOLD: Zero.

12 If you believe no, please raise your hand.

13 (Hands raised.)

14 CHAIRPERSON GOLD: Six.

15 And no abstentions.

16 And finally, has alpha-methyl styrene been
17 clearly shown through scientifically valid testing,
18 according to generally accepted principles to cause male
19 reproductive toxicity? If you believe yes, please raise
20 your hand.

21 (No hands raised.)

22 CHAIRPERSON GOLD: I see zero.

23 If you believe no?

24 (Hands raised.)

25 CHAIRPERSON GOLD: Six.

1 And no abstentions.

2 So the committee is unanimous on voting no for
3 developmental, female reproductive and male reproductive
4 toxicity for alpha-methyl styrene.

5 So thank you all. That concludes our discussions
6 and votes about specific chemicals that we needed to
7 reconsider under the Labor Code listing. And so we'll now
8 move to the next agenda item.

9 And I actually have a couple of introductory
10 comments to make before we engage in this discussion. It
11 seemed like it would be helpful in the purposes of
12 background and to provide some focus to this discussion to
13 give just a very brief sort of summary of where we were
14 and what initiated this process.

15 So let me say -- so I have several points. The
16 first is that the public comments that we received and
17 that OEHHA received concerning the tables for the animal
18 and epidemiology studies were collated and were
19 distributed to the DART Committee for them to review and
20 consider in today's discussion. And specifically by way
21 of providing some focus to this discussion, I want to
22 briefly review the origin of these tables and this
23 discussion.

24 Originally, over a year ago, some Committee
25 members had suggested -- had made some suggestions for

1 improving the summary table for animal toxicology studies,
2 which is one of the tables under discussion today. We
3 have two. Then about a year ago, OEHHA asked for similar
4 input regarding the table summarizing epidemiologic
5 studies and a draft was provided, which is the other table
6 that we'll discuss today.

7 These tables were meant to be summary tables,
8 always accompanying the original papers on each chemical
9 that the Committee reviews, and generally accompanying the
10 text that OEHHA staff provides to the Committee.

11 So these summary tables were not meant to replace
12 the text that OEHHA has generally provided to the
13 Committee, nor to replace the Committee members' reviews
14 of each of the original data papers for each of the
15 chemicals as you've heard we do today. They were just
16 intended to be summary tables to highlight the
17 methodologic approaches and results in each paper, so as
18 to facilitate the Committee's review.

19 This point may have been lost a little bit in the
20 last couple of meetings because we've just focused on the
21 reexamination of the chemicals that were originally listed
22 under the Labor Code in the hazard identification
23 documents to determine if they should still be listed, and
24 no text accompanied those tables for this purpose.
25 Although, we did receive the original papers.

1 However, it is intended that for consideration of
2 new chemical listings that will be coming before us, that
3 the text will accompany -- the summary texts will
4 accompany the summary tables and Committee members, of
5 course, will be provided with the original data papers for
6 them to review, each of them critically.

7 So we are aware that -- also that several
8 national and other groups and agencies, including
9 committees of the National Academy of Sciences and the
10 National Toxicology Program and others are reviewing and
11 considering systematic reviews for weight of the evidence,
12 evaluations for chemicals, and for ways to present data in
13 tables to assist in these reviews, but no final accepted
14 formats have been agreed upon for these reviews for
15 developmental and reproductive toxicity.

16 So in conclusion, the purpose of today's study is
17 not to vote on the tables, but rather for the Committee to
18 provide input to the OEHHA staff as to what would be most
19 helpful to us as a Committee for them to summarize for us,
20 so that we can make our decisions based on the materials
21 that we received to review on the topic, and all of the --
22 and that the Committee members will use all of their
23 experience in critically reviewing published papers to
24 draw their conclusions and to provide this guidance.

25 So we are providing -- so we're here today in

1 this piece of the discussion to provide guidance to the
2 OEHHA staff. Again, the summary tables are not intended
3 to replace the text that OEHHA staff generally provide for
4 each paper on each chemical nor to replace Committee
5 member's own reviews of those papers. The tables are
6 meant to be helpful to the Committee, so the Committee
7 should be sure to give their input today, as to what would
8 be helpful to them to have included in the tables by
9 OEHHA.

10 And I think that concludes my sort of general
11 introductory comments. I just wanted to put everything in
12 context and try and focus the discussion a little bit.

13 Okay. At this point, I invite public comments on
14 this topic of the animal and epidemiologic summary tables.
15 Again, I'll reiterate we did receive public comments. The
16 Committee has received them. They were collated by OEHHA
17 and given to -- staff and given to us, and so we've
18 reviewed those.

19 And I see no further comments?

20 Okay. So then I open it up to the Committee and
21 I have not appointed any one person, because this is an
22 open-Committee discussion for this purpose. So I invite
23 comments of the Committee to advise OEHHA on these tables.

24 Dr. Baskin.

25 COMMITTEE MEMBER BASKIN: I like the tables you

1 provide presently. I think they're extremely helpful.
2 And a few additions would be -- I'm not a statistician,
3 you know, epidemiology expert, but we're all kind of
4 required now to give kind of a -- when we see a paper, you
5 know, is this a five star paper or a one star paper, you
6 know, perspective, you know, double blinded, you know,
7 control study versus a case report, so to speak. And in
8 the scientific literature, it's done like that too.

9 So I don't know if I'm an advocate for like, you
10 know, a rating of whether this is a good paper or not,
11 because I think that's very subjective and maybe going
12 down the wrong road, but I would like to see a little more
13 detail about, you know, power analysis statistics, and
14 maybe more right-hand column.

15 I think now Dr. Moran's presentation today, and
16 in the tables, you know, it's listed no statistics or some
17 statistics, but maybe just a little more embellishment in
18 that area.

19 CHAIRPERSON GOLD: Thank you.

20 Anyone else?

21 Dr. Woodruff.

22 COMMITTEE MEMBER WOODRUFF: I like having the
23 tables. I think the tables are new, right, relatively?

24 CHAIRPERSON GOLD: No, I think we've always had
25 tables.

1 COMMITTEE MEMBER WOODRUFF: I mean before this
2 meeting.

3 CHAIRPERSON GOLD: They've just been slightly
4 modified recently. Yeah, but there have always been
5 summary tables.

6 COMMITTEE MEMBER WOODRUFF: So I like the tables.
7 I think we provided comments on the tables and the kinds
8 of information that would be -- I think would be helpful
9 to have in the tables to give a little more information,
10 and because I know we're going to -- we've only actually
11 really seen information for animal studies. Have we
12 actually even evaluated any human studies? I don't even
13 remember anymore if that's happened at any of our
14 Committee meetings.

15 So -- and I think having information -- well, I'm
16 not going to go over all the details of what we presented,
17 but I think more information about the study -- about
18 issues related to interpreting the study are useful. I
19 think in terms of thinking about evaluating study quality,
20 which I know is a very actively discussed topic right now
21 going on in environmental health, I know NTP has an
22 approach and we have been looking at methods that have
23 been applied by Cochrane and GRADE. And also EPA has been
24 starting to look at this, as well as there are things
25 going on internationally that if -- I would not do study

1 quality issues right now on this table, but it would be
2 worth having a discussion about those different aspects,
3 because it's pretty -- that is a whole field in itself, in
4 terms of evaluating study quality and strength of evidence
5 across all the different endpoints.

6 And I think we have discussed this, and I think
7 it is -- would be very useful to have NTP come to do a
8 presentation about how they're evolving in terms of their
9 strength of evidence evaluations, so -- and their tables.
10 And they have also been putting together a lot of tools
11 for extracting study data and information to make it
12 easier to see both things that are going on with the
13 different methods in the studies, but also to have all the
14 data available for the different endpoints, so that they
15 can easily be graphed and evaluated.

16 For example, I do not actually think -- it's not
17 really -- I actually do not like just reporting
18 statistical significance in the study or not, because that
19 actually does not give you the underlying information
20 about the study, and it's evaluating the study basically
21 on a finding. And it's better to have graphical
22 information about outcomes, so that we can look across
23 different studies across the same outcome, so...

24 CHAIRPERSON GOLD: Thank you. Others?

25 Dr. Pessah.

1 COMMITTEE MEMBER PESSAH: So I really appreciate
2 the tables. If I may make one technical suggestion.
3 Instead of providing the primary literature as separate
4 files, if you could just link them onto the table where
5 you cite -- so, for example, I'm looking at Potter 2003,
6 if you'd just make a soft link to PubMed or to the PDF, it
7 would be so much easier. That can easily be done, I
8 think.

9 CHAIRPERSON GOLD: We might have to be careful
10 about PDF, depending on where people are, but -- a PDF
11 would probably work, but PubMed may or may not, so
12 depending.

13 Other comments?

14 You want to make a comment?

15 DIRECTOR ALEXEEFF: Yes. George Alexeeff.

16 Yeah, so we have been providing tables always
17 from -- for years. And so this has been kind of a process
18 to improve -- improve the information that the Panel
19 receives in the tables. So we're constantly listening to
20 the types of issues that the Panel members are identifying
21 in papers, and the kind of things that they like to see.
22 So we'll be continuing to do that, but I think this
23 process has been helpful to us to hear, you know, what
24 sort of things you look for.

25 I mean, it was -- I forget who actually said this

1 of the Panel members, or maybe I'm just paraphrasing a few
2 Panel members, that basically they themselves were kind of
3 making tables and -- of the data. And so if we can
4 actually address that and make the kind of tables that the
5 Panel can use to -- you know, to organize the data or to
6 quickly glance or refresh their memory or to, you know,
7 look at the data as whole, that's something we would like
8 to accomplish.

9 So we'll just continue, you know, improving them.
10 And if as comments -- as we continue to provide you
11 tables -- and one of the reasons that one of the chemicals
12 is delayed that we had thought of working on, chloroform,
13 because it is a more complicated -- it has epi data and
14 other data, and it's a much more complicated analysis, a
15 bigger challenge in terms of addressing the table.

16 So my guess is when that chemical comes before
17 the Panel, you may have some more ideas about tables as
18 well, because that's a little more complicated one than
19 some of these here where you only have three or four
20 studies. It's not as difficult to -- especially when the
21 studies don't have a lot of information, it's not too
22 difficult to add a lot -- whatever they have, so -- but
23 when the studies are much more complicated, that might be
24 something that, you know, you can provide us advice on at
25 that time, because there will be different types of

1 endpoints and information in those studies.

2 So we'll do our best to sort of figure out what's
3 best for the -- what the Panel is looking for, but we're
4 always open to improvement.

5 CHAIRPERSON GOLD: So it might be that when we
6 review the chloroform, since you used that as an example,
7 that we take a few minutes at the end to say how hopeful
8 was this table? How could we tweak it to make it better?

9 DIRECTOR ALEXEEFF: Yeah, I think so. I haven't
10 seen the tables myself, but that's the inclination -- the
11 sensing I get from the staff, that it's a much more
12 challenging chemical than the other ones we've seen thus
13 far.

14 CHAIRPERSON GOLD: Okay. Dr. Woodruff, did you
15 have another comment?

16 COMMITTEE MEMBER WOODRUFF: Yeah. Well, I think
17 that we should have information about all the endpoints
18 that are relevant and related. And there should be
19 data -- one, it would be easier to group by endpoint. So
20 endpoint and then have the studies, and then endpoint and
21 then have the studies, rather than study and then
22 endpoint, because then you're looking across studies for
23 one endpoint.

24 And then I would have all the endpoints that are
25 relevant to our discussions, so not just the ones that are

1 necessarily highlighted by the study authors.

2 CHAIRPERSON GOLD: So I would make a little
3 caveat on that. And I think maybe this is a Rorschach
4 test of who likes what. But the one caveat I would make
5 is that I think it's important to list endpoints, whether
6 they show a positive relationship or not, so that
7 everything that was examined should be listed whether or
8 not they found an association or a difference, because
9 that's informative as well.

10 Yes.

11 COMMITTEE MEMBER WOODRUFF: Yeah, I agree. And
12 also this DRAGON tool that NTP -- I think it's -- I don't
13 know if EPA is involved with this too, but NTP has been
14 putting together. It allows you to like get all the data
15 from the studies, put it in, and then you can actually
16 regraph them, so you get all -- a visual of all the
17 information.

18 DIRECTOR ALEXEEFF: Yeah, we are looking at that
19 tool --

20 COMMITTEE MEMBER WOODRUFF: Yeah, I know.

21 CHAIRPERSON GOLD: -- but we haven't actually
22 used it in any report that we've prepared as far as I
23 know.

24 DR. ZEISE: Well, that's another -- there are a
25 variety of tools that are under development, and so we've

1 been looking at DRAGON at ICF/Clement, which is very
2 interesting, but it isn't -- it's still in a state of
3 flux, and actually they're -- we've been talking with them
4 and they've been --

5 COMMITTEE MEMBER WOODRUFF: Oh, it is.

6 DR. ZEISE: Yeah, they're basically iterating the
7 tool further. So that's under --

8 COMMITTEE MEMBER WOODRUFF: Oh. Okay. I got it.

9 DR. ZEISE: That's still under development. And
10 there's another tool out of the University of North
11 Carolina that also looks very good, but again, that's in a
12 state of development. So we're following these tools and
13 we're going to see how we should be adapting them as we go
14 along to see how useful they are.

15 COMMITTEE MEMBER WOODRUFF: Um-hmm.

16 CHAIRPERSON GOLD: I mean, there's also the
17 CONSORT tool. And then I think you wanted to use the --
18 so there are lots of tools around. And I don't think
19 there's any one -- accepted one.

20 But you could even think about the analogy to
21 meta-analysis data. And then, you know, the point
22 estimates then, if you -- let's just say you had one for
23 each endpoint. Are the size of those endpoints are
24 determined by the size of the study? Which is an issue
25 that we come up repetitively -- you know, in all these

1 animal studies, some of them are quite small. Some are
2 sort of medium sized, and the point estimate ought to
3 reflect that along with the confidence interval.

4 So that's jumping way ahead though. I'm not sure
5 we're there yet.

6 Yeah, Isaac.

7 COMMITTEE MEMBER PESSAH: So there is something
8 that came up today that really has me stumped about how to
9 deal with. And that is when you presented proprietary
10 information, I don't know, but up till now it's been
11 generally negative information. In other words, not a lot
12 of clear positive effects. That's okay, if that's all the
13 information.

14 But we've heard that maybe there's other
15 information that are not forthcoming. Can we at least get
16 some indication of whether there's information that's
17 being withheld as opposed to not being able to get all of
18 the information?

19 CHAIRPERSON GOLD: Yeah, given that it's
20 proprietary, I'm not so sure, but maybe Carol has
21 something to say.

22 CHIEF COUNSEL MONAHAN-CUMMINGS: The short answer
23 no.

24 We really rely on the folks that do the studies
25 and the companies that pay for them to provide us with

1 what they feel is relevant information. But there's no
2 way for us to know what studies are out there, unless
3 somebody tells us, when they're not published.

4 DIRECTOR ALEXEEFF: But I would like to -- George
5 Alexeeff -- comment that, you know, we've often received
6 studies from organizations about chemicals. And they
7 often have positive results as well as negative results.
8 There's very -- really no distinction. These are -- at
9 least the studies that we've seen are those that are
10 required to be submitted for various things, such as, you
11 know, pesticides, or maybe FDA or something like that.

12 So those studies are -- although they're not
13 published, they're some place, and there's usually very --
14 there's no reluctance, or oftentimes -- let's just put
15 it -- I'll just put it bluntly. Oftentimes, we've
16 received reports and we've identified more endpoints than
17 we previously had thought, so -- and so that's definitely
18 there -- they're just providing us the information.

19 But if there's an in-house study that's not
20 required for any particular purpose, then it's up to
21 the -- you know, the people who own the study to decide,
22 you know, if they even hear our call or request, and to
23 submit it if they desire. There may be -- you know, a lot
24 of these times, at least in people that I've spoken to,
25 you know, the study was useful information for them to

1 proceed along their lines, but it may not meet the kinds
2 of standards that they would have wanted for publishing or
3 it wasn't meant for that. It was meant for them just to
4 make a decision. And it was good enough for that, but not
5 necessary for this Committee, and maybe they wouldn't want
6 to release a study like that.

7 CHAIRPERSON GOLD: And I would just add that that
8 goes beyond proprietary data. I mean, authors make their
9 own choices about what they're going to submit for
10 publication. And we know that there's publication bias,
11 and the negative studies often don't get published. And
12 we'll never, I don't think, hear about those.

13 Okay. Yes, public comment, for a couple of
14 minutes.

15 DR. LAWYER: I'm Dr. Arthur Lawyer, Technology
16 Sciences Group, Davis, California.

17 Just a comment to -- on the proprietary studies.
18 I was involved in deltamethrin, which you might remember
19 from last year and involved in the one coming up in your
20 next meeting, chlorsulfuron. For those heavily regulated
21 chemicals, such as pesticides or pharmaceuticals, and even
22 the TSCA industrial chemicals if they're new -- let's take
23 the pesticides. When there is a study done, whether or
24 not they thought it was -- or it wasn't required or not,
25 if there's an adverse effect found, they're actually

1 required under those various laws to submit them.

2 So for a pesticide, for example, something that
3 everybody cares about, there are laws about adverse effect
4 reporting, and those databases, in fact, are available.
5 They're not as easy as Medline and such, but they are
6 available to us. And this staff is very, very good at
7 finding those studies.

8 But to George's comment, often, you know, it's in
9 everybody's interest to report them, but I just wanted to
10 make sure you understood that the -- there's very -- it's
11 very difficult in the heavily regulated chemicals to
12 withhold anything that would be a positive finding. I
13 thought that might help.

14 CHAIRPERSON GOLD: Thank you.

15 Dr. Woodruff.

16 COMMITTEE MEMBER WOODRUFF: Yes. That's very
17 true for the pesticides. So for a lot of TSCA chemicals
18 we just aren't going to know if they have them. And the
19 chemical that was spilled in West Virginia, those studies
20 came out six days after the spill. So I just think we --
21 unless you have a legal authority, we're not necessarily
22 going to know whether we have those studies or not.

23 DR. LAWYER: I'm with you. Thank you.

24 CHAIRPERSON GOLD: Okay. One further public
25 comment.

1 MR. SHESTEK: Thank you. Good afternoon. Tim
2 Shestek with the American Chemistry Council. Just kind of
3 a question and also a comment. We were one of the
4 organizations that did submit comments. I was curious,
5 what sort of the next steps, in terms of dialogue, that we
6 might have with OEHHA staff or this Committee as this
7 issue goes forward? I wanted to just let folks know that
8 we're certainly available. And there are technical folks
9 that did put together our comments. I'd be more than
10 happy to try to answer questions or engage with OEHHA
11 staff as this moves forward. So thank you.

12 CHAIRPERSON GOLD: Well, we appreciate the
13 efforts. As I said, we've all seen them. OEHHA staff has
14 seen them. I think they're reviewing them in their
15 considerations of how the tables might be revised or made
16 more helpful. I assume if they have questions, they'll
17 contact you.

18 Good enough. Okay. Anything further on this?

19 All right.

20 So we have a couple of final issues. One is the
21 update on Section 27000, list of chemicals which have not
22 been adequately tested as required. Who's making this
23 presentation?

24 Carol.

25 Oh, yeah, it says Carol.

1 (Thereupon an overhead presentation was
2 presented as follows.)

3 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. This has
4 to do with some more chemicals that I can't pronounce. As
5 you may recall, I think that you've done this once before
6 as this particular group of members of the Committee.
7 There's a second list that's required under Prop 65, a
8 list of chemicals that I don't know who uses this list,
9 but it's mandatory under the law for us to maintain the
10 list and for you to opine on taking chemicals on and off
11 of it.

12 The criteria is that these are chemicals that --
13 where the government has requested testing or required
14 testing on the chemicals, and those have not been
15 completed, whatever the tests are.

16 There's different kinds of testing that's
17 required. And I think that in your materials you've got
18 some examples of what those might be in terms of endpoints
19 and different kind of testing requirements for both cancer
20 and reproductive toxicity. So once a year generally we
21 give you the two different things to vote on.

22 One is chemicals that should be added to this
23 list, because the U.S. EPA or Department of Pesticide
24 Regulation are requesting studies be done, and the second
25 job is to confirm that we should remove certain chemicals

1 from the list, because U.S. EPA or DPR have verified that
2 the testing has been done.

3 So it's kind of an odd thing for you, because
4 you're just really deferring to U.S. EPA and DPR. We
5 don't have other agencies that we are able to collect that
6 information from, but under the law and the regulations,
7 you're required to do this task, so -- and, you know, if
8 in some -- in the perfect world we could, you know, amend
9 Prop 65, which is virtually impossible, we would take this
10 provision out, because, like I said, I don't know of
11 anybody that uses the list. Maybe somebody does, but we
12 never get inquiries on it.

13 So in any event we've got two slides here for you
14 of chemicals that we're requesting that you add to the
15 list. The first has been up for here a while -- as I
16 mentioned, I'm not going to read off the chemicals. These
17 were in your materials, so if you had a chance to look at
18 them.

19 So there's two slides here.

20 --o0o--

21 CHIEF COUNSEL MONAHAN-CUMMINGS: The second slide
22 of additional chemicals. And these are ones that we want
23 to add to the list. So I don't know if, Dr. Gold, you
24 want to ask for a vote on that before we get to the one
25 about taking chemicals off the list.

1 Yes.

2 CHAIRPERSON GOLD: So these are actually to be
3 listed or for us -- or for you to investigate for us to
4 make a decision about what they --

5 CHAIRPERSON GOLD: No. These having nothing to
6 do with the Prop 65 list that you work on normally. This
7 is a separate list that's maintained under the law.
8 That's in the Section 2700 of the -- of our regulation
9 that, as I mentioned, I don't know what the purpose was at
10 the time it was required.

11 CHAIRPERSON GOLD: So in other words, they're
12 being listed because they haven't been adequately tested?

13 CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

14 CHAIRPERSON GOLD: They're just going on a list
15 of inadequately tested chemicals?

16 CHIEF COUNSEL MONAHAN-CUMMINGS: Correct. And
17 then periodically -- and we'll have a second group here,
18 the two agencies let us know that they have received the
19 tests and we can take them off.

20 CHAIRPERSON GOLD: I see. Okay. Yes, some
21 questions.

22 Dr. Rocca.

23 CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Rocca.

24 COMMITTEE MEMBER ROCCA: Are any of the chemicals
25 listed here currently listed under Proposition 65 as

1 causing reproductive toxicity?

2 CHIEF COUNSEL MONAHAN-CUMMINGS: I don't know
3 that. We don't compare the two lists.

4 COMMITTEE MEMBER ROCCA: Well, I think that would
5 be important. If we say it's not adequately tested here,
6 and we have another list that says it's a toxicant.

7 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it kind of
8 depends on what the testing that is required by the agency
9 is. It's not necessarily -- they don't necessarily fit
10 together. So, you know, in the event that we know that
11 the chemicals have had some testing done, we can always
12 follow up on those and find out if -- you know, that it's
13 something that we should consider -- you should consider
14 for listing or we should under the authoritative bodies,
15 we can do that, but this is a -- it's not normally
16 compared, the two lists.

17 CHAIRPERSON GOLD: This is unrelated to listing
18 under Prop 65, right?

19 CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

20 CHAIRPERSON GOLD: This is just whether you're
21 putting on our list that it says there hasn't been
22 adequate testing.

23 CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. And, you
24 know, just a -- you know, my somewhat educated guess of
25 why it's in there in the first place is that when the

1 proposition was passed, the people said that they weren't
2 getting enough information about exposures to chemicals
3 that cause cancer or reproductive toxicity. And so one of
4 the ways that they wanted to kind of put some pressure on
5 the government would be to put out this list that says,
6 you know, folks haven't done the testing that they're
7 required to do. That's my guess, but I don't know that
8 that has that effect. I doubt that U.S. EPA checks our
9 list.

10 CHAIRPERSON GOLD: All right. First, Dr.
11 Woodruff, then Dr. Pessah.

12 COMMITTEE MEMBER WOODRUFF: So are things that go
13 onto this list only things that EPA is considering for
14 testing or could we say -- could you add other things to
15 the list? Is it a requirement that it has to be being
16 considered by U.S. EPA?

17 CHIEF COUNSEL MONAHAN-CUMMINGS: It has to be a
18 chemical that's being required to have testing by a State
19 or federal government. So what we used to do is send out
20 requests to a number of different federal agencies and ask
21 them, you know, do you have any chemicals you think would
22 qualify for this list. And the only folks that ever get
23 back to us are U.S. EPA and Department of Pesticide
24 Regulation. So that's why -- I mean, I would imagine that
25 many of these have to do with pesticides.

1 COMMITTEE MEMBER WOODRUFF: Right. I guess I'm
2 wondering is like -- so like we were -- some of the
3 chemicals we were considering this morning, and it was
4 like, well, I wish we had more data on this. Can you
5 stick those on the list?

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Not this one.
7 No.

8 COMMITTEE MEMBER WOODRUFF: I see.

9 CHIEF COUNSEL MONAHAN-CUMMINGS: Although, you
10 know, to the extent that we could mention to U.S. EPA it
11 would be nice if we had some more testing. I mean,
12 they're probably aware that the -- some of these chemicals
13 need to be looked at again, but there's so many for
14 everybody to look at, it's -- like I said, this is a very
15 odd ministerial kind of act for this Committee.

16 CHAIRPERSON GOLD: Dr. Pessah, did you have
17 something.

18 COMMITTEE MEMBER PESSAH: She actually answered
19 one of my questions. How long is the list, at this point?
20 Do we know? Just roughly.

21 CHIEF COUNSEL MONAHAN-CUMMINGS: I don't have it
22 in front of me.

23 COMMITTEE MEMBER PESSAH: Hundreds or thousands?

24 CHIEF COUNSEL MONAHAN-CUMMINGS: No, no, no. No,
25 I would say it's probably not much more than 100.

1 COMMITTEE MEMBER PESSAH: Okay. And the list is
2 found at the OEHHA website?

3 CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, you can
4 get it on the website. I kind of was thinking that you
5 had received it with your materials.

6 CHAIRPERSON GOLD: It is kind of buried, this
7 list, but it is in there. It's in the 2700 --

8 COMMITTEE MEMBER PESSAH: Got it.

9 CHAIRPERSON GOLD: -- section, but towards the
10 middle of it.

11 CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah, towards
12 the end there's this -- there's a document that says
13 draft. And if you look at that, there's -- it shows where
14 we were going to be adding and deleting from that list.
15 And so you can see that it's not very long, not nearly as
16 long as the Prop 65 list. We've got, what, 750 chemicals
17 on that list. Except now, we're taking five of them off
18 today.

19 So other questions?

20 COMMITTEE MEMBER PESSAH: No, that was it. Thank
21 you.

22 CHAIRPERSON GOLD: Any other questions?

23 So we need to take a formal -- Dr. Baskin.

24 COMMITTEE MEMBER BASKIN: Are we just like
25 signing onto it? I'm kind of getting the impression I'm

1 just -- I don't seem to have a lot of information. Is
2 this like these chemicals could be bad, not be bad, and
3 I'm --

4 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's not
5 the determination you're making. So essentially, this is,
6 what we call, ministerial where you don't really have much
7 of a -- any discretion. And so -- and you are deferring
8 to the two agencies that they -- that they know that
9 they've asked for certain information, and they've either
10 received it or not.

11 COMMITTEE MEMBER BASKIN: Okay. So --

12 CHIEF COUNSEL MONAHAN-CUMMINGS: So you're not
13 really determining whether or not these are bad chemicals.

14 COMMITTEE MEMBER BASKIN: So other people who
15 have looked at this carefully have decided that we don't
16 have a lot of information.

17 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, I think
18 that U.S. EPA, for example, has a certain set of tests
19 that they require for say new pesticides or other
20 chemicals that are coming on the market. And so they have
21 this set, and so they periodically will make sure that all
22 of these -- the box has been checked that all of the tests
23 have been done that they required. And then they use
24 those to make their own decisions, which may or may not
25 impact our Prop 65 list at some point, but...

1 CHAIRPERSON GOLD: So like if we had information
2 that one of these chemicals had been extensively tested,
3 we would vote against this? Is that another way of
4 thinking about it?

5 CHIEF COUNSEL MONAHAN-CUMMINGS: No.

6 (Laughter.)

7 CHIEF COUNSEL MONAHAN-CUMMINGS: Although we
8 could get back to U.S. EPA and say I don't know if you
9 know this, but there's, you know, a number of tests that
10 have already been done on this chemical and -- or
11 whatever. I mean, we could do that for you as -- you
12 know, to -- because we're staff for the Committee, but
13 it's just an odd thing. I'm sorry, I can't explain it to
14 you any further than that. It's -- you don't -- the
15 actual phrasing in the statute just says that the
16 Committee identifies the chemicals.

17 So I suppose that you could say something about,
18 you know, that you think the U.S. EPA has the data, but I
19 mean I don't know that that would have a lot of effect.

20 CHAIRPERSON GOLD: Right. No, I was just posing
21 the question to try and get a handle on what it is we're
22 trying to do here. And so if we knew that there were --
23 was extensive data, then we wouldn't vote in favor of
24 putting it on this list. But in the absence of that, we
25 can vote to put it on the list?

1 CHIEF COUNSEL MONAHAN-CUMMINGS: Pretty much,
2 yeah. And, you know, it's not -- the data requirement
3 comes from the federal or State agencies, right? And so
4 they say the things that they want to see. And that's
5 why, you know, the list has -- it looks different than the
6 Prop 65 list because it's got a list of different kinds of
7 tests that need to be done.

8 So, for example, they want a rabbit test or a
9 mouse test or that sort of thing, a cancer test. And so
10 that's under their requirements for whatever program
11 they're considering the chemical under.

12 CHAIRPERSON GOLD: Dr. Woodruff, you have a
13 question.

14 COMMITTEE MEMBER WOODRUFF: Yes. Then it could
15 be that, you know, if there's a bunch of chemicals that we
16 consider and we decide there's not enough information
17 really to make a decision about their developmental or
18 reproductive toxicity, could OEHHA send a note to EPA to
19 that effect, so that then they can look and consider it
20 about whether it goes into this queue of things that need
21 testing information?

22 CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sure we
23 could pass that along. I don't know what would happen to
24 it --

25 COMMITTEE MEMBER WOODRUFF: Well, I don't know.

1 CHIEF COUNSEL MONAHAN-CUMMINGS: -- after it gets
2 to U.S. EPA, but we'd be happy to do that. I mean, I'm --
3 if you're familiar with any of these chemicals and you
4 have concerns about them, then we'd be happy to let U.S.
5 EPA know that or DPR.

6 COMMITTEE MEMBER WOODRUFF: Right. I mean, I
7 think one of the things that's come up in our discussions
8 is, "Oh, this chemical is used a lot", and we have no data
9 on it, and then we can't vote to list it, but that doesn't
10 mean it's safe, right?

11 CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

12 COMMITTEE MEMBER WOODRUFF: So I think that an
13 outcome could be for the Committee is to say well, maybe
14 this is one that should be passed along to EPA that should
15 be considered for that -- whatever process they have to
16 decide about testing.

17 CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. These are
18 only chemicals that are already -- there has to be a
19 jurisdiction by the particular agency that says, you know,
20 you can require certain information on say pesticides or
21 toxics under the TRI program or other kinds of
22 authorities.

23 And so say it's a food chemical, you know, we'd
24 have to let FDA know that they should probably do some
25 testing, but FDA doesn't give us information for this

1 list. So in any event, we can pass along the information
2 from the Committee and say, you know, we've got -- here's
3 some chemicals we considered, you know, on behalf of the
4 Committee, and these are the ones, and it was not possible
5 for the Committee to make an informed decision with no
6 data. I mean, we could do that certainly.

7 CHAIRPERSON GOLD: What you're asking us to do
8 right now is just to vote on whether these should be
9 listed as having inadequate data?

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.
11 Inadequate data for the first two sets, and then one more
12 slide has the ones that we can remove because they
13 received it.

14 But just based on the conversation here, we could
15 also, if you want to, point out chemicals that you want us
16 to bring to the attention of these groups, we can do that
17 too.

18 CHAIRPERSON GOLD: Okay. Well, why don't we take
19 them one at time then.

20 So are we --

21 DIRECTOR ALEXEEFF: I have a question. So I was
22 wondering, Carol, since I'm now asking you now in front of
23 everybody -- but I should have asked you someplace else.
24 But based upon this discussion here, I'm wondering if
25 we're able to modify the motion in a way that basically

1 says this list of chemicals has been reported to us from
2 U.S. EPA as being inadequately tested and meet the
3 requirements of Section 27000?

4 CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. Yeah, and
5 I think that's kind of the finding we're asking for.

6 DIRECTOR ALEXEEFF: Okay. So we're just -- so
7 that way they're not making the determination that it is
8 inadequate, but they're just saying, yes, these are the
9 chemicals that EPA has informed OEHHA.

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Right. And that
11 information is in your packet also, where we got the
12 letters back from U.S. EPA and DPR saying this stuff. So
13 essentially, what you're -- what you'd be voting on is are
14 you willing to defer to them that these are the --
15 basically the chemicals that they would like to have put
16 on and removed from this list? It's not an independent
17 finding.

18 It's kind of like, as an analogy, we do these
19 listings under the Labor Code that we talked about
20 earlier. And essentially, we have to look at did this
21 agency say that this chemical causes cancer, for example.
22 And if they did, we have to put it on the list. If
23 they've identified it, then we have to do that. We don't
24 do independent scientific determination. We just list it.

25 And that's the way this law is set up. And so I

1 think that's probably -- the carry-over to this list is
2 that, you know, we just want to know in one place what
3 chemicals that people should be testing, for example, or
4 that they have -- did you have something else?

5 COMMITTEE MEMBER PESSAH: So I was just wondering
6 so these are specific chemical structures that -- I mean,
7 the ones that you're presenting here are specific. But
8 I'm looking on the list and you've got nicotine and
9 derivatives. That's a pretty extensive list if you just
10 say derivatives, because there are neonicotinoids and --
11 so how -- are we saying chemical by chemical or we can do
12 classes of chemicals?

13 CHIEF COUNSEL MONAHAN-CUMMINGS: You can do
14 classes, you can do combinations, you can do whatever is,
15 you know, reported to us that needs to be on there. And,
16 you know, since we're -- this list isn't a -- it doesn't
17 have any impact in terms of warnings or discharges or any
18 of that stuff. It really has no regulatory purpose, so
19 that's all I can tell you.

20 CHAIRPERSON GOLD: So are we ready to vote on the
21 ones that EPA -- that should put on their list as having
22 inadequate testing?

23 Is the group ready to vote on that? I'm hearing
24 that we have at least three things maybe to vote on.
25 Yeah. Ms. Rocca.

1 COMMITTEE MEMBER ROCCA: I just wanted to be sure
2 of the exact wording of what it is we're voting on.

3 CHAIRPERSON GOLD: So I'm going to ask Dr.
4 Alexeeff to repeat his wording.

5 DIRECTOR ALEXEEFF: We should ask the
6 stenographer to read it back.

7 CHAIRPERSON GOLD: We could do that too.

8 DIRECTOR ALEXEEFF: No. Let me just see if I can
9 restate it, that --

10 CHIEF COUNSEL MONAHAN-CUMMINGS: George, do you
11 want me to read it off from the statute?

12 DIRECTOR ALEXEEFF: Well, let's see what it says.

13 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. It says,
14 "On or before January 1989, and at least once per year
15 thereafter, the Governor shall cause to be published a
16 separate list of those chemicals that at the time of
17 publication are required by State or federal law to have
18 been tested for potential to cause cancer or reproductive
19 toxicity, but that the State's qualified experts have not
20 found to have been adequately tested as required".

21 Okay. So if you want to -- if you want to frame
22 it as a voting question, I guess what we'd be saying is
23 you as the State's qualified experts, do you find, based
24 on the information you have from U.S. EPA, that these
25 chemicals have not been adequately tested according to the

1 requirements of U.S. EPA?

2 COMMITTEE MEMBER ROCCA: I can vote on that.

3 CHAIRPERSON GOLD: Now, are we ready to vote?

4 Oh, No. Dr. Pessah, you have a question.

5 COMMITTEE MEMBER PESSAH: So are there criteria
6 that we can refer to that U.S. EPA uses to deem them --

7 CHIEF COUNSEL MONAHAN-CUMMINGS: No.

8 COMMITTEE MEMBER PESSAH: No. We just take their
9 word for it.

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

11 COMMITTEE MEMBER PESSAH: Okay.

12 CHAIRPERSON GOLD: And in essence, for this first
13 thing, we're just voting on your first two slides, right?

14 CHIEF COUNSEL MONAHAN-CUMMINGS: That's correct.
15 So we're wanting to add these chemicals and the -- you
16 know, the types of tests we don't have on, you know, the
17 slide, but there are certain types of tests that U.S. EPA
18 says that they need to have.

19 CHAIRPERSON GOLD: Okay. So is the group now
20 ready to vote on whether these chemicals that have been
21 listed on the first two slides that Carol has shown us
22 have not been adequately tested as required by EPA?

23 Okay. All in favor of voting in that direction,
24 please raise your hand?

25 (Hands raised.)

1 CHAIRPERSON GOLD: Okay. I have six and that
2 would be zero noes and no abstentions.

3 CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

4 CHAIRPERSON GOLD: So you want to take your
5 second point?

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Yeah. What --
7 let me just point out without trying to make this
8 discussion too long is that also in your materials,
9 there's a -- the copy of our actual regulation, the 2700,
10 and it does go in a little bit more detail about what the
11 various mandates are that DPR and the Environmental
12 Protection Agency have, and what they're actually
13 requiring them under, for example, the Birth Defect
14 Prevention Act of 1984, the FIFRA, which is the Federal
15 Insect Fungicide and Rodenticide Act, and that's for both
16 U.S. EPA and CDPR, so -- and then, you know, there's some
17 discussion of what a data gap -- what it might be, that
18 sort of thing. So if that helps with the criteria
19 question.

20 And then for this list that's up here now,
21 there's one, two, three, four, five, six -- six chemicals
22 here that either Department of Pesticide Regulation or
23 U.S. EPA says that they now have the testing that they
24 required for those chemicals. And so the question would
25 be do you, based on the information that you have -- we've

1 received from U.S. EPA or CDPR, agree that we should
2 remove these chemicals from the list of those that need to
3 be tested?

4 CHAIRPERSON GOLD: Okay. So are there questions
5 about this vote?

6 All right. Are we ready to vote?

7 Okay. So can we approve this list to be removed
8 from the list of inadequately tested chemicals?

9 All those in favor aye?

10 (Hands raised.)

11 CHAIRPERSON GOLD: Six. So that would be zero
12 noes and no abstentions.

13 CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

14 CHAIRPERSON GOLD: Do you have one more? Oh,
15 well, the other one I guess relates to Dr. Woodruff. If
16 there are questions about chemicals that we would like to
17 add to EPA's list of things -- of chemicals that require
18 additional testing or have been inadequately tested?

19 And the question is whether you want to take that
20 up now, which we can spend a few minutes on, or we can
21 think about it and come up with a list for next time.
22 I'm -- whatever the Committee's pleasure.

23 COMMITTEE MEMBER WOODRUFF: I'm flexible about
24 doing it, but I do think though that when we have these --
25 I mean, I think we should -- we could put on the agenda

1 for next time to look back over our -- all the previous
2 chemicals we've looked at, because I would say almost in
3 every situation if we didn't vote to list it, it was often
4 because we didn't have information. And I think
5 California should be telling EPA that those are chemicals
6 that are inadequate and they should consider for testing.

7 CHIEF COUNSEL MONAHAN-CUMMINGS: That's fine.

8 CHAIRPERSON GOLD: So what I would suggest is for
9 the agenda for the next time compile the list of chemicals
10 that we've reviewed --

11 CHIEF COUNSEL MONAHAN-CUMMINGS: For what time
12 frame?

13 CHAIRPERSON GOLD: -- re-reviewed under the Labor
14 Code.

15 CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Good.

16 CHAIRPERSON GOLD: I would start there.

17 COMMITTEE MEMBER WOODRUFF: Not all. I think
18 that's doable.

19 CHAIRPERSON GOLD: I think that's a manageable
20 list. And the ones that we decided there wasn't enough
21 information -- or at least it seemed there wasn't enough
22 information, that would be a -- we could start with those.

23 COMMITTEE MEMBER WOODRUFF: That's fair.

24 CHAIRPERSON GOLD: Does that sound -- Dr. Rocca.

25 COMMITTEE MEMBER ROCCA: I have a practical

1 question about your list here. Your last chemical, maneb,
2 it says it's been removed for reproductive toxicity, but
3 remains on for teratogenicity. So will this be a chemical
4 that should be coming before this Committee again, now
5 that there's additional information?

6 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, that's the
7 question we talked about earlier, of whether or not we
8 compare -- whether we track these chemicals, I guess,
9 Jim -- or do we normally compare this list to any of our
10 others? I'm not sure you know that.

11 DR. DONALD: No, we don't generally directly
12 compare this list to the list of chemicals either that --
13 the existing list of chemicals or our tracking database
14 for chemicals that may become candidates for this
15 Committee to look at, but we certainly could do that.

16 COMMITTEE MEMBER ROCCA: Yeah, I'm suggesting
17 that this should be a candidate, since EPA says it's a
18 teratogen.

19 DR. DONALD: Well, no, what EPA is saying is that
20 it has not yet been adequately tested for teratogenicity,
21 but they're now saying it has been adequately tested.

22 COMMITTEE MEMBER ROCCA: But there is
23 reproductive toxicity data.

24 DR. DONALD: Yes.

25 COMMITTEE MEMBER ROCCA: Okay. Thank you.

1 CHAIRPERSON GOLD: I'm actually thinking since
2 it's kind of fresh in our thinking, if we went over the
3 list of chemicals that we did today, perhaps we could come
4 up with a list that we think could be added to the list of
5 that have inadequate -- inadequately tested, and then ask
6 the staff to go back to November's meeting, since I --
7 I'll speak for myself -- can't remember those, and bring
8 them before us, and then we can make a similar
9 determination about those. Is that --

10 CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

11 CHAIRPERSON GOLD: Okay. So just going back over
12 the list -- are people up for this? Is this okay to take
13 five minutes to do this?

14 Okay. So n-butyl glycidyl ether, we've all voted
15 no for all three outcomes. Is that one we want to send to
16 EPA to recommend that they put on their list as having
17 been inadequately tested?

18 Dr. Rocca.

19 COMMITTEE MEMBER ROCCA: According to the papers
20 that we reviewed, there is no developmental toxicity
21 information here.

22 CHAIRPERSON GOLD: And you would like some?

23 COMMITTEE MEMBER ROCCA: Not I, but --

24 (Laughter.)

25 CHAIRPERSON GOLD: You would like EPA to add it

1 to its list of chemicals for which they might want
2 developmental toxicity --

3 COMMITTEE MEMBER ROCCA: Right. And I don't know
4 what this chemical is regulated under. I just know that
5 based upon what has been presented to us here, that I
6 would say we all voted that it wasn't a developmental
7 toxicant just because there was no data.

8 CHAIRPERSON GOLD: Right. So this seems like a
9 good candidate. Anyone disagree with that?

10 COMMITTEE MEMBER NAZMI: Can I come back to Dr.
11 Baskin's slippery --

12 CHAIRPERSON GOLD: Dr. Nazmi, please.

13 COMMITTEE MEMBER NAZMI: -- slippery slope ideal,
14 because is it not quite feasible that we may vote that we
15 would like more research and more studies to be conducted
16 among nearly all of these chemicals that we're voting on?

17 CHAIRPERSON GOLD: And so does that mean we
18 shouldn't indicate?

19 COMMITTEE MEMBER NAZMI: I'm opening it for
20 discussion. I mean, at what point do we say well -- you
21 know, when would it be bad to have more information and
22 more research on a chemical? I guess that's the question.
23 Why would we not want more?

24 CHAIRPERSON GOLD: Dr. Baskin.

25 COMMITTEE MEMBER BASKIN: I mean, I don't know a

1 lot about a lot of these chemicals. And my wife's a
2 chemist, and she goes, "Wooh, you're looking at a chemical
3 formula". And I go, "I am".

4 (Laughter.)

5 COMMITTEE MEMBER BASKIN: So I Google the
6 chemical as part of my review. And I find out that New
7 Jersey has a list of every single chemical I think in the
8 workplace if you get splashed with it. It's kind of
9 actually very practical.

10 And some of these chemicals are incredibly
11 dangerous and nobody would touch them with a 10-foot pole.
12 However, the reproductive toxicology and developmental
13 toxicology there's either no information or the
14 information we have says it's not dangerous. That doesn't
15 mean the chemical is not dangerous, and shouldn't be used.

16 And so, I mean, I think we're reviewing this the
17 best we can, but I try to remember that I think we're
18 looking at a little microcosm sometimes. And so I kind of
19 worry the same thoughts. I mean, you could take every
20 single one of these and say we don't have any information.

21 For example, the one today that had incredible
22 histology of a bad testes, but it was N of 1, I'd like
23 more information on that. But economically, do we want to
24 put every chemical on the list?

25 I mean, if we have some obvious chemical that

1 should go on the list, obviously. And I think when I
2 first got on the Committee, we talked about like low-lying
3 fruit. A lot of that has been chipped away and some of
4 the stuff we're reviewing today is just because there's
5 been legislation changes.

6 So I'm for safe chemicals and a safe environment
7 like everybody, but I'm also for being practical. So I
8 don't know. That seems like some of this needs to come
9 down from above as opposed to filtering from us outward.

10 CHAIRPERSON GOLD: Yeah. I would just add that
11 maybe we could put the caveat that from our perspective,
12 we would like more reproductive toxicity and developmental
13 toxicity information. What we have before us pertains to
14 that, but is inadequate.

15 COMMITTEE MEMBER BASKIN: I mean, if somebody
16 were to ask me what chemicals would be on the list, I
17 would go at it a different way. I would say what are the
18 most ubiquitous chemicals in the environment and we should
19 throw our resources at them, as opposed to kind of the
20 other way around.

21 CHAIRPERSON GOLD: I think those were the
22 low-hanging fruit though.

23 (Laughter.)

24 CHAIRPERSON GOLD: But, Dr. Woodruff, you had a
25 comment.

1 COMMITTEE MEMBER WOODRUFF: Yeah. I would just
2 say that one of the challenges that we face in this
3 Committee is that we don't have information about these
4 chemicals. And I think, for me, to just say, oh, well,
5 it's not a reproductive or developmental toxicant does not
6 cover adequately the range of what we know -- what we
7 might know about this chemical, because a lack of data
8 does not mean it's not a problem. It just means we don't
9 know.

10 And I do think if you're saying that these
11 chemicals are being widely used in commerce, I think it is
12 something that we should ask the Government or the
13 companies to provide data on, because people are exposed
14 to them.

15 So I -- if the list is very long, which it could
16 very well be, I think that's fine, because this is -- we
17 have to be concerned about what the public health issue is
18 with this. And I feel very uncomfortable having to vote
19 on all these chemicals where I have no data.

20 CHIEF COUNSEL MONAHAN-CUMMINGS: One thing I
21 could -- sorry -- just clarify though, it's true that
22 maybe the general public doesn't understand what it means
23 to have a chemical on or off the list.

24 COMMITTEE MEMBER WOODRUFF: Right. I totally
25 agree with you. I know that the criteria is different. I

1 just guess I'm saying is if we have the ability to ask, in
2 some way, to say, yes, we agree that there's -- for
3 whatever reason this is not developmental or reproductive
4 toxicant, we agree that it shouldn't be listed, because,
5 A, it's either been proven to be that, or B, because we
6 have no data.

7 But I do think that it's something that if we
8 have like some mechanism like this to be able to comment
9 on no data, that we should provide that information,
10 because I think it provides transparency to our process.
11 And I'm not sure it's really -- that's, I think, makes the
12 process more transparent, and I do not think it's our
13 responsibility to -- you know, those kind of issues about
14 how much the cost.

15 I would not want us -- if we're going to really
16 talk about what the costs of these are, then I'd want us
17 to have a fuller discussion about this, if that's going to
18 be an issue in how we vote for this, because that concerns
19 me that we're thinking about the cost to the -- doing the
20 tests, but there's also a cost to the public, and
21 that's -- well, A, that's seems beyond this Committee, but
22 B, if that's a factor, then we should maybe take this up
23 at another meeting.

24 CHAIRPERSON GOLD: Dr. Pessah, did you have a
25 comment?

1 COMMITTEE MEMBER PESSAH: Well, just that we had
2 a proof of principle here today with methyl n-butyl
3 ketone. We, I think, decided that one should go out for
4 more information before we could make a decision. But I
5 think the whole point there is if you know the chemistry,
6 and you know the metabolic route leads to a real baddy,
7 and you want to err on the safe side if you don't have the
8 information, you want the information.

9 So I view that as not a slippery slope, but a
10 real scientifically based way to proceed. You know,
11 mechanisms, metabolism, if the information isn't there for
12 the parent compound that we're entertaining, but it is
13 there for a metabolite, then we better know that we have
14 all the information we need.

15 So that could be one criteria is, you know,
16 what's known about how the chemistry of this compound goes
17 and what the metabolism is and what the metabolites do?

18 CHAIRPERSON GOLD: Dr. Nazmi.

19 COMMITTEE MEMBER NAZMI: Completely agree with
20 you. So you're referring to -- I guess, correct me if I'm
21 wrong -- biological plausibility of the mechanism. Is
22 that not going to be somewhat dependent on concentration?
23 In, you know, industrial or in practical settings, it will
24 be largely based on concentration or exposure or method of
25 exposure, right?

1 COMMITTEE MEMBER PESSAH: Right. So again, I
2 think for this particular compound, there is some very
3 weak epidemiological data or workplace data that suggests
4 people that are being exposed have ill effects. I saw
5 that on one of the documents.

6 COMMITTEE MEMBER NAZMI: Right.

7 CHAIRPERSON GOLD: So I think going back to Dr.
8 Woodruff's point, I'm not sure we should be afraid of
9 telling them that there are chemicals out there that have
10 sort of, you know, a hint of a concern, but inadequate
11 data and getting those on the list, because I think that's
12 how the science advances is that people see that we have
13 data needs, in order to make policy decisions. And I
14 personally don't see a problem with pushing that process
15 along a little bit.

16 DIRECTOR ALEXEEFF: George Alexeeff. I have
17 another suggestion to overlay on these, and that is that
18 the criteria that we used to bring these lists to you has
19 to do with, at this point, DPR, Department of Pesticide
20 Regulation's and U.S. EPA's criteria for those chemicals
21 for which they can request data for.

22 So possibly we should go back and come back to
23 the Committee and let you know what were the categories of
24 information. I think we can all guess for Department of
25 Pesticide Regulation has to do with pesticides. So if a

1 pesticide came before this Committee, and we came across a
2 situation and say, okay, we're telling you it's a
3 pesticide and you're looking at the information. You're
4 saying, "Boy, we wish we had more data".

5 Then the question is well, is it still a
6 pesticide? Is it really still registered? And if so,
7 then that would be definitely a reason to ask DPR to --
8 you need to look at this one again or -- and maybe the
9 same thing with U.S. EPA. I don't exactly know what the
10 actual statute is that they're required to report under,
11 if it's TRI or others. But we could look at that and then
12 we could report back to the Committee on that, and then
13 we'd have some -- a narrower criteria if, as opposed to
14 requesting U.S. EPA to -- that there's chemicals to be
15 tested for which they have no authority to ask the test,
16 except maybe under TSCA, which is actually kind of a high
17 bar.

18 CHAIRPERSON GOLD: Dr. Rocca.

19 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it is --
20 right now, it's TSCA for U.S. EPA and FIFRA. And that
21 would be true for DPR, because they wouldn't be asking for
22 information on anything but a pesticide.

23 COMMITTEE MEMBER ROCCA: Several comments. That
24 clarification as well as some of the other comments have
25 been persuasive to me that there is an authoritative body

1 here, in fact two of them, that that is their full-time
2 job, and that probably we don't need to tell them that we
3 want more data.

4 The other thing is before we would do that, I
5 think it's important that we compare the list of chemicals
6 to what is already considered to have adequate information
7 or inadequate information. It could be that some of the
8 chemicals we reviewed today have already been considered
9 inadequate by the EPA or by Pesticide. So I think that we
10 would want to do that before we would just come up with
11 lists.

12 CHAIRPERSON GOLD: So we have two possibilities
13 it seems to me. One is we could request the staff to tell
14 us which among the chemicals that we've reviewed at this
15 meeting and the prior meeting are already on the list as
16 having inadequate data, and then we could review them at
17 the next meeting and say we would like them listed, or we
18 could just go ahead and say from the ones from today which
19 ones we think have inadequate data are in need of more
20 data, and suggest -- have the staff compare that to the
21 existing list. And if they're not on there, to suggest to
22 EPA that they should be listed.

23 So does the Committee have a preference for which
24 way to go on this?

25 Dr. Rocca.

1 COMMITTEE MEMBER ROCCA: I would rather see the
2 list first than have us debate something and then find out
3 that it's moot.

4 CHAIRPERSON GOLD: It's already here.

5 COMMITTEE MEMBER ROCCA: Yeah.

6 CHAIRPERSON GOLD: Other people have thoughts?

7 COMMITTEE MEMBER WOODRUFF: Yeah. I think that
8 that's fair. And then I think also, just thinking about
9 some of the comments that people are raising about this, I
10 think it actually -- it's something we might want to think
11 a little bit more about, because I think for -- part of
12 this is being able to comment on the adequacy of some of
13 the data to make a decision.

14 And I'm not -- you know, if we decide, oh,
15 there's not enough data, then we've kind of made a
16 decision. So I think we need to think about that more
17 carefully, so -- and I'm happy -- I think we should check
18 the list and see if there's anything that's already
19 underway, as a first step.

20 CHIEF COUNSEL MONAHAN-CUMMINGS: Well, one thing
21 to point out is that you have the list -- the entire list
22 of the chemicals that U.S. EPA and DPR have said they need
23 more data on. And sometimes what we do is just take one
24 of the tests off. We don't take the actual chemical off
25 like, for example, this last one here the maneb with ETU,

1 would stay on for teratogenicity testing, but we're just
2 taking off the little -- on the list, it's got the names
3 of the types of tests that they want.

4 So if -- but if you just glance through here,
5 there's only -- I mean, less -- maybe 75 chemicals on here
6 at the most, and none of them, from what I can see, have
7 been considered by this Committee, so -- but one of
8 the -- one thing to also keep in mind is once U.S. EPA has
9 enough of the test data, then one would presume that they
10 would use that to make their decision under FIFRA or TSCA
11 or whatever, and once they do that, then we would rely on
12 U.S. EPA's decision and proposed listing of the chemical
13 under an authoritative body listing mechanism.

14 So those are -- I just don't think you can
15 compare these two lists and say, you know, there's -- you
16 can take one and graft it onto the other as easily as it
17 might appear.

18 But having said all that, what I would suggest is
19 if you -- I can't remember if you voted on this second
20 list about removing them, but in the event that you do
21 that, and then what we could do for the next meeting is we
22 can do a little bit more coherent presentation to you on
23 what all of this does, and we can also contact U.S. EPA
24 and DPR and see if they have a process whereby we could
25 make some recommendations to them. So we could, you know,

1 maybe at the May meeting, if we had time.

2 CHAIRPERSON GOLD: Yeah, I think if you could get
3 organized for the May meeting to give us a little more
4 detail about these listing mechanisms, because personally
5 I'm having trouble mapping these chemicals on these lists
6 that are in our handouts. And so right away I have a
7 discrepancy. And so that's number one is if we could get
8 a little more clarity on the process than what's actually
9 on the EPA list for being inadequately tested.

10 And then also, if the staff could take a look --
11 so we won't do it now -- at the chemicals that we looked
12 at this time and last time and where we seem to suggest
13 that, gee, it would have been nice to have more data, you
14 know, put those in a list and we can consider them
15 alongside the EPA list next time. Would that be possible?

16 CHIEF COUNSEL MONAHAN-CUMMINGS: We can do that,
17 sure.

18 CHAIRPERSON GOLD: Okay. So do we still have
19 something remaining to vote on? I'm --

20 CHIEF COUNSEL MONAHAN-CUMMINGS: Did you guys
21 already vote on whether or not --

22 CHAIRPERSON GOLD: I think we did, yes.

23 CHIEF COUNSEL MONAHAN-CUMMINGS: -- we should
24 take these off?

25 COMMITTEE MEMBER WOODRUFF: Yes.

1 CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

2 CHAIRPERSON GOLD: I think we're done with this
3 topic for today.

4 CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

5 CHAIRPERSON GOLD: All right. Let me get my
6 agenda back out.

7 COMMITTEE MEMBER NAZMI: I'm sorry. Can I make
8 one final comment?

9 CHAIRPERSON GOLD: Yes, please, Dr. Nazmi.

10 COMMITTEE MEMBER NAZMI: For the agenda item,
11 perhaps for next meeting, if we can maybe more precisely
12 define what we might mean by, it would be nice to have
13 more data if we're going to develop some sort of a
14 protocol or some sort of a process by which we determine,
15 yes, this chemical for this reason requires us to have
16 more data. That might just clarify how we want to
17 approach that new list.

18 CHIEF COUNSEL MONAHAN-CUMMINGS: We could maybe
19 give you some suggestions on that for you to discuss at
20 the next meeting.

21 CHAIRPERSON GOLD: It occurs to me -- sorry.

22 CHIEF COUNSEL MONAHAN-CUMMINGS: And we'd be
23 happy to hear from you all some suggestions for that, too.
24 And we can just kind of put them together and put it as a
25 discussion item.

1 COMMITTEE MEMBER NAZMI: Right. Sounds great.

2 CHAIRPERSON GOLD: I think things that we -- just
3 as a first stab at that, things that we saw some
4 suggestive evidence, but the evidence was really
5 inadequate to make a definitive statement, that would be a
6 good place to start for where having some additional data
7 would be helpful. I'm sure there are other points that
8 the Committee can think of, but that comes immediately to
9 mind.

10 Okay. Now, are we done with this topic?

11 So we have staff updates next, is that correct?

12 DIRECTOR ALEXEEFF: I think we're done with staff
13 updates. We have a general public comment.

14 CHAIRPERSON GOLD: Yes, I know okay. So no
15 further staff comments beyond what we had this morning.

16 Okay. I understand there is a general public
17 comment to be made?

18 CHIEF COUNSEL MONAHAN-CUMMINGS: The person left.

19 (Laughter.)

20 CHAIRPERSON GOLD: So we will have no general
21 public comment today.

22 So Dr. Alexeeff is going to summarize our
23 Committee actions, is that correct?

24 DIRECTOR ALEXEEFF: Okay. Well, I think before I
25 summarize the Committee actions, I just wanted to announce

1 that, you know, this is -- unfortunately, this will be Dr.
2 Rocca's last meeting on the Committee. And we're really
3 sorry to see her go. She's actually contributed quite a
4 bit to this process in the short time that she's been on
5 the Committee. And I think that she's left a really good
6 mark and a really high bar for anyone who wants to follow
7 her.

8 And, you know, it's -- she's going to be reunited
9 with her family on the east coast, and, you know, being
10 transferred back there to the Philadelphia area, so that's
11 wonderful for her. And, you know, if you know those east
12 coast kind of little towns and things, it can be a
13 wonderful place to live. And I'm sure she's going to be
14 really happy there, even though, I mean, the south bay. I
15 mean, you know, who could complain about that.

16 So we -- you know, we really appreciate all the
17 work you've done, and I mean you've really done an
18 incredible insightful job on almost every chemical,
19 whether you are a leader or not. And I think everyone in
20 the panel really appreciates the effort that you displayed
21 in your tasks here. And we know that you have a lot of
22 other things to do. And we, at OEHHA and with the State,
23 really appreciate your service that you've offered to the
24 State, because we realize that it's essentially, you know,
25 a lot of work on your part that's not really being, you

1 know, compensated. So we really appreciate that.

2 I don't know if you had any parting comments?

3 COMMITTEE MEMBER ROCCA: Actually, I do, as long
4 as you've brought it up. Yeah, I wanted to thank the
5 staff for all the help that they have given us in
6 preparing these materials, and in getting us all the extra
7 materials that we asked them to find at the last minute.
8 And I also want to say it's been an honor and a pleasure
9 to serve on this Committee.

10 DIRECTOR ALEXEEFF: As we were thinking about Dr.
11 Rocca, we're not really sure if we made an adequate
12 statement that Dr. Hillary had to -- also had to leave the
13 Committee due to being transferred out of state or having
14 a new job out of state, Hillary Klonoff-Cohen. So
15 consequently, we will be considering the need for
16 additional members and such. But we also just wanted to
17 make a mention that Dr. Klonoff-Cohen as well.

18 DIRECTOR ALEXEEFF: All right. Now, we're down
19 to the summarization of actions here. So the Committee
20 actually did a lot of things today, so I'm just going to
21 summarize the actions.

22 The Committee considered -- well, let's say it
23 this way. The Committee identified the following
24 chemicals to be placed on the list of reproductive
25 toxicity, based upon them -- well, actually, the Committee

1 considered a number of chemicals to be placed on the list
2 and did not identify any to be placed on the list today,
3 based upon clearly shown through scientifically valid
4 testing, according to generally accepted principles. So
5 the chemicals that the Committee considered were n-butyl
6 glycidyl ether, phenyl glycidyl ether, diglycidyl ether,
7 methyl isopropyl ketone, and alpha-methyl styrene. And
8 the Committee also deferred an action on methyl n-butyl
9 ketone.

10 The Committee also provided comments with regards
11 to the tabulation of epidemiologic and animal data. And
12 the Committee also added chemicals and deleted chemicals
13 from the Section 27000 list of chemicals, which have not
14 been adequately tested as required.

15 So I think that summarizes the actions of the
16 Committee today.

17 CHAIRPERSON GOLD: Okay. Does the staff have
18 anything else that they want to bring to our attention?

19 Public?

20 Committee?

21 So I want to thank the Committee for their hard
22 work and diligence in reviewing all these materials and
23 for the staff for preparing them and getting us all
24 organized for this meeting. The work is greatly
25 appreciated, and we will reconvene in May. So have a good

1 evening.

2 Thank you.

3 (Thereupon the Developmental and
4 Reproductive Toxicant Identification
5 Committee adjourned at 2:42 p.m.)
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1 C E R T I F I C A T E O F R E P O R T E R

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

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

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

15 IN WITNESS WHEREOF, I have hereunto set my hand
16 this 1st day of April, 2014.

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22
23 JAMES F. PETERS, CSR, RPR
24 Certified Shorthand Reporter
25 License No. 10063